OXYGEN CONSUMPTION MODULATION: EFFECTS OF AN OPIOID AGONIST ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY

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As with many long-term goals, a successful outcome will ultimately depend on perseverance and to some extent on talent. The last eight years were spent acquiring the scientific knowledge to study the phenomenon of interest, developing and conducting the research, and writing the dissertation, most of which was completed while maintaining a full-time clinical practice. These times were marked by personal sacrifices and challenges and I am tremendously grateful to many individuals who have supported me throughout this journey.

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DEDICATION

This dissertation is dedicated to my husband,

Michael John Urbaitis,

for whom there are no words to adequately express

the deepness of my gratitude and absolute admiration,

and to

Mary Frances Whitley Towler

(5 Nov 1917 – 8 Jan 2002),

for her unconditional love and complete devotion.

ABSTRACT

OXYGEN CONSUMPTION MODULATION: EFFECTS OF AN OPIOID AGONIST ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY

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Nursing procedures, such as routine lateral positioning, that increase sympathetic stimulation and metabolic demand may have adverse physiological consequences for critically ill patients compromised by cardiorespiratory dysfunction and insufficient compensatory mechanisms to increase oxygen delivery (DO_2) (Gawlinski & Dracup, 1998). A prospective, single group, quasi-experimental, repeated measures, factorial design was used to evaluate the clinical efficacy of a preprocedural morphine intervention (0.10 mg/kg iv) to attenuate oxygen consumption (VO_2) response following lateral positioning in a convenience sample of 30 mechanically ventilated, cardiovascular surgical patients with low DO_2 ($M = 355$, $SD = 71$). Subjects were randomized to either the left or right 45-degree lateral position. Mixed-venous oxygen saturation (SvO_2) and VO_2 via indirect calorimetry were measured at baseline and every 1-minute for 10 minutes following turning procedures, with and without the morphine intervention. Without morphine, lateral positioning was associated with a 17.3% peak increase in VO_2I from baseline, typically occurring between minutes 4 and 5 after the turn, and a 7.2%

decrease in SvO_2 from baseline to minute 1 following the turn. When morphine was received before the turn, mean VO_2I was not significantly lower at minutes 1 ($\rho = .64$) and 5 ($\rho = .41$) following the turn; however, mean SvO_2 was significantly higher at minutes 1 ($\rho = .000$) and 5 ($\rho = .001$) following the turn. Furthermore, the probability of SvO_2 returning to baseline within 10 minutes following the turn was 73% with morphine and only 50% without morphine ($\rho = .05$). Preliminary findings suggested morphine *blunted* cardiovascular responses and resulted in *undesirable* reductions in DO_2I and cardiac index and increases in oxygen extraction; therefore, the routine use of preprocedural morphine for attenuating oxygen demand-induced VO_2 response is *not* recommended.

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CHAPTER I

INTRODUCTION

Turning critically ill patients to a side-lying or lateral position every 1 to 2 hours is standard nursing practice in the intensive care unit (ICU) (Ahrens, 1993; Bridges, Woods, Brengelmann, Mitchell, & Laurent-Bopp, 2000; Brooks-Brunn, 1995; Davis et al., 2001; Gawlinski, 1993b; Yeaw, 1996). Lateral positioning, a type of cardiorespiratory physiotherapy, refers to the use of a body position as an evidence-based treatment intended to increase oxygen transport by improving pulmonary ventilation and perfusion distribution, increasing lung volumes, reducing the work of breathing, minimizing myocardial workload, and enhancing mucociliary clearance (Dean, 1994; Stiller, 2000). Patients with pulmonary pathology demonstrate improved oxygenation of arterial blood (PaO_2) when positioned with their "healthy" lung in a dependent (down) position because ventilation and perfusion are preferentially distributed to the dependent lung regions as a result of normal gravitational and hydrostatic forces (Fontaine & McQuillan, 1989; Hess, Agarwal, & Myers, 1992; Remolina, Khan, Santiago, & Edelman, 1981; Zack, Pontoppidan, & Kazemi, 1974).

For most individuals, lateral positioning has many benefits and few risks (Gawlinski, 1993b). However, critical care nurses are at times reluctant to turn patients because altering position can trigger cardiorespiratory fluctuations including cardiac dysrhythmias, hypotension, low cardiac output and hypoxemia (Bridges, 2001; Gillespie

& Rehder, 1987; Remolina et al., 1981; Rivara, Artucio, Arcos, & Hiriart, 1984; Winslow, Clark, White, & Tyler, 1990). Physiological responses to lateral positioning may be either adaptive or maladaptive and largely depend on the effects of the intervention on oxygen delivery (DO_2) and oxygen consumption (VO_2) (Gawlinski & Dracup, 1998; Paratz, 1992).

Researchers have demonstrated that manually placing a critically ill patient in a lateral position produces an immediate increase in VO_2 by as much as 20% to 50% above baseline values (Cohen, Horiuchi, Kemper, & Weissman, 1996; Davis et al., 2001; Gawlinski & Dracup, 1998; Horiuchi, Jordan, Cohen, Kemper, & Weissman, 1997; Swinamer, Phang, Jones, Grace, & King, 1987; Verderber & Gallagher, 1994; Weissman et al., 1984). Increases in VO_2 associated with lateral positioning have been attributed to numerous factors including (a) an increase in skeletal muscle activity, (b) sympathetic stimulation and increase in plasma concentrations of epinephrine and norepinephrine, and (c) procedural pain and anxiety (Cohen et al., 1996; Horiuchi et al., 1997; Stanik-Hutt, Soeken, Belcher, Fontaine, & Gift, 2001; Swinamer et al., 1987). Prior to positioning a critically ill patient with low DO_2, it is important for nurses to have an integrated and thorough understanding of the acute effects of low intensity exercise, its metabolic demands and a comprehensive assessment of the patient's cardiorespiratory reserves and ability to meet these demands (Dean, 1994).

Tissue oxygen deprivation. Even at rest, critically ill patients have significantly greater metabolic requirements because of the physiologic and psychological stress of

acute illness (Epstein & Breslow, 1999). This stress is often compounded by blood and fluid losses, surgical trauma, wound healing, infection, pain and anxiety (Edwards, Redmond, Nightingale, & Wilkins, 1988; Jacobi et al., 2002; McGee, Wilson , & Veremakis, 1988). Under normal conditions, oxygen consumption increases when oxygen demand increases. A sudden increase in oxygen demand is countered by physiological compensatory mechanisms that increase oxygen availability to the tissues. Adaptive mechanisms that maintain tissue oxygenation include (a) a reserve capacity accessible by increasing oxygen extraction (O_2ER) from the oxyhemoglobin molecule, and (b) the ability to increase DO_2 by augmenting cardiac output (Gawlinski, 1993b; Gawlinski & Dracup, 1998). Normally, both of these mechanisms are capable of increasing by approximately threefold and result in a nine-fold increase in VO_2 to meet the oxygen demands of the tissues (Nelson, 1986).

To sustain higher metabolic requirements during critical illness, tissues require greater amounts of DO_2, the product of arterial oxygen content (CaO_2) and cardiac output (CO). However, critically ill patients may not be able to increase CO spontaneously and therefore may have a substantially diminished "safety factor" in regard to increasing VO_2 (Nelson, 1986). Critical illness is frequently associated with altered regulatory mechanisms that may adversely affect blood flow distribution, DO_2, and VO_2, thus, impairing tissue perfusion. Consequently, oxygen demand may be markedly increased despite a diminished oxygen supply (McGee et al., 1988). If oxygen supply and demand balance is not restored in a timely manner, tissue oxygen deprivation (i.e., hypoxia)

manifested by disruptions of normal cellular function may result (Epstein & Henning, 1993; Heinrichs & Weiler, 1994; Smith & Steele, 1991; Verderber & Gallagher, 1994). Inadequate restoration of DO_2 and continuation of occult tissue oxygen deprivation are mechanisms of multiple system organ failure, the most common cause of death in critically ill patients (Baigorri & Russell, 1996).

Anemia and myocardial depression. Cardiovascular surgical patients are a subset of critically ill patients who are at risk to have decreased DO_2 due to (a) an insufficient amount of hemoglobin (i.e., anemia) and (b) depressed myocardial function resulting in decreased blood flow (i.e., ischemia). Postoperative complications associated with extracorporeal circulation including excessive bleeding, hemolysis and hemodilution contribute to significant anemia and decreased CaO_2 following cardiovascular surgery (Weiland & Walker, 1986). Additionally, more than 95% of cardiovascular surgical patients who have normal preoperative myocardial function develop depressed myocardial contractility and low cardiac output during the first 8 to 24 hours following surgery due to the effects of anesthesia, extracorporeal circulation, hypothermia, and cardioplegic arrest (Eillis, 1997; Fleischer & Stuart, 1994; Ley, 1993). When myocardial function is depressed, cardiac output cannot increase sufficiently to compensate for decreased CaO_2 that accompanies a reduction in hemoglobin (Hb) (Pier, 1993). The combination of anemia and decreased myocardial contractility increases patient susceptibility to tissue hypoxia because the oxygen transport system cannot supply adequate quantities of oxygen to sustain normal cellular function (Misasi & Keyes, 1994;

Norris, 1993; Szaflarski, 1996). Consequently, for patients with compromised DO_2, nursing procedures that increase oxygen demand, such as lateral positioning, can produce cardiorespiratory instability (Gawlinski & Dracup, 1998; Nelson, 1986; Winslow et al., 1990).

Tissue oxygenation assessment. Although *direct* measurement of DO_2 and VO_2 in the critical care setting is limited by current medical technology, clinicians are able to evaluate cardiorespiratory function and the adequacy of global tissue oxygenation by continuously monitoring mixed-venous oxygen saturation (SvO_2) through reflectance spectrophotometry (Ahrens, 1999; Jesurum, 1998). Fiberoptic instrumentation differentiates oxygenated blood from deoxygenated blood in the pulmonary artery. When DO_2 is compromised, an increase in oxygen demand will be associated with an increase in VO_2 and O_2ER and a decrease in SvO_2 (Epstein & Henning, 1993; Lehot & Durand, 1993). Low SvO_2 (< 60%) or a rapid and sustained decrease in SvO_2 (> 10% for more than 5 minutes) signals an imbalance between oxygen delivery and oxygen consumption that requires further assessment of the components of the oxygen transport system (CO, stroke volume, heart rate, Hb, SaO_2, VO_2, O_2ER) to select an appropriate therapy (Nelson, 1986).

Researchers have reported that cardiovascular surgical patients typically experience a decrease in SvO_2 from 8% to 12% immediately after lateral positioning which gradually returns to baseline within four to five minutes (Atkins, Hapshe, & Riegel, 1994; Gawlinski & Dracup, 1998; Noll & Fountain, 1990a; Pena, 1989; Tidwell, Ryan,

Osguthorpe, Paull, & Smith, 1990; Winslow et al., 1990). Depending on the patient's circulation time (i.e., flow), the largest changes in SvO_2 typically occur 1 to 2 minutes following lateral positioning (Gawlinski & Dracup, 1998). While studying vulnerable populations with impaired cardiac function and low cardiac output, Gawlinski and Dracup (1998) observed clinically significant reductions in SvO_2 following lateral positioning in as many as 48% of subjects and have attributed the findings to an increase in VO_2 rather than a decrease in DO_2. Lewis and colleagues (1997) reported profoundly low SvO_2 (< 33%) following lateral positioning in cardiovascular surgical patients who had low hemoglobin levels.

DO_2 augmentation vs. VO_2 conservation. Patient survival may be improved when SvO_2 and cardiorespiratory variables are analyzed at serial intervals and guide the clinical management of patients at risk for tissue oxygen deprivation (Creamer, Edwards, & Nightingale, 1990; Edwards, 1990, 1991; Schallom & Ahrens, 1999). The goal of many interventions for critically ill patients is to insure that oxygen delivery to the tissues meets or exceeds oxygen demands (Nelson, 1986). Therapeutic approaches to managing tissue hypoxia are typically designed to maximize VO_2 by increasing DO_2; however, patients with impaired myocardial function may not respond to therapies aimed at increasing cardiac output (Shoemaker, Appel, & Kram, 1991; Shoemaker, Patil, Appel, & Kram, 1992). Critical care nurses are challenged to promote vital organ function by maintaining adequate tissue oxygenation in patients who have oxygen demands that exceed supply. Interventions that enhance patient tolerance to nursing procedures by maintaining or

restoring the balance between oxygen supply and demand promote physiologic adaptation (Thompson, 1991). Only when sufficient knowledge of pathological processes has been acquired will it be possible to identify patients who have altered adaptive mechanisms, anticipate human responses to situational stressors that are likely to threaten physiological adaptation, and prescribe nursing interventions to alleviate the effects of such stressors (Carrieri-Kohlman, Lindsey, & West, 1993; Lindsey, Carrieri-Kohlman, & Page, 1993). Thus, further research is needed to (a) describe the pathophysiological phenomenon of tissue oxygen deprivation related to routine nursing care procedures, (b) define temporal relationships of tissue oxygenation variables when oxygen demands exceed supply, and (c) test interventions that decrease oxygen demand, thus preventing the pathogenesis of tissue oxygen deprivation, and improving patient tolerance to routine nursing care procedures.

Oxygen consumption modulation. Historically, nurses have attended to pain management, comfort measures and stress management. Interventions were *primarily* directed at alleviating patient discomfort rather than decreasing oxygen demand. With recently acquired scientific knowledge that validates the high metabolic demands associated with critical illness, these nursing interventions are now recognized for their importance in decreasing oxygen demand (Pooler-Lunse & Price, 1997). By utilizing therapies aimed at modulating oxygen consumption (Baigorri & Russell, 1996), the balance between oxygen supply and demand may potentially be preserved and patients may demonstrate improved tolerance to nursing procedures known to increase VO_2 (i.e.,

oxygen demand-induced VO_2 response). As a nursing theorist, Levine (1966, 1967, 1996) advocated for energy conservation in nursing practice to maintain a balance between the supply of energy-producing nutrients and the rate of energy-using activities. Rather than merely limiting activity, Levine encouraged the proper disbursement of energy expense through activities that were gauged to the patient's capability, safety and comfort level (Levine, 1966, 1967, 1996). To date, nursing research has not validated oxygen consumption modulation theory. Further research is needed to test and refine the conceptual relationships of oxygen consumption modulation theory and to investigate nursing interventions that decrease oxygen demand and prevent oxygen deficiency, including complications associated with tissue hypoxia (Winslow et al., 1990).

According to published reports, analgesia, anesthesia, sedatives and paralyzing agents lower metabolic rate and minimize VO_2 by decreasing skeletal muscle activity (Colonna-Romano & Horrow, 1994; Davis et al., 2001; Klein et al., 1988; Smith & Steele, 1991; Weissman et al., 1986). In managing the patient with low DO_2, administration of a pharmacological agent to optimize the relationship between DO_2 and VO_2 and to improve the patient's response to nursing interventions warrants clinical investigation (Jesurum, 1997). During the past decade, emphasis placed on early extubation and ICU transfer following cardiovascular surgery has resulted in anesthesia practices shifting from high-dose opioids to short-acting sedatives (Jesurum, Alexander, Anderson, & Houston, 1996; Meade et al., 2001). Consequently, cardiovascular surgical patients frequently require continuation of anesthetic agents (i.e., propofol) in the early

postoperative period to maintain sedation and to avoid inadvertent disruption of invasive therapies including endotracheal intubation and hemodynamic monitoring instrumentation (Gawlinski, 2001).

Propofol (Diprivan®) (2,6-diisopropylphenol) is a short-acting, nonbarbiturate, intravenous anesthetic agent that is used in the intraoperative and postoperative periods (Clinical Pharmacology Online, 2000). Onset of action following a single dose of propofol is very rapid (~ 2 to 3 minutes) and the effect is very brief (~ 10 to 15 minutes) (Nasraway, 2001). Similar to the benzodiazepines, propofol has no analgesic properties but does cause hypnosis and anxiolysis. Additionally, propofol can cause cardiorespiratory depression and hemodynamic destabilization, specifically hypotension, because of its negative inotrope, negative chronotrope and vasodilatation effects. However, responses are dose dependent and cardiac output is usually not affected with low dosages. In moderate to low dosages, propofol may attenuate VO_2 and carbon dioxide production (VCO_2) and concomitant usage of opiates may intensify these responses (Kowalski & Rayfield, 1999; Mosby's Drug Consult, 2002).

Cohen and Horiuchi (1996) studied the effects of propofol in 16 critically ill, mechanically ventilated patients during chest physiotherapy. Although the researchers did not control for the effects of other analgesics or sedatives during the procedure, the findings indicated that high doses of propofol (0.75 mg/kg iv) significantly decreased VO_2I (VO_2 indexed to body surface area [ml/min/m^2], $M_1 = 277$, $SD = 105$ vs. $M_2 = 394$, $SD = 104$) during chest physiotherapy procedures as did low doses of propofol (0.35

mg/kg iv) (M_1 = 348, SD = 88 vs. M_2 = 413, SD = 85, $\rho < .05$). Unfortunately, both low and high dose propofol regimens significantly decreased DO_2I (DO_2 indexed to body surface area) and CO; consequently, SvO_2 and O_2ER remained stable. Reductions in systemic arterial blood pressure and heart rate were also observed with both doses of propofol. Cardiovascular responses (i.e., decrease in blood pressure) were attributed to the drug's direct effect on sympathetic vascular tone. Although left and right-sided cardiac filling pressures were not significantly different between propofol and placebo groups, the difference between baseline measurements and measurements obtained during activity trended slightly lower in the propofol group (Cohen et al., 1996). Clearly, in patients who have low DO_2I, interventions that result in further reductions in DO_2I and CO are not desirable and other alternatives need to be considered. According to the theory of pathologic oxygen supply dependency, critical reductions in DO_2I during periods of high demand may limit VO_2 and result in profound tissue oxygen deprivation (Baigorri & Russell, 1996; Leach & Treacher, 1994).

Although sedative agents, such as propofol, reduce the stress response and may improve patient tolerance to routine ICU procedures, an analgesic may be an appropriate initial therapy when pain or discomfort may be associated with a procedure or triggers acute agitation (Harding, Kemper, & Weissman, 1994; Jacobi et al., 2002; Klein et al., 1988). In a recently published study involving 6,200 acute and critically ill patients, turning was identified as the most painful and distressing procedure experienced by adults during their hospitalization, in comparison to wound dressing change, drain

removal, or tracheal suction (Puntillo et al., 2001). Using a visual analog scale (0-100) to measure their pain, critically ill patients reported significantly higher pain intensity scores immediately after turning than before turning ($M_1 = 25$ vs. $M_2 = 48$, $\rho = 0.002$) (Stanik-Hutt et al., 2001). Although lateral positioning is performed many times a day, analgesics are not routinely administered prior to the procedure (Puntillo et al., 2001). In fact, Puntillo et al. (2001) reported that 96.8% ($n = 739$) of patients did not receive opioids prior to turning.

Opioid agonists. First and foremost, opiates relieve pain or the responsiveness to noxious stimuli. Secondary, although important, actions include sedation and anxiolysis. Opiates are frequently used in the critical care setting to manage pain and agitation simultaneously. Both the sedative and analgesic properties of the opiates are mediated through the mμ and kappa receptors (Hall, Oyen, & Murray, 2001; Nasraway, 2001). Morphine sulfate (hereafter termed morphine), an opioid agonist against which all other analgesic agents are compared, acts primarily on the mμ receptor sites distributed throughout the central and peripheral nervous system and is the preferred analgesic for controlling acute postoperative pain (Kruger & McRae, 1999; Mason, 1993; Shapiro et al., 1995). When stimulated, the mu_1 (spinal) and mu_2 (supraspinal) receptor subtypes that are located in the central nervous system produce analgesia, sedation, euphoria, respiratory depression, and decreased gastric motility (Hall et al., 2001). Opioids alter the perception and response to pain by inhibiting the ascending neuronal pain pathways. Researchers have reported that morphine decreases metabolic rate and VO_2 in patients

undergoing interventional and surgical cardiovascular procedures (Alderman, Barry, Graham, & Harrison, 1972; Colonna-Romano & Horrow, 1994; Rodriguez et al., 1983; Rouby et al., 1979). Although the exact mechanism of action is unclear, researchers have suggested morphine reduces VO_2 through its effects on suppressing skeletal muscle activity, attenuating adrenergic cardiovascular stress response (i.e., "hemodynamic sedation"), and reducing pain and discomfort (Bernard, Bourreli, & Pinaud, 1988; Duke, Johns, Pinsky, & Goertzen, 1979; Hall et al., 2001; Rouby et al., 1981).

Guided by the principles of adaptation (Roy & Andrews, 1991), energy conservation (Levine, 1996), and oxygen consumption modulation therapy (Baigorri & Russell, 1996; Epstein & Breslow, 1999), the investigator proposed that critically ill patients who received morphine, with or without a concomitant propofol infusion, before turning (i.e., preprocedural) would demonstrate improved tolerance to the procedure as measured by cardiorespiratory parameters. Conceivably, if patients with low DO_2 received morphine before procedures associated with an increase in energy expenditure and oxygen consumption (i.e., lateral positioning, bathing, weighing, suctioning), tissue oxygenation may improve and patients may demonstrate improved adaptation to these routine procedures. Theoretically, as oxygen demand is reduced, VO_2 and O_2ER should decrease and SvO_2 should increase or remain stable. Improved physiological adaptation and avoidance of tissue hypoxia may result in fewer complications associated with lateral positioning including cardiac arrhythmias, hypotension, and cardiac arrest (Winslow et al., 1990).

Problem of Study

Cardiovascular surgical patients who have anemia and impaired myocardial function are at risk for developing tissue hypoxia because they lack the ability to increase oxygen transport to maintain the balance between oxygen supply and demand. Administering an opioid agonist to patients who have low DO_2 prior to routine nursing care procedures that increase oxygen demand (i.e., turning, suctioning, weighing, bathing) may improve physiological adaptation by decreasing VO_2, avoiding oxygen deprivation and improving tissue oxygenation. Additional benefits may include increased patient comfort and satisfaction although these outcomes were not addressed in this study. The twofold purpose of this clinical trial was to (a) describe the physiological adaptation patterns of severely ill patients with compromised cardiorespiratory reserve and low DO_2 following lateral positioning, and (b) evaluate the clinical efficacy of a preprocedural morphine intervention on attenuating oxygen demand-induced VO_2 response following lateral positioning in cardiovascular surgical patients with low DO_2.

Specific Aims

The specific aims of the study were:

1. Describe the effects of lateral positioning on VO_2 and SvO_2 in cardiovascular surgical patients with low DO_2, with and without the effects of morphine.

2. Compare the contribution of tissue oxygenation variables including DO_2, VO_2, and O_2ER to the variance in SvO_2 in cardiovascular surgical patients with low DO_2, with and without the effects of morphine.

3. Compare SvO_2 recovery time to baseline following lateral positioning in cardiovascular surgical patients with low DO_2, with and without the effects of morphine.

Rationale for Study

Atherosclerotic heart disease, a progressive narrowing of the coronary artery lumen from an accumulation of lipid and fibrous deposits, remains the leading cause of death for men and women in the United States (American Heart Association, 2001). According to the American Heart Association (2001), 12,400,000 people in the United States have coronary heart disease. Despite the emergence of interventional cardiology procedures and antiplatelet pharmaceutical therapies, surgical revascularization (coronary artery bypass graft surgery [CABG]) continues to be a frequently performed procedure for treatment of coronary heart disease. The number of CABG procedures performed annually is expected to increase in the 21st century, especially among the elderly (Subramanian, Liu, Cromwell, & Thestrup-Nielsen, 2001). In 1998, an estimated 739,000 cardiovascular surgical procedures were performed in the United States (American Heart Association, 2001). Of these, approximately 553,000 coronary artery bypass graft procedures were performed on 336,000 patients and 51% of these procedures were performed on individuals over the age of 65 years. Each year, the U.S. Medicare program spends about $4 billion on procedures related to CABG surgery (Liu, Subramanian, & Cromwell, 2001).

Cardiovascular surgery population. Therapeutic advancements in interventional cardiology, pharmacology, and cardiovascular surgery technology have resulted in

patients being referred for cardiac operation at later stages of their disease process. Consequently, there has been a distinct change in the demographics of the cardiovascular surgical population over the past decade. The optimal cardiovascular surgical candidate is characterized as being less than 65 years of age, having a left ventricular ejection fraction (LVEF) of greater than .50, and without a prior history of cardiovascular surgery. Since the late 1980s, however, there has been a growing trend for cardiovascular surgical patients to be greater than 70 years of age, have extensive multiple vessel coronary heart disease, a LVEF of less than .35, and require reoperative cardiac procedures (Eillis, 1997; Jones, Weintraub, Craver, Guyton, & Cohen, 1991; Ley, 1993; O'Mara, 1993; Weintraub, Wenger, Jones, Craver, & Guyton, 1993). Elderly patients (> 70 years) consistently have worse outcomes after non-elective vs. elective cardiac surgery and in comparison with younger patients (Avery, Ley, Hill, Hershon, & Dick, 2001; Craver et al., 1999; Rady, Ryan, & Starr, 1998; Subramanian et al., 2001). Postoperative morbidity disproportionately increases the utilization of intensive care resources in elderly patients requiring cardiovascular surgery (Krueger, Goncalves, Caruth, & Hayden, 1992; Subramanian et al., 2001). Avery and colleagues (2001) recently reported that total direct hospital costs for octogenarians undergoing CABG were $4,818 (26.8% per case) higher than costs for younger CABG patients (65 to 75 years of age) and were primarily related to ICU costs. Postoperative complications occurring more frequently in octogenarians following CABG included low cardiac output state, reintubation and atrial fibrillation. Not surprisingly, in comparison to their younger cohorts, octogenarians had longer ICU

(69.2 vs. 43.3 hours, $\rho = .002$) and postoperative length of stays (LOS) (10.09 vs. 7.45 days, $\rho = .001$) and were twice as likely to be discharged to a skilled nursing facility. Octogenarians had a threefold increased risk of inhospital-mortality (13.5% vs. 3.4%, $\rho = .0004$). Factors that were associated with increased mortality included emergent surgery, surgical complexity, ventricular function, and the number of preexisting comorbid conditions (Avery et al., 2001).

With the anticipation of more elderly, complex cardiovascular surgical patients having advanced stages of cardiovascular disease and decreased LVEF, it is expected that postoperative myocardial depression and low cardiac output syndrome will be observed more frequently and pose greater challenges for the critical care nurse to maintain adequate tissue oxygenation. Not surprisingly, the need for postoperative mechanical support (i.e., intra-aortic balloon counterpulsation) for persistent, severe cardiogenic shock and failure to separate from extracorporeal circulation increased from 1.4% in 1981 to 4.7% in 1987 (Jones et al., 1991). Depressed myocardial contractility and hemodilutional anemia following extracorporeal circulation (i.e., cardiopulmonary bypass) are the primary culprits contributing to low DO_2 and complications associated with tissue hypoxia in the postoperative period. Future research efforts are needed that focus on perioperative and postoperative therapies to avoid tissue oxygen deprivation and hypoxia to improve patient outcomes following cardiovascular surgery (Rady et al., 1998).

Postoperative myocardial depression. Cardiovascular surgical patients with normal preoperative cardiac myocardial function are likely to experience transient myocardial depression during the postoperative period due to the effects of anesthesia, extracorporeal circulation, electrolyte imbalances, hypothermia, myocardial edema, coronary artery spasm, and decreased coronary artery perfusion. In the United States, severe myocardial depression as a postoperative complication occurs in approximately 26,000 or 10% to 15% of cardiovascular surgical patients annually (Lee & Gray, 1990; Ley, 1993). Hypotension, low cardiac output, decreased mixed-venous oxygen saturation, and decreased tissue perfusion may occur as a result of myocardial depression in the postoperative period (Ley, 1993). Low cardiac output syndrome (LCOS), clinically defined as a sustained cardiac index (CI) less than 2.0 L/min/m^2, is a multifaceted phenomenon that results in low DO_2 and inadequate tissue perfusion (Eillis, 1997; Fleischer & Stuart, 1994). Consequently, LCOS following cardiovascular surgery is associated with a higher risk of cardiac death, higher probability of postoperative complications including neurological impairment, renal and respiratory failure, prolonged hospitalization, and higher costs (Fleischer & Stuart, 1994). In a prospective study of 500 patients undergoing CABG procedure, additional costs attributed to left ventricular failure following cardiovascular surgery were $5,186.00 per patient (Taylor et al., 1990).

Postoperative anemia. Anemia, a reduction in the blood concentration of hemoglobin, is a common physiologic consequence of cardiovascular surgical procedures resulting in a decrease in systemic oxygen delivery (Szaflarski, 1996). Men who have a

hemoglobin level less than 12.5 g-/dl, as well as women who have a hemoglobin level less than 11.5 g-/dl, are considered anemic. Over 95% of patients who remain in ICU over 2 days have hemoglobin concentrations below normal (Corwin, 1999; Corwin & Krantz, 2000).

Traditionally, postoperative anemia was corrected with blood transfusion. However, during the last fifteen years, patients and health care providers have become more aware of the adverse clinical outcomes of blood transfusion including the transmission of blood borne pathogens, immunosuppression, and graft versus-host disease (Surgenor, Hampers, & Corwin, 2001). Liberal transfusion practices are associated with higher mortality and morbidity in critically ill patients (Hebert et al., 1999). Subsequently, this has contributed to a growing acceptance among health care providers to tolerate lower hemoglobin levels in the postoperative period and to adopt restrictive transfusion practices to avoid the risks of allogenic blood transfusion (Klein, 1995, 1996). The cost of hemoglobin reduction is a lower oxygen carrying capacity of the blood, which at a given flow decreases DO_2 (Pasquale, Cipolle, & Cerra, 1993a).

Because data exist to suggest that lower levels of hemoglobin are well tolerated, recently published transfusion guidelines recommend tolerating anemia to a hemoglobin level of 7.0 g-/dl and minimizing blood transfusion in critically ill populations, including those with cardiovascular disease (Hebert et al., 2001). However, some researchers recommend maintaining a hemoglobin level between 10-12 g-/dl for critically ill patients with acute ischemic cardiac disease and those with impaired ventricular function because

these patients lack compensatory mechanisms to increase cardiac output and DO_2 (Baxter et al., 1993). Despite recent evidence that suggests that red blood cell transfusion may not be helpful and may even be harmful for patients with cardiovascular disease, anemia is generally associated with increased risk of organ dysfunction and mortality (Surgenor, O'Connor et al., 2001). Maintaining adequate DO_2, in the presence of clinical anemia, and while adhering to restrictive transfusion practices presents a dilemma for today's health care team.

Lateral positioning. Immobilization of cardiovascular surgical patients may maintain hemodynamic stability by preventing cardiorespiratory fluctuations such as hypotension and decreased SvO_2 and SaO_2. In addition, immobilization assists in maintaining intravascular instrumentation and reduces nursing time and resources required to reposition a patient (Chulay, Brown, & Summer, 1982). In the supine position, the abdominal contents and diaphragm shift cephalad, thus reducing the size of the thoracic cavity and functional residual capacity (FRC). A reduction in FRC promotes closure of the dependent airways and alveoli, resulting in preferential ventilation of the nondependent regions of the lungs, decreased ventilation-perfusion (V/Q) balance in dependent lung regions that have greater blood flow (i.e., intrapulmonary shunting), and hypoxemia (Gavigan, Kline-O'Sullivan, & Klumpp-Lybrand, 1990; Hess et al., 1992; Ng & McCormick, 1982). Maintenance of the supine position predisposes the patient to atelectasis, oxygen desaturation, and pneumonia (Gavigan et al., 1990). Changing body position promotes optimal ventilation-perfusion balances in the different lung regions

through gravitational effects that enhance oxygen transport (Ibanez et al., 1981; Remolina et al., 1981; Zack et al., 1974).Turning and positioning immobilized cardiovascular surgical patients every 1 to 2 hours is an established nursing practice to prevent postoperative pulmonary complications (Brooks-Brunn, 1995; Metzler & Harr, 1996; Zevola, Raffa, & Brown, 2002; Zevola, Raffa, Brown, Hourihan, & Maier, 1997).

Cardiovascular surgical patients have specific risk factors for developing postoperative pulmonary complications, including atelectasis and hypoxemia, due to the operative entry into the pleural space, hypothermia, impairment of diaphragmatic activity, increased airway resistance and dead space associated with endotracheal intubation, and the residual effects of anesthesia that reduce the ability to clear secretions (Gavigan et al., 1990). Postoperative atelectasis demonstrated by radiographic abnormalities occurs in 51% to 90% of the cardiovascular surgery population (Brooks-Brunn, 1995; Chulay et al., 1982; Gavigan et al., 1990). Despite improvements in the management of surgical patients, postoperative complications are the leading cause of postoperative morbidity and account for 24% of all deaths occurring within six days of surgery (Brooks-Brunn, 1995).

Nursing implications. Maintaining adequate oxygenation to promote vital organ function is a primary responsibility of the medical team and critical care nurse. It is important that the nurse caring for a critically ill patient is able to anticipate and recognize alterations in tissue oxygenation before and during treatment procedures and to be aware of the persistence of complications following the procedure. Frequently, the

nurse is the first to witness a hypoxic event and the first to intervene to correct problems associated with tissue oxygenation (Misasi & Keyes, 1994).

Using reflectance spectrophotometry, nurses can monitor SvO_2 continuously to assess the patient's oxygen supply and demand relationship during nursing procedures and to evaluate interventions aimed at improving patient tolerance to nursing procedures such as hyperoxygenation, administration of analgesics and sedatives, and timing and grouping routine procedures. Nursing interventions that enhance patient tolerance to routine care procedures by maintaining or restoring the balance between oxygen supply and demand promote physiological adaptation in critically ill patients with compromised cardiorespiratory reserves. Therefore, clinical research is needed to develop the science of nursing related to clinical phenomena associated with severe illness states in order to enhance the understanding of vulnerable populations and to guide decision-making in clinical practice. Additionally, clinical research is needed to identify effective nursing interventions to address important clinical problems and improve patient outcomes by minimizing complications that result in decreased patient satisfaction, increased use of resources, longer duration of hospitalization, and higher costs.

If interventions aimed at optimizing DO_2 are not attainable, it is appropriate to consider interventions that reduce VO_2 (Ball, 2000; Jesurum, 1997; Pooler-Lunse & Price, 1997; Third European Consensus Conference in Intensive Care Medicine, 1996). Administering an opioid agonist prior to performing routine nursing care procedures that increase oxygen demand (e.g., turning, suctioning, weighing, bathing) may improve

patient tolerance to procedures by decreasing VO_2, avoiding oxygen deprivation and improving tissue oxygenation.

Several of the clinical research priorities identified by the American Association of Critical-Care Nurses' Research Committee for the 1990s were addressed in this study including (a) the effect of nursing activities and interventions on hemodynamic parameters, (b) optimal application of invasive and noninvasive oxygenation technology to improve patient outcome, (c) techniques to optimize oxygenation and prevent pulmonary complications, and (d) techniques for real-time monitoring of tissue perfusion and oxygenation (Lindquist et al., 1993). The purpose of this study was to (a) describe the physiological adaptation patterns of critically ill patients with compromised cardiorespiratory reserves following lateral positioning, and (b) test the clinical efficacy of a nursing intervention that was hypothesized to improve physiological adaptation to lateral positioning by decreasing oxygen expenditure and improving oxygen supply and demand balance.

Conceptual Framework

Roy's Adaptation Model (Andrews & Roy, 1991; Andrews & Roy, 1986; Pioli & Sandor, 1989; Roy, 1970, 1971, 1984, 1988, 1989; Roy & Andrews, 1991) served as the conceptual framework for studying oxygen consumption modulation in critically ill patients with low DO_2. The model was selected because it acknowledges the effects of environmental stimuli on human beings and incorporates the role of both intrinsic and extrinsic factors in mediating responses to potential stressors. Additionally, variables

comprising tissue oxygenation and the pathogenesis of tissue hypoxia were incorporated into the conceptual framework.

Oxygen transport and tissue perfusion provide a physiologically based framework for clinical reasoning and decision making in the management of patients with cardiorespiratory illness. Nursing assessment and intervention should be directed at remediating, minimizing and preventing cardiorespiratory dysfunction by systematic analysis of the oxygen transport pathway and the mechanisms responsible for disrupting tissue oxygenation. Following a thorough assessment of the oxygen transport pathway, treatment can then be specifically directed. Assessment and treatment outcome measures should reflect the integrity and function of the oxygen transport pathway, cardiorespiratory function, and the efficacy of nursing interventions aimed at restoring tissue oxygenation. Formulas and normal values for hemodynamic and oxygenation variables are presented in Table 1.

Roy Adaptation Model

According to the Roy Adaptation Model (Roy & Andrews, 1991), the person is a purposeful, holistic, adaptive system, constantly interacting within a changing environment. Individuals receive and process internal and external stimuli (*input*) and produce a response (*output*) that is manifested as an adaptive or ineffective behavior. Responses are considered adaptive or ineffective in relation to the goals of human existence which include survival, growth, reproduction, and, mastery. Adaptive behaviors maintain the integrity of the individual, whereas, ineffective behaviors disrupt

the integrity of the individual. Output responses serve as feedback or additional input into the human system and the person responds by increasing or decreasing efforts to cope with the stimuli. To generate a purposeful response, it is essential for the human system to function as a whole through the interdependence of its parts.

Adaptation, a fundamental principle of the model, implies that the human system has the capacity to adjust effectively to changes in the environment and, in turn, affects the environment. Roy describes the process of adaptation as analogous to the functioning of a simple system having four aspects: inputs, controls, outputs, and feedback. In describing the human system (Figure 1), Roy applies the general systems theory and incorporates the concepts of adaptation level, stimuli, coping mechanisms, responses, and feedback (Andrews & Roy, 1986; 1980; 1989; 1991)

An individual's ability to adapt to internal and external stimuli is determined by innate or acquired coping mechanisms that are biological, psychological, and social in origin. Roy grouped coping mechanisms into two major categories including the regulator and cognator subsystems (Roy & Andrews, 1991). The regulator subsystem responds automatically through neural, chemical, and endocrine coping mechanisms, while the cognator subsystem responds through four cognitive-emotive channels including perceptual/information processing, learning, judgment, and emotion. Although it is not possible to directly observe the specific processes of the regulator and cognator subsystems, the behaviors that result from the regulator and cognator mechanisms can be observed in four adaptive modes: physiological; self-concept; role function; and,

interdependence. A model depicting the interrelationship of the four adaptive modes, coping mechanisms, stimuli, and responses is illustrated in Figure 2. Behavior in one mode may have an effect on one or all of the modes through feedback processes. Likewise, a given stimulus may affect more than one mode and a response may be indicative of adaptation in more than one mode. Roy categorizes responses as either adaptive or ineffective. In contrast to adaptive responses that promote the integrity or wholeness of the person, ineffective responses may threaten the person's survival, growth, reproduction or mastery. Responses are human behaviors that are internal or external to the individual and can be measured empirically.

Stressors are internal and external stimuli that activate the coping mechanisms and produce an adaptive or ineffective response. Roy (1984) categorized the type of stimulus depending upon the degree of effect it has on the individual. The *focal* stimulus is the condition or circumstance that is most immediately and directly influencing the person's adaptation. *Contextual* stimuli are all other factors in the environment contributing to the person's response to the focal stimulus. *Residual* stimuli have an undetermined effect on the person's response to focal and contextual stimuli, but cannot be validated (Roy, 1984; Roy & Andrews, 1991).

An important element in the maintenance of homeostasis is the control of stress factors. During the initial postoperative period, cardiovascular surgical patients may simultaneously experience (a) recovery from anesthesia, (b) increases in metabolic response to injury, (c) escalating pain and anxiety, and (d) rapid rewarming and shivering

(Bernard et al., 1988). Collectively, these stressors impose additional burdens on the cardiovascular system and are associated with increases in CO, VO_2, carbon dioxide production, and resting energy expenditure (Rodriguez et al., 1983).

Health, as described by the Roy Adaptation Model (Roy & Andrews, 1991) reflects adaptation and is a state and a process of being and becoming an integrated and whole person. In illness and health, the goal of nursing is to positively enhance the interaction of the person with the environment to promote adaptation. By promoting adaptation, the nurse positively influences the person's quality of life, health, and death with dignity. Nursing promotes adaptation through interventions aimed at increasing, decreasing, or maintaining stimuli to which the person is exposed.

The act of manually placing a patient with low DO_2 into a lateral position subjects the patient to many physiological and psychological stressors that may threaten or improve homeostasis. Responses to lateral positioning have been attributed to an increase in skeletal muscle activity and energy expenditure that is associated with an increase in oxygen demand (Gawlinski & Dracup, 1998; White, Winslow, Clark, & Tyler, 1990). Lateral positioning is also known to produce anxiety, discomfort, pain, and fear in patients (Puntillo et al., 2001). The psychological stress associated with this procedure may also increase sympathetic stimulation and oxygen demand (Epstein & Breslow, 1999).

An individual's response to a nursing intervention will be determined by the compilation of internal and external stimuli and innate and acquired coping mechanisms.

Without adequate coping mechanisms to facilitate adaptation, the patient may experience ineffective responses to standard nursing procedures. According to the theory's explicit assumptions, (a) humans demonstrate less ability to adapt physiologically to changes within their environment during illness, therefore, (b) nursing interventions aimed at eliminating, reducing, or neutralizing the stimulus responsible for disrupting the environment may promote physiological adaptation. Effective nursing interventions will restore physiological integrity and promote adaptation (Roy & Andrews, 1991). Clinical research is needed to identify nursing interventions that promote physiological adaptation in patients who have cardiorespiratory dysfunction and impaired tissue oxygenation.

Tissue Oxygenation

Oxygenation, according to the Roy Adaptation Model, is the first of five basic physiological needs and is dependent on ventilation, alveolar - capillary gas exchange, and gas transport, the integrated functions of the cardiovascular and respiratory systems (Thompson, 1991). Oxygen delivery from alveolar air to cell mitochondria requires transport through the alveolar-capillary membrane, convective transport by the blood, diffusion from the capillaries to the tissues, and uptake by the individual cells (Leach & Treacher, 1994). The primary function of oxygen is to facilitate mitochondrial production of adenosine triphosphate (ATP) through oxidative phosphorylation. Energy released by hydrolysis of ATP mediates all biochemical cellular processes, including the maintenance of ionic concentrations (Ahrens & Rutherford, 1993; Baigorri & Russell, 1996). Normal cellular function is contingent on blood flow to transport adequate quantities of oxygen

and substrate and to remove metabolic waste products (Little & Edwards, 1993; Shoemaker, 1993). The adequacy of tissue oxygenation depends on the volume of oxygen delivered and the volume consumed in relation to the metabolic needs of the surrounding tissue (Snyder, 1987). In health, oxygen supply and demand are well matched such that an increase in oxygen demand is rapidly balanced by an increase in oxygen availability.

Components of Tissue Oxygenation

Oxygen supply (i.e., DO_2) refers to the amount of oxygen delivered to the tissues each minute and is dependent on the amount of oxygen in arterial blood (i.e., CaO_2) and the rate that blood flows to the tissues (i.e., cardiac output) (Aberman, 1987). The fundamental role of the lungs is to achieve uptake of oxygen from the atmosphere for delivery to the pulmonary capillaries. Once in the pulmonary capillary, the majority of oxygen combines reversibly with hemoglobin to form oxyhemoglobin and is carried to the tissues. Through the physiological processes of ventilation and gas exchange, the lungs load approximately 4 ml of oxygen onto hemoglobin each minute for every 1-kilogram of body mass and are capable of increasing this amount by roughly 15 times (Pasquale, Cipolle, & Cerra, 1993b). Arterial oxygen saturation (SaO_2), the ratio of oxygenated hemoglobin to total hemoglobin, is normally greater than 90% (Rutherford, 1993).

Hemoglobin has the ability to change affinity for oxygen, thus varying oxygen saturation. As the oxygen tension at which 50% of hemoglobin is saturated (P50) increases, the affinity of hemoglobin for oxygen decreases. In comparison, a decreased

P50 corresponds to a higher affinity that facilitates loading oxygen onto the hemoglobin molecule (Pasquale et al., 1993b; Vierheller, 1993). As blood travels from the lungs to the tissues, the carbon dioxide (CO_2) level increases and the pH decreases. Consequently, the reduction in oxyhemoglobin affinity facilitates the dissociation of oxygen from the hemoglobin molecule to the tissues. In the tissue capillary bed, oxygen dissociates from hemoglobin and diffuses intracellularly where it is consumed by the mitochondria for aerobic metabolism. Thus, the affinity of hemoglobin for oxygen, together with flow distribution, translates blood flow into available oxygen for tissue consumption.

The cardiovascular system affects oxygen supply through variation in the cardiac output and the internal distribution of blood flow through autoregulation. Cardiac output, the volume of blood ejected from the left ventricle each minute, provides the flow that transports oxygen to the tissues and is the largest contributing factor to DO_2 (Padwosjki, 1993). Under stressful conditions, a basal cardiac output of 3 to 4 L/min/m^2 may increase roughly 5 times to meet oxygen demands (Pasquale et al., 1993b). Non-nutritive blood flow to organs with low oxygen extraction constitutes an oxygen reserve. To compensate for decreased oxygen availability, neural and hormonal reflex mechanisms are activated that curtail non-nutritive blood flow. Thus, blood flow is preferentially shunted away from tissues with low extraction to ensure perfusion of "vital" organs with high extraction (Schlichtig, Cowden, & Chaitman, 1986).

Depending on the oxygen needs of the tissue, a variable amount of oxygen is extracted from that which is delivered (Pasquale et al., 1993b). The amount of oxygen

extracted from the capillary beds as blood passes to the venous circulation is referred to as oxygen consumption (VO_2). Oxygen demand, the amount of oxygen required by the tissues for aerobic metabolism, is difficult to quantify in the critical care setting. Because VO_2 reflects the global sum of oxidative metabolism, as well as the adequacy of circulation, it is used clinically as an indirect estimate of oxygen demand (Weissman et al., 1984). When cardiorespiratory function is adequate, VO_2 and oxygen demand are assumed to be approximately equal. Therefore, when oxygen demands increase, VO_2 increases (White et al., 1990).

Normally, DO_2 is 550 to 600 ml/min/m^2 and VO_2 is 120 to 140 ml/min/m^2 (Ahrens & Rutherford, 1993). Cardiorespiratory variables indexed to body surface area are represented by an "I" following the acronym (e.g., CI, SVI, DO_2I, VO_2I). Because DO_2 is three to four times greater than VO_2, an oxygen reserve exists in excess of what is required to meet the metabolic demand (Smith & Steele, 1991; West, 1985). The difference between these values is the amount of oxygen returned to the lungs and is reflected by SvO_2. Within the normal range of 60% to 80%, SvO_2 is usually indicative of adequate oxygen supply and demand balance (Ahrens & Rutherford, 1993). To summarize the oxygen transport process, hemoglobin binds with oxygen in the lungs, is transported by the cardiac output to the tissues (i.e., DO_2), unloads approximately 25% of the oxygen (i.e., O_2ER), and returns to the heart with 75% saturation (i.e., SvO_2).

Regulation of Oxygen Supply and Demand

During normal physiological conditions, cellular metabolism and VO_2 regulate DO_2 (Epstein & Henning, 1993). When oxygen demand is stable and adequate amounts of oxygen are available to the tissues, VO_2 plateaus and is independent of DO_2. Additional increases in DO_2 will not result in an increase in VO_2. The biphasic relationship between DO_2 and VO_2 is referred to as "*supply independence*" and is characteristic of physiological adaptation. If oxygen demand increases, VO_2 increases accordingly (Schumacker & Samsel, 1993; Shoemaker, 1993).

In response to an increase in oxygen demand, compensatory mechanisms include (a) an increase in cardiac output and DO_2, (b) an increase in the amount of oxygen extracted from the hemoglobin molecule, (c) vasoregulation to increase flow, and, (d) a shift in the oxyhemoglobin dissociation curve to facilitate oxygen unloading. To support the tissue's need for increased oxygen, DO_2 is augmented globally by an increase in CO and locally by capillary recruitment or autoregulation. Tissues requiring large amounts of oxygen open capillary beds to increase the amount of O_2 delivered to the tissues. If DO_2 does not increase accordingly, VO_2 will initially be maintained by an increase in O_2ER reflected by the reduction in SvO_2 (Enger & Holm, 1990). The relationship between mixed-venous oxygen content (CvO_2), oxygen consumption, and cardiac output dictates that either a (a) decrease in CaO_2 or CO or (b) increase in VO_2 will result in a decrease in CvO_2 (West, 1985). The relationship between CO (i.e., flow or Qt), VO_2 and arterial-

mixed-venous oxygen content difference ($C[a - v]O_2$) is expressed by the Fick equation (Divertie & McMichan, 1984) where,

$$Qt \approx \frac{VO_2}{(C[a-v]O_2)\,L/min} \text{ or, } CvO_2 \approx CaO_2 - \frac{VO_2}{Qt} \qquad \langle 1 \rangle$$

Patients who lack the ability to increase DO_2 are dependent upon a higher O_2ER to meet their needs (Routsi et al., 1993; Smith & Steele, 1991). When oxygen demand is increased, the amount of hemoglobin desaturation is able to increase from about 25% to a maximum arteriovenous saturation difference of 80% (Dantzker, 1987). However, if O_2ER rises above the normal value of .24 to .29, the potential for tissue hypoxia exists (Ahrens & Rutherford, 1993). Unless DO_2 increases or oxygen demand decreases, the continuation of tissue oxygen deprivation will disrupt normal cellular function.

Conditions that frequently affect the critically ill patient such as pain, fever, activity, carbohydrate load, and stress cause an increase in oxygen demand. Circulating catecholamines, hormones, prostaglandin metabolites, and various cytokines have been theorized to be the mediators of a hypermetabolic stress response (Smith & Steele, 1991). *Hypermetabolism* is described as an increase in total caloric expenditure and may be expressed as the percentage of measured resting energy expenditure (REE) in relation to values predicted by the Harris-Benedict formula (PEE-HB). According to literature sources, results vary greatly and the ratio REE/PEE-HB in critically ill populations has fluctuated between 0.8 and 1.85 (Boulanger, Nayman, McLean, Phillips, & Rizoli, 1994;

Brandi, Santini et al., 1999). According to Selye (1970, 1976, 1978), the physiologic effects of the stress response that are mounted by the autonomic nervous system to protect against threatening stimuli and reestablish equilibrium increase myocardial workload and VO_2. During these circumstances, cellular oxygen needs increase to sustain efficient generation of ATP (Epstein & Henning, 1993). Consequently, acutely ill patients require augmented DO_2 to meet their additional metabolic needs (McGee et al., 1988).

Hypermetabolic demands of critically ill patients may exceed the limited capabilities of DO_2 and O_2ER to maintain tissue oxygenation. When DO_2 reaches a critically low level, oxygen reserve is depleted and the tissues can no longer compensate by increasing O_2ER (Dantzker, 1987; Edwards, 1990). Consequently, VO_2 linearly decreases with further reductions in DO_2 (Epstein & Henning, 1993). Oxygen debt develops when oxygen demand exceeds the limits of extraction and flow.

Although much controversy exists in the literature about the theories and thresholds constituting critical DO_2, researchers have found that several subgroups of critically ill patients reach critical DO_2 threshold when O_2ER increases to .60 - .65 (Dantzker, Foresman, & Gutierrez, 1991; Ronco et al., 1993), while others have reported a DO_2 value of approximately 300 to 330 ml/min/m^2 or 8 to 13 ml/kg/min, to be critical (Komatsu et al., 1987; Schumacker & Cain, 1987; Shibutani et al., 1983). Komatsu et al. (1987) found that immediately after extracorporeal circulation, cardiovascular surgical patients who maintained a DO_2 above 300ml/min/m^2 did not experience tissue oxygen deprivation, as evidenced by normal blood lactate levels. Likewise, Shibutani et al.

(1983) studied 58 anesthetized cardiovascular surgical patients and reported that VO_2 decreased proportionately when DO_2 dropped below 330 ml/min/m^2 however, above this level of DO_2, VO_2 was stable (M = 109 ml/min/m^2 , SD = 16). Although researchers have concluded that DO_2 and VO_2 will remain linearly related or *supply dependent* until DO_2 increases above the critical level and tissue oxygen requirements are met (Chan & Abraham, 1993; Schumacker & Samsel, 1993), it is doubtful that a "universal" critical level of DO_2 and VO_2 exists for all patients. Patients in cardiogenic shock, for example, have lower critical DO_2 levels compared with patients in septic shock who require much higher DO_2 levels before VO_2 increases (Edwards, 1990, 1991).

According to the theory of pathological *supply dependency*, if DO_2 is not sufficiently restored to satisfy the oxygen demands of peripheral tissues, VO_2 will decrease or increase linearly and proportionally with changes in DO_2, despite tissue oxygen deprivation (Baigorri & Russell, 1996; Enger & Holm, 1990). When DO_2 decreases below a critically low level, the altered relationship between DO_2 and VO_2 prevents further disparities between oxygen delivery and consumption (Leach & Treacher, 1994; Vincent, 1990). Under these conditions, VO_2 is completely regulated by DO_2 such that a decrease in DO_2 will result in an immediate decrease in VO_2. A hallmark of pathologic supply dependency is the inability to increase oxygen extraction in response to a primary reduction in DO_2; whereby, O_2ER becomes "*fixed*" even in the presence of increased demand (Dantzker, 1991). Eventually, the anaerobic pathway will be activated as evidenced by lactic acidosis. Because oxygen extraction compensatory mechanisms

are impaired, continuous SvO_2 monitoring as an indicator of DO_2 - VO_2 balance has limited utility in patients demonstrating oxygen supply dependency (Enger & Holm, 1990; Vincent, 1990).

Concerns of *mathematical coupling* and measurement error have been well described in the tissue oxygenation literature and relate to the use of shared variables (SvO_2, CO) for performing DO_2 and VO_2 calculations. Consequently, some investigators have expressed skepticism regarding the theory of supply dependency when supported by regression analyses using data obtained by the same instrument to calculate DO_2 and VO_2 (Nightingale, 1990; Schumacker & Cain, 1987). Specifically, Baigorri and Russell (1996) argued that factitious positive relationships (i.e., linear) between DO_2 and VO_2 could arise from mathematical coupling of shared measurement error and many of the studies demonstrating pathological dependence of VO_2 on DO_2 were based on shared variables (Astiz, Rackow, Kaufman, Falk, & Weil, 1988; Kaufman, Rackow, & Falk, 1984; Mohsenifar, Hay, Hay, Lewis, & Koerner, 1993).

Controversies exist in the literature regarding the validity of oxygen supply dependency even when issues pertaining to measurement error are eliminated. For instance, measurement error related to the mathematical coupling effect has been discounted by Weg and colleagues (1991) who demonstrated oxygen supply dependency through regression analysis using independent instruments (i.e., Fick method, direct measurement) to measure DO_2 and VO_2 in patients with acute respiratory failure. The researchers concluded that VO_2 is pathologically dependent on DO_2 when DO_2 decreases

below 330 ml/min/m^2. In comparison, several researchers who have used independent instruments to explore DO_2 and VO_2 relationships in various critically ill subpopulations have demonstrated weak correlations between DO_2 and VO_2 and have disputed the theory of supply dependency (Annat, Viale, Percival, Froment, & Motin, 1986; Carlile & Gray, 1989; Vermeij, Feenstra, & Bruining, 1990; Wysocki, Besbes, Roupie, & Brun-Buisson, 1992). Comparing measurement techniques, Vermeij et al. (1990) found 6.3% estimated variation in DO_2 and 16% in calculated VO_2 while measured VO_2 was associated with a 1.5% estimated variation. Most of the studies involved very small, non-random samples and, therefore, the results were interpreted cautiously. To avoid methodologic error when studying DO_2 and VO_2 relationships, researchers support VO_2 measurement by gas analysis and DO_2 calculation as the product of CO and CaO_2 (Pasquale et al., 1993b).

Oxygen Supply and Demand Imbalance

When oxygen demand exceeds actual VO_2, tissue oxygen debt accumulates over time and results in anaerobic metabolism. Research has demonstrated that progressive oxygen debt, anaerobiosis, and increasing acidosis are ominous prognostic indicators (McGee et al., 1988). According to McGee and colleagues (1988) tissue oxygen debt is most commonly the result of a (a) critical deficiency of at least one variable of DO_2, (b) metabolic demand that exceeds DO_2 reserves, (c) pathologic processes that impede aerobic metabolism, or (d) inadequate perfusion distribution to regional vasculature. For critically ill patients with impaired myocardial function, oxygen supply and demand imbalance is most likely related to a (a) primary circulatory problem that causes a

reduction in blood flow or (b) increase in metabolic demand without an equivalent increase in blood flow. To improve the chance for survival, oxygen supply and demand imbalance must be identified and corrected promptly before the patient progresses to a state of oxygen deprivation. Expeditious reversal of oxygen debt by reestablishing blood flow or reducing oxygen demand may prevent irreversible cellular injury that, if not corrected, may progress to multiple system organ failure and death (Epstein & Henning, 1993).

Mechanisms responsible for causing tissue hypoxia include (a) decreased oxygen diffusion across the alveolar-capillary membrane (i.e., hypoxemia, pulmonary edema), (b) decreased oxygen carrying capacity (i.e., anemia), (c) decreased blood flow to the tissues (i.e., LCOS, ischemia), and, (d) decreased ability of the tissues to obtain or use oxygen (i.e., hystotoxia, sepsis) (McGee et al., 1988; Misasi & Keyes, 1994; Weilitz, 1993). When hemoglobin concentration is reduced (i.e., anemia), the capacity of blood to transport oxygen is reduced. For every 1.0 g-/dl deficit of hemoglobin, it is estimated that cardiac output has to increase by 9% to maintain a similar level of DO_2 (Yu, 1999). Hemoglobin becomes more important in the transport of oxygen for patients with impaired myocardial function who are unable to generate high cardiac output. Following cardiovascular surgery, anemia is a predictable complication related to the effects of hemodilution and acute red blood cell loss from surgical trauma (Weiland & Walker, 1986).

In addition to anemia, oxygen transport may be further compromised by transient myocardial depression in the postoperative period. When the amount of blood ejected from the left ventricle is insufficient to maintain systemic perfusion and oxygen demand exceeds the limits of DO_2 and O_2ER, ischemic injury occurs as a result of oxygen transport failure. *Ischemia* is the reversible cellular damage that occurs when the blood supply to a regional or global area is inadequate to deliver sufficient amounts of oxygen to meet the metabolic requirements. Myocardial depression, manifested as low CO, precipitates a reduction in DO_2 that is accompanied by (a) increased O_2ER and (b) decreased VO_2 and SvO_2 (Edwards, 1990). Astiz et al. (1988) discovered that following acute myocardial infarction, 50 patients who had low CO (M =1.6 L/min/m^2) also had reduced DO_2 (M = 278 ml/min/m^2) and VO_2 (M = 131 ml/min/m^2). Other researchers have reported similar findings in patients with low CO (Edwards, 1991; Snell & Calvin, 1993). Low cardiac output (< 2.5 L/min/m^2), caused by a reduction in stroke volume unrelated to preload, is the underlying pathological disorder responsible for diminished tissue perfusion and ischemic injury in patients with systolic dysfunction (Edwards, 1991).

Tissue hypoxia may be profound and life threatening. Interventions should be aimed at improving myocardial function, restoring hemoglobin concentration, and minimizing oxygen requirements (Misasi & Keyes, 1994). A conceptual model that illustrates the pathological progression of tissue hypoxia related to decreased flow (i.e.,

decreased perfusion) and the variables that influence physiological adaptation is presented in Figure 3 (Jesurum, 1997).

Critically ill patients who have anemia and depressed myocardial function have altered tissue oxygenation related to decreased DO_2. Independent nursing procedures such as endotracheal suctioning, repositioning, and bathing are focal stimuli that alter tissue oxygen requirements by increasing skeletal muscle activity and contributing to discomfort, pain, or fear. Analgesia, sedation, impaired cardiorespiratory function, mechanical ventilation, presence of fever, shivering, vasoactive medications, residual affects of anesthetics, excessive intake of carbohydrates, hemoglobin level, hypermetabolic state, and disruption of circadian rhythms are contextual stimuli affecting the patient's ability to maintain an optimal oxygen supply and demand relationship. Previous experiences with nursing procedures that resulted in pain, discomfort, and fear can place additional psychological stress on the patient anticipating future procedures. These experiences, referred to as residual stimuli, may result in further increases in energy expenditures and VO_2.

Lateral positioning, either passive or active, requires energy expenditure. An increase in oxygen demand associated with lateral positioning may overwhelm the compromised patient who is unable to increase oxygen delivery (White, 1993). When oxygen demands exceed supply, ineffective responses such as decreased SvO_2, hypotension, dysrhythmias, and cardiac arrest may be observed. Nurses facilitate patient adaptation by supporting available coping mechanisms and by altering stimuli that

adversely affect the patient. The administration of morphine prior to lateral positioning is a nursing intervention that can be used to decrease oxygen demands and prevent tissue oxygen deprivation.

Adaptation to lateral positioning occurs through neurochemical regulation and is manifested by physiological integrity and oxygen supply and demand balance. For the purposes of evaluating the effects of morphine, criteria that were used to indicate achievement of physiological adaptation and stabilization of the tissue oxygenation following lateral positioning included a (a) decrease in mean VO_2 and O_2ER, and (b) increase in mean SvO_2. According to Roy (Andrews & Roy, 1986), "If oxygenation needs are met, then physiological integrity is achieved." A model illustrating the pathophysiological phenomenon of impaired tissue oxygenation related to decreased oxygen delivery and a nursing intervention to modulate tissue oxygen consumption and promote adaptation following lateral positioning is presented in Figure 4 (Jesurum, 1996).

Theoretical Propositions

The theoretical propositions tested in the study were:

1. Functions within the physiologic mode (e.g., VO_2, DO_2, O_2ER) vary systematically and interdependently in response to a focal stimulus (i.e., lateral positioning) to maintain a state of equilibrium or adaptation (e.g., SvO_2).

2. Nursing interventions (e.g., lateral positioning) intended to facilitate adaptation (e.g., skin integrity, ventilation-perfusion balance) may provoke ineffective responses (e.g., increased VO_2 and O_2ER, decreased SvO_2, hypoxia).

3. Nursing interventions (e.g., morphine administration) will result in a more rapid adaptive response (e.g., increased SvO_2, decreased O_2ER and VO_2) to a focal stimulus (i.e., lateral positioning) than when the intervention (i.e., morphine) is withheld.

Assumptions

The hypotheses tested in this study were deduced from the explicit assumptions of the Roy Adaptation Model. For the purposes of this study, the following assumptions applied:

1. During illness, people may demonstrate less ability to adapt physiologically to changes within their environment (Andrews & Roy, 1986).

2. When a person's physiological needs are met, physiological integrity is achieved (Andrews & Roy, 1986).

3. Adaptation may be facilitated by enhancing an individual's coping mechanisms through effective nursing interventions aimed at eliminating, reducing, or neutralizing the stimulus responsible for disrupting the environment (Roy & Andrews, 1991).

4. At any given point in time, the individual's response to stress or a stimulus may be considered adaptive or ineffective. While exposed to the stimulus or stressor, the individual's response may change over time (Roy & Andrews, 1991).

5. The ability to adapt depends on the intensity, frequency, and duration of the stressor (Andrews & Roy, 1986).

6. Stress occurs when individuals are confronted with an environmental demand that exceeds their response capability (Roy & Andrews, 1991).

Hypotheses

Lateral positioning produces an acute increase in oxygen demand that is manifested by an increase in VO_2 and a decrease in SvO_2. Morphine, however, decreases oxygen demand and oxygen consumption. Therefore, it was postulated that a preprocedural morphine intervention may attenuate oxygen demand-induced VO_2 response following lateral positioning, thus improving tissue oxygenation. Consequently, patients with low DO_2 would demonstrate improved physiological adaptation because the situational stressor was effectively altered by a nursing intervention. Using a prospective, quasi-experimental, within-subjects repeated measures, factorial design, the hypotheses were clinically tested by evaluating the physiologic responses to lateral positioning with and without morphine.

The research hypotheses were:

1. There are no significant differences in VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning between cardiovascular surgical patients with low DO_2I who receive morphine before turning and those who receive morphine and propofol (H_0: $\mu 1_{MS} = \mu 1_{MS+P}$; $\mu 5_{MS} = \mu 5_{MS+P}$; $\alpha = .10$, two-tailed).

2. There are significant differences in mean VO_2I at minutes 1 and 5 following lateral positioning when cardiovascular surgical patients with low DO_2I receive morphine before turning compared with VO_2I at minutes 1 and 5 following lateral positioning without morphine (H_0: $\mu 1 = \mu 1_{MS}$; $\mu 5 = \mu 5_{MS}$; $\alpha = .025$, two-tailed).

3. There are significant differences in SvO_2 at minutes 1 and 5 following lateral positioning when cardiovascular surgical patients with low DO_2I receive morphine before turning compared with SvO_2 at minutes 1 and 5 following lateral positioning without morphine (H_0: $\mu 1 = \mu 1_{MS}$; $\mu 5 = \mu 5_{MS}$; $\alpha = .025$, two-tailed).

4. There is a significant difference in the proportion of variance in SvO_2 accounted for by VO_2I at minute 3 following lateral positioning when cardiovascular surgical patients with low DO_2I receive morphine before turning compared with SvO_2 at minute 3 following lateral positioning without morphine (H_0: $zr1 = zr2$; $\alpha = .05$, two-tailed).

5. There is a significant difference in SvO_2 recovery time following lateral positioning when cardiovascular surgical patients with low DO_2I receive morphine before turning compared with turning without morphine (H_0: $\mu 1 = \mu 2$; $\alpha = .05$, two-tailed).

Definition of Terms

The terms that were defined for the purposes of this study are lateral positioning, morphine, oxygen consumption, oxygen delivery, oxygen extraction ratio and mixed-venous oxygen saturation. The definitions are as follows:

1. Lateral positioning was conceptually defined as a focal stimulus (Roy & Andrews, 1991)and nursing intervention intended to promote adaptation of the individual by preventing complications associated with immobility. The term was operationally defined as manually turning a subject from the supine position to either a left or right 45-degree side-lying position.

2. Morphine sulfate (i.e., morphine) administration was conceptually defined as a nursing intervention and contextual stimulus (Roy & Andrews, 1991) to promote physiological adaptation to the focal stimulus of lateral positioning. Morphine (0.10 mg/kg) was operationally defined as an opioid agonist administered intravenously 20 minutes before the second lateral positioning procedure.

3. Oxygen consumption (VO_2) was conceptually defined as a physiological response resulting from regulator and cognator mechanisms (Roy & Andrews, 1991). VO_2 was operationally defined as the total amount of oxygen (ml) used by the cells each minute for metabolic processes as measured with a closed system metabolic monitor (i.e., indirect calorimetry) (Puritan-Bennett® Metabolic Monitor 7250™, Puritan-Bennett Corporation, Carlsbad, CA).

4. Oxygen delivery (DO_2) was defined conceptually as a physiological response resulting from regulator and cognator mechanisms (Roy & Andrews, 1991). DO_2 was operationally defined as the amount of oxygen (ml) attached to hemoglobin, transported by blood flow or cardiac output, and delivered to the tissues each minute (West, 1985). DO_2 was calculated using the Fick formula using measurements of cardiac output, hemoglobin, and arterial oxygen saturation (SaO_2) (Ahrens & Rutherford, 1993).

5. Oxygen extraction ratio (O_2ER) was conceptually defined as a physiological response resulting from regulator and cognator mechanisms (Roy & Andrews, 1991). O_2ER was operationally defined as the percent of available oxygen that is consumed by the tissues or the ratio of oxygen consumption to oxygen availability and was calculated using measurements of DO_2 and VO_2 (Ahrens & Rutherford, 1993).

6. Mixed-venous oxygen saturation (SvO_2) was conceptually defined as a physiological response resulting from regulator and cognator mechanisms (Roy & Andrews, 1991). SvO_2 was operationally defined as the percentage of oxygen saturation in the pulmonary artery as measured with the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter (Model 52510, Abbott Critical Care Systems, Chicago, IL).

Limitations

The study was limited by the following:

1. Dependent variables were not measured in both the left and the right 45-degree lateral positions on each subject. The turn sequence (supine to 45-degree left lateral or supine to 45-degree right lateral) was randomized and subjects were positioned and tested in the same position during both phases of the study (with and without morphine). Therefore, the position that produced that largest oxygenation changes was not determined. Consequently, it is unknown whether the maximum effect of morphine was tested in each subject. While some investigators have reported that the greatest reductions in SvO_2 were observed following the supine to left lateral position change (Gawlinski, 1993b; Shively, 1988), others have documented that the largest SvO_2 fluctuations occurred after subjects were turned from the supine to right lateral position (Tidwell et al., 1990). Regardless of the position that produced the greatest changes in oxygenation, no statistically significant differences were found between SvO_2 measurements obtained in the left lateral or right lateral positions (Gawlinski, 1993b; Shively, 1988; Tidwell et al., 1990; Winslow et al., 1990).

2. Propofol is routinely used following cardiovascular surgery at the research facility and 50% of the subjects who were enrolled in the study received a continuous infusion of propofol infusion during the study procedures. Although the administration of propofol during study procedures was *potentially* a confounding variable, the scenario was representative of current clinical practice throughout the United States and may

actually enhance the relevance and generalizability of study findings. Synergistic effects of morphine and propofol were explored by comparing the differences in physiological responses and cardiorespiratory parameters between subjects who received morphine and those who received morphine *and* propofol, prior to and following lateral positioning. These analyses constituted Hypothesis 1.

3. To avoid the *carry over* effects of morphine, control (phase I) *preceded* treatment (phase II) for all subjects; therefore, treatment effects (i.e., morphine) and order effects were confounded. The option of incorporating a "*wash out period*" to allow the effects of morphine to dissipate would have introduced the confounding effect of *time* on dynamic physiological variables. Reducing the amount of time between treatment and control conditions was critical to the validity of the study. Nevertheless, internal validity was compromised because treatment and control conditions were confounded.

4. DO_2I was manually calculated and the calculation was modified by deleting the amount of oxygen dissolved in the plasma ($0.0031 \times PaO_2$) from arterial oxygen content (CaO_2). For the study, CaO_2 was defined as the amount of oxyhemoglobin minus the amount of oxygen physically dissolved in the plasma and was calculated using the formula (Ahrens & Rutherford, 1993):

$$CaO_2 \approx 1.34 \times Hb \times SaO_2 \left[\text{minus}\,(0.0031 \times PaO_2)\right] \qquad \langle 2 \rangle$$

where, SpO_2 was substituted for SaO_2. The calculation assumed that hemoglobin remained constant throughout the 50-minute data collection period. Although these methods represented a limitation of the study, several researchers have supported the

deletion of arterial oxygen tension because of the insignificant contribution to overall tissue oxygenation relative to the excessive financial burden and time involvement associated with serial blood gas analysis (Aberman, 1987; Ahrens & Rutherford, 1993; Hayden, 1992; McGee et al., 1988).

5. Because of instrumentation limitations, there was a 3-minute lag time after the "turning" event until the averaged CCO value displayed on the Q-Vue™ CCO Monitoring System reliably represented time points following the turn. Therefore, cardiac measurements displayed on the Q-Vue™ CCO Monitoring System during the period immediately following the turn to minute 3 following the turn were not used for data analyses. The "Fast" mode function of the Q-Vue™ CCO Monitoring System was selected to provide a moderate amount of artifact (i.e., background noise) rejection and an approximate response time of 3 minutes to detect a 90% change in flow (Abbott Critical Care, 1997). CCO values displayed in the Fast mode reflected an average of the previous 3 minutes of data.

6. Metabolic requirements and VO_2 differences related to gender, age, and stature were not evaluated.

7. The non-random sample limits the external validity of the study. Random sample selection was not clinically feasible; therefore, consecutive sampling technique was utilized. Thus, cautions should be exercised in generalizing the findings beyond the selected sample.

Summary

Cardiovascular surgery is a costly but common treatment modality for individuals who suffer from ischemic coronary heart disease and acquired valvular disease. As the population ages, more people with advanced stages of cardiovascular disease and impaired myocardial function are expected to require cardiovascular surgery. Consequently, the demands on resources for cardiovascular surgery will continue to increase (Krueger et al., 1992; Rady et al., 1998; Taylor et al., 1990). Cardiovascular surgical patients are at risk for developing postoperative pulmonary complications and may be further compromised by prolonged immobilization and supine positioning during the postoperative period thus increasing their risks for developing atelectasis, oxygen desaturation, and pneumonia (Gavigan et al., 1990).

Maintaining adequate oxygenation to promote vital organ function is a primary responsibility of the critical care nurse (Pooler-Lunse & Price, 1997). Nursing interventions that enhance patient tolerance to nursing procedures by maintaining or restoring the balance between oxygen supply and demand promote client adaptation and successful recovery following cardiovascular surgery. Lateral positioning, an established, independent, and routine nursing intervention to prevent complications associated with immobility, including atelectasis and nosocomial pneumonia, may increase sympathetic stimulation and increase oxygen demand. Cardiovascular surgical patients who have decreased hemoglobin levels and impaired myocardial function may not be able to sufficiently increase DO_2 to maintain oxygen supply and demand balance and therefore,

may be at risk for developing tissue oxygen deprivation following lateral positioning. Though typically considered a benign procedure, lateral positioning is not without substantial risks in vulnerable populations. If the balance between DO_2 and VO_2 is compromised in patients who have marginal cardiorespiratory reserves, VO_2I should be assessed as a treatment parameter to guide interventions that decrease VO_2 (i.e., sedation, pain control, permissive hypothermia) (Yu, 1999)

In the critically ill population, morphine has been used during the postoperative period to decrease metabolic rate and oxygen demand (Rodriguez et al., 1983). This study evaluated oxygen supply and demand balance when cardiovascular surgical patients with low DO_2I received morphine before lateral positioning. Roy's Adaptation Model (Roy & Andrews, 1991) served as the conceptual framework of this study. Five hypotheses were tested to determine if cardiovascular surgical patients with low DO_2I had significantly lower VO_2I and higher SvO_2 when morphine was received prior to turning. Furthermore, SvO_2 recovery times were evaluated following lateral positioning, with and without the effects of morphine. According to the results of the first hypothesis, if there were no significant effects of the interaction between propofol and morphine on mean VO_2I and SvO_2 following lateral positioning, groups who received propofol and those who did not would be collapsed into one group for the analyses of Hypotheses 2 through 5.

CHAPTER 2

REVIEW OF THE LITERATURE

Maintaining adequate tissue oxygenation to promote vital organ function is a primary responsibility of the critical care nurse. Cardiovascular surgical patients who have decreased hemoglobin and myocardial depression are particularly vulnerable to tissue oxygen deprivation because they have limited ability to increase oxygen delivery (DO_2). Normal compensatory mechanisms that maintain tissue oxygenation balance including the ability to increase cardiac output and DO_2, redistribution of blood flow, and increasing oxygen extraction (O_2ER) may be impaired in critically ill patients with limited cardiorespiratory reserves. Consequently, routine care procedures that increase oxygen requirements may jeopardize tissue oxygen balance for this vulnerable group of critically ill patients. Tissue oxygen deprivation occurs when oxygen demands exceed oxygen consumption and is associated with anaerobic metabolism, lactic acid accumulation, and disruptions in normal cellular function; unless corrected, eventually cellular death occurs. Interventions that enhance patient tolerance of routine care procedures by supporting the balance between oxygen supply and demand may enhance physiological adaptation and, therefore, prevent complications associated with tissue hypoxia including cardiac dysrhythmias, hypotension and cardiac arrest.

Within the critical care setting, the amount of energy expenditure associated with various nursing and patient care activities is most frequently evaluated using continuous mixed-venous oxygen saturation (SvO_2) monitoring. SvO_2, the amount of oxygen attached to hemoglobin (Hb) in pulmonary arterial blood, is a global indicator of the relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2) of all organ systems and is measured continuously using a fiberoptic pulmonary artery catheter that differentiates oxygenated blood from deoxygenated blood in the pulmonary artery (Jesurum, 1998). When DO_2 is compromised, an increase in oxygen demand (and therefore, VO_2) will be associated with an increase in oxygen extraction (O_2ER) and a decrease in SvO_2 (Gawlinski & Dracup, 1998). Cardiorespiratory measurements indexed to body surface area are represented by an "I" following the acronym (e.g., DO_2I, VO_2I, CI, SVI, LVSWI).

Decisions to perform routine nursing procedures associated with an increase in oxygen consumption in patients with low DO_2 should be driven by a comprehensive cardiorespiratory assessment and a well-designed, evidence-based protocol. The twofold purpose of this study was to (a) describe the physiological adaptation patterns of cardiovascular surgical patients with low DO_2 following lateral positioning, and (b) evaluate the effects of a preprocedural morphine intervention on tissue oxygenation following lateral positioning in cardiovascular surgical patients with low DO_2.

Research Trends in Tissue Oxygenation

During the last quarter century, tissue oxygenation research from within the disciplines of nursing, medicine and physical therapy has followed several avenues. Early research tended to focus on measurement issues including (a) the assessment of tissue oxygenation within various patient populations (Bland & Shoemaker, 1985; Bland, Shoemaker, Abraham, & Cobo, 1985; Creamer et al., 1990; Edwards, 1991; Lehot & Durand, 1993; Norwood & Nelson, 1986; Osguthorpe, Tidwell, Ryan, Paull, & Smith, 1990; Pomes Iparraguirre, Giniger, Garber, Quiroga, & Jorge, 1988), and (b) determining the validity, reliability and application of SvO_2 monitoring in clinical practice (Chulay et al., 1992; Divertie & McMichan, 1984; George, Stechmiller, & Hamby, 1992; Gettinger, DeTraglia, & Glass, 1987; Hecker, Brown, & Wilson, 1989; Karis & Lumb, 1988; Pond, Blessios, Bowlin, McCawley, & Lappas, 1992; Rouby et al., 1990).

Once instruments were available to study tissue oxygenation in the clinical setting, researchers naturally turned their attention to describing temporal relationships between various components of tissue oxygenation during pathological and non-pathological states (Gawlinski, 1998; Gawlinski & Dracup, 1998; Komatsu et al., 1987; Leach & Treacher, 1994; McConachie, Edwards, Nightingale, & Mortimer, 1989; Noll & Byers, 1994, 1995; Noll & Fountain, 1990b; Routsi et al., 1993; Schmidt, Frank, Forsythe, & Estafanous, 1984). After a sufficient amount of research had been conducted to describe the clinical presentation of tissue oxygen deprivation, researchers refocused their efforts on studying the treatment of oxygen supply and demand imbalance, in

particular, augmentation of DO_2 (Edwards, Brown, Nightingale, Slater, & Faragher, 1989; Komatsu et al., 1987; Meier-Hellmann et al., 1994; Pasquale et al., 1993b; Schumacker & Cain, 1987; Schumacker & Samsel, 1993; Shibutani et al., 1983; Shoemaker et al., 1991; Shoemaker et al., 1992). Thus, the concept of "second line of therapy" was popularized and referred to resuscitation therapies designed to increase oxygen transport above traditional "normal" values with the intent of preventing or treating tissue ischemia (Yu, 1999).

More recently, emerging trends surrounding tissue oxygenation research have reverted to physiological measurement and treatment issues. Researchers have conducted biometric evaluations of new instruments and methods to assess tissue oxygenation continuously, regionally and less invasively (Ferguson, 1996; Naguib, Osman, al-Qattan, & Taha, 2000; Nishiyasu, Tan, Kondo, Nishiyasu, & Ikegami, 1999; Taylor & Simonson, 1996; van der Hoeven, Maertzdorf, & Blanco, 1999). Using less invasive instruments such as gastric tonometry and biomarkers including intramucosal pH (pHi) and partial pressure of gastric carbon dioxide ($PgCO_2$) permits early assessment of regional hypoperfusion states that may manifest prior to systemic indicators of global tissue hypoxia oxygen debt (Noone, Bolden, Mythen, & Vaslef, 2000). Recently, investigators have advocated assessing simultaneous regional and systemic oxygenation indices (SvO_2, lactate levels, indirect calorimetry) to provide a comprehensive oxygenation profile (Gupta et al., 1999; Kiening, Unterberg, Bardt, Schneider, & Lanksch, 1996; Siegemund,

van Bommel, & Ince, 1999; Thaler, Frey, Marzoli, & Messmer, 1996; Vollmar & Menger, 1997).

With the ability of measure regional oxygenation in the clinical setting, research focusing on treatment of tissue hypoxia has shifted from testing clinical algorithms for achieving *"supernormal"* DO_2 to "third line therapies" directed towards increasing specific organ (gut) perfusion (Yu, 1999). Researchers have also begun to study the effects of stored-blood products (i.e., allogenic red blood cell transfusion) on the oxygen transport system. Within the past few years, changes in blood transfusion practices in the critical care setting have prompted researchers to evaluate the effects of stored blood products (Casutt et al., 1999; Horn et al., 1997; Van der Linden et al., 2001) and blood substitution products (Ali, Ali, Steinke, & Shepherd, 2001; Carmichael, 2001; Patel & Mehra, 1998) on tissue oxygenation. Preliminary findings are provoking researchers and clinicians to question the treatment efficacy of traditional transfusion practices on improving oxygen delivery and utilization and patient outcomes (Casutt et al., 1999).

Controversy exists among researchers regarding the efficacy of treatment strategies to augment DO_2 to exceedingly high levels using high-dose inotrope support and volume resuscitation. Clearly, these types of strategies have limited utility in populations with significant cardiac impairment. A meta analysis of seven studies that tested interventions to achieve supraphysiologic goals of cardiac index, DO_2 and VO_2 did not significantly reduce mortality rates of critically ill patients (Heyland, Cook, King, Kernerman, & Brun-Buisson, 1996). Results of such strategies on patient mortality and

morbidity are inconsistent (Hayes et al., 1994; Shoemaker et al., 1992; Yu, 1999) and difficult to compare due to differences related to methodologies and target populations. However, some of the evidence suggests that in surgical trauma patients, early optimization and achievement of cardiorespiratory goals may have a favorable effect on mortality. The concept of "fourth line therapy" has been proposed by Yu (1999) who advocates for future research directed at measuring cellular metabolic requirements and directing therapy at individual organ cells.

Over a span of thirty years, nursing research within the area of tissue oxygenation has largely focused on issues pertaining to the effects of routine care procedures on tissue oxygenation variables. The effects of nursing procedures such as positioning (Gawlinski & Dracup, 1998; Pena, 1989; Shively, 1988; Tidwell et al., 1990; Winslow et al., 1990), dangling (Lane, Winslow, Woods, & Dixon, 1997; Winslow, Lane, & Woods, 1995), standing (Waite & Parsons, 1990; Winslow, White, Madson, Weaver, & Powell, 1996), bathing (Atkins et al., 1994; Peters, 1998; Verderber & Gallagher, 1994; Winslow, Lane, & Gaffney, 1985; Winslow & Smith, 1991), bed-making (Flores & Zohman, 1970; Lane & Winslow, 1987; Palmer & Griffith, 1971), back massage (Lewis et al., 1997; Tyler, Winslow, Clark, & White, 1990), range-of-motion exercises (Verderber & Gallagher, 1994), chest physiotherapy (Weissman & Kemper, 1991), and endotracheal suctioning (Clark, Winslow, Tyler, & White, 1990; Kinloch, 1999; Lookinland & Appel, 1991; Mancinelli-Van Atta & Beck, 1992; McIntosh, Baun, & Rogge, 1993; Walsh,

Vanderwarf, Hoscheit, & Fahey, 1989) on tissue oxygenation have been systematically evaluated and reported in the research literature.

In the following discussion, classical studies were selected for review based on their relevance to the aims of this research study. Three primary categories of research were identified for inclusion and comprised the (a) effect of lateral position on cardiorespiratory variables (i.e., *position effect*), (b) effects of lateral positioning on tissue oxygenation (i.e., *turning effect*), (c) oxygen consumption modulation therapies specifically related to pharmaceutical agents, and (d) relationship between SvO_2 and tissue oxygenation variables.

Effect of Lateral *Position* on Cardiorespiratory Variables

Although the present study is concerned with the immediate physiological response to lateral positioning (*turning effect*), it is important to illustrate and distinguish the findings of studies that have evaluated the effect of lateral position on physiological measurements (*position effect*). By turning a patient, the nurse anticipates that oxygenation will improve due to improved ventilation-perfusion matching in the lungs. However, gas exchange also occurs between the cells of the different organ systems and their blood supply. If cardiac output (CO) is diminished and organ perfusion suffers due to deterioration in the hemodynamic state, any possible improvement in lung perfusion may be negated by decreased systemic perfusion (Wheeler, 1997).

Effect of Lateral Position on Arterial Oxygenation

While several investigators have studied the effect of the activity of turning and positioning on oxygenation, other investigators have evaluated the effects of different body positions (e.g., supine, lateral, prone) and the degrees of backrest elevation on arterial, venous, and tissue oxygenation variables in critically ill populations, with and without unilateral lung pathology (Banasik, Bruya, Steadman, & Demand, 1987; Banasik & Emerson, 1996, 2001; Briones, Dickenson, & Bieberitz, 1991; Chan & Jensen, 1992; Emerson & Banasik, 1994; George, Hoffman, Boujoukos, & Zullo, 2002; Noll & Fountain, 1990a; Ross & Jones, 1995; Zack et al., 1974). Specifically, researchers have evaluated the effects of different body positions on ventilation, lung volumes, intrapulmonary perfusion, and ventilation-perfusion relationships. Depending on respiratory pathology, body position *can* influence pulmonary volume and regional ventilation-perfusion relationships. Arguably, if certain positions are consistently associated with improved ventilation-perfusion and consequently higher arterial oxygen tension (PaO_2), nurses can make methodical decisions regarding body position and turning schedules (Banasik & Emerson, 1996). Because gas exchange is an important component of oxygen delivery, it is necessary to understand the effect of body position on gas exchange.

While studying the effect of lateral position on 38 subjects who had hypoxemia, Zack and colleagues (1974) were among the first researchers to report a significant position effect on PaO_2 between left and right lateral positions ($M = 9.5$ mm Hg, $\rho =$

.003). The researchers observed that mean PaO_2 was significantly higher when patients with unilateral lung disease were positioned with the unaffected lung in the dependent position as compared to lying with the affected lung in a dependent position (n = 19, M = 9.7 mm Hg, $\rho < .05$). In patients with bilateral lung pathology (n = 13), PaO_2 was generally higher in the right lateral (n = 9, M = 84 mm Hg) vs. left lateral position (M = 79 mm Hg) although the results were not statistically significant. In addition to the left lung being anatomically smaller, the compressive effects of the heart and mediastinal structures on the contiguous lung in the left lateral decubitus position could, theoretically, accentuate oxygenation problems (Zack et al., 1974). At low lung volumes, ventilation to the dependent lung decreases. In subjects without pulmonary disease, body position does not significantly affect gas exchange or arterial oxygenation (Remolina et al., 1981; Zack et al., 1974).

Since Zack and colleagues (1974) reported their findings, many other researchers have studied the effect of body position on PaO_2 values and support the conclusion that, in spontaneously breathing and mechanically ventilated critically ill patients with unilateral lung disease, lying with the "healthy" lung in a downward or *dependent* position is associated with higher PaO_2 values (Ibanez et al., 1981; Remolina et al., 1981; Rivara et al., 1984). Alveolar-arterial oxygen difference ($AaDO_2$) and calculated intrapulmonary shunt (Qs/Qt) are also significantly reduced when the unaffected lung is in a dependent position (Dhainaut, Bons, Bricard, & Monsallier, 1980; Seaton, Lapp, & Morgan, 1979). When the non-diseased lung is in the dependent position, researchers

have attributed the improvement in arterial oxygenation to a decrease in right-to-left intrapulmonary shunting and enhanced ventilation-perfusion matching (Gillespie & Rehder, 1987).

Because left lower lobe atelectasis occurs frequently following coronary artery bypass graft surgery, it is expected that PaO_2 would be lower in the left lateral position. Indeed, Banasik and colleagues (1987) demonstrated that cardiovascular surgical patients who were mechanically ventilated had significant differences in mean PaO_2 between the 45-degree left and right lateral positions (without backrest elevation) and the supine position ($\rho = .026$). There were no significant differences in arterial oxygen saturation (SaO_2) or arterial carbon dioxide tension ($PaCO_2$) between the three positions. In comparing the right vs. left lateral positions, over 70% of cardiovascular surgical patients ($N = 60$) were observed to have lower PaO_2 in the left lateral position as compared with the right lateral position (left, $M = 111.5$; right, $M = 116.7$; $\rho = .019$). When patients with left lung atelectasis ($n = 11$) were removed from the analyses, PaO_2 differences related to position were not statistically appreciated in subjects without unilateral lung disease or in those with bilateral lung disease ($\rho = .11$). However, subjects with left lower lobe atelectasis demonstrated significant differences in mean PaO_2 between left and right lateral positions ($\rho = .03$). These findings support those of Ibanez et al (1981) who studied 10 mechanically ventilated patients with unilateral lung disease, mostly as a result of pneumonia, and found that when the affected lung was in the non-dependent (uppermost) position, PaO_2 was increased.

Banasik and colleagues (1987) concluded that for the group, the PaO_2 differences between left and right lateral positions were not clinically important; however, a few individuals demonstrated large differences between positions (i.e., 10 to 50 mm Hg). Based on the clinically unimportant differences observed in PaO_2 between left and right lateral positions, the authors concluded that the benefits of turning and changing positions outweigh the risks. Additionally, the authors concluded that SaO_2 (as measured on a blood analyzer) was not a useful indicator of changes in oxygenation resulting from body position due to the oxyhemoglobin saturation curve and relative hyperoxygenation status of the sample (mean PaO_2 = 115 mm Hg).

In a second study conducted by Banasik et al (1996) that evaluated the effects of body position on tissue oxygenation variables in cardiovascular surgical patients (N = 120), the authors observed statistically significant within-subject differences in mean PaO_2 (ρ = .02) and SaO_2 (ρ = .001) between the 45-degree left lateral, 45-degree right lateral, and supine positions. Similar to earlier results, PaO_2 was lower in the left lateral position (M = 110.2, SD = 31.7) as compared with the right lateral (M = 112.8, SD = 32.5) or supine positions (M = 113.9, SD = 33.1); however, mean differences were not clinically impressive. These results were consistent regardless of the type of cardiovascular procedure performed (e.g., coronary artery bypass graft [CABG] vs. valvular surgery) or the presence or absence of preoperative chronic lung disease. Mean SaO_2 was lower in the supine position (M = 95.1, SD = 7.1) in comparison with the left lateral (M = 95.6, SD = 2.0) or right lateral (M = 95.9, SD = 1.8) positions. As predicted,

for two-thirds of the subjects who had postoperative unilateral lung atelectasis, the lowest PaO_2 was observed when subjects were positioned with the atelectatic lung in the dependent position. Like Remolina et al. (1981) who concluded that supine and lateral positions do not affect PaO_2 in the absence of lung disease, Banasik and colleagues (1996) concluded that patients who have preexisting lung disease are not at greater risk of experiencing oxygenation fluctuations due to body position than those who do not have preexisting lung disease. Of the subjects with bilateral lung disease, 50% had the highest PaO_2 in the supine position. Mean PaO_2 was unaffected by the turning sequence or repeated turning. Additionally, no significant difference in venous oxygen tension (PvO_2) was found among the three body positions. Although statistically significant, the *position-induced* differences in PaO_2 and SaO_2 were small and clinically inconsequential; therefore, Banasik and colleagues (1996) concluded that the known benefits of lateral positioning outweigh the potential risks. These results are similar to those of other researchers who found that PaO_2 is improved when the non-diseased lung is dependently positioned (Ibanez et al., 1981; Zack et al., 1974).

In comparison, Chan and Jensen (1992) evaluated the effects of three positions with 30-degree backrest elevation, including (a) supine, (b) 30-degree right lateral, and (c) 30-degree left lateral on PaO_2 and calculated intrapulmonary shunt in 30 patients receiving mechanical ventilation following coronary artery bypass graft surgery. Unlike the previous researchers, Chan and Jensen (1992) did not find a statistical or clinical significant difference in PaO_2 ($\rho = .98$) or Qs/Qt ($\rho = .20$) between the three positions.

Even among a subgroup of patients who had documented left lower lobe atelectasis (n = 5) no statistical differences in mean PaO_2 were found. Systemic arterial and pulmonary arterial pressures were consistently higher in the left lateral position and lowest in the supine position. The researchers attributed the unexpected lack of significant findings to (a) the use of large tidal volumes or "high-volume" mechanical ventilation (15 ml/kg) with positive end-expiratory pressure (PEEP 5 cm H_2O), (b) frequent repositioning, (c) 30-degree backrest elevation, and (d) increased preload that may have prevented the low ventilation-perfusion regions and permitted the recruitment of capillaries to enhance ventilation-perfusion relationships. Postoperative lung abnormalities peak 24 hours following cardiovascular surgery (Brooks-Brunn, 1995; Seaton et al., 1979); however, data were collected between 4 and 10 hours following surgery. It is likely that the severity of pulmonary shunting and magnitude of *position effect* were not captured during the study period and may explain the lack of significant findings. The research was limited by the multiple comparisons involving a small number of subjects who demonstrated left lower lobe atelectasis (n = 5).

Thus, it appears that early postoperative turning in hemodynamically stable cardiovascular surgical patients does not compromise oxygenation. However, patients with low PaO_2 and unilateral lung disease should be monitored for positional alterations in oxygenation. As demonstrated in a limited number of studies involving cardiovascular surgical patients, the supine and right lateral positions are associated with higher PaO_2 than is the left lateral position, especially when left lower lobe atelectasis is present.

Differences in PaO_2 between the left lateral, right lateral, and supine positions, however, may be clinically unimportant. These findings are similar to those of researchers who have consistently demonstrated that patients with unilateral lung disease have improved oxygenation when the non-diseased lung is positioned dependently.

Effect of Lateral Position on Tissue Oxygenation

SvO_2 monitoring may be useful for evaluating the effects of lateral position on tissue oxygenation. Theoretically, SvO_2 may decrease if the lateral position produces a decrease in cardiac output related to a decrease in venous return. In comparison, SvO_2 may increase if SaO_2 improves in the lateral position as a result of enhanced ventilation-perfusion matching. However, researchers have determined that the effects of lateral position on SaO_2 are not clinically significant in cardiovascular surgical patients (Banasik et al., 1987; Banasik & Emerson, 1996). Additionally, in one study, the effects of lateral position were not observed on mean PvO_2 (Banasik & Emerson, 1996). Noll and Fountain (1990a) speculated that if patient comfort improves when lying in a lateral position, VO_2 may decrease and SvO_2 may increase. Four studies were evaluated that studied the effect of position effect on tissue oxygenation variables, three of which evaluated changes in SvO_2.

While researchers have examined the effect of turning patients and the effect of different body positions on various physiologic variables in diverse critically ill populations, studies specific to the effect of lateral position on tissue oxygenation are limited in number. In addition to studying the immediate effects of lateral positioning

(*turning effect*) on SvO_2, Shively (1988) also evaluated the position effect on SvO_2 following a stabilization period. In studying a nonrandom sample of 30 hemodynamically stable, cardiovascular surgical patients, Shively reported a significant interaction between position and time ($\rho = .0001$) and indicated that SvO_2 was lowest immediately following lateral positioning when patients were turned to the left lateral position. However, because the results of simple effects and cell mean comparisons were not reported, it is difficult to determine if the effects related to the left lateral position were persistent at 15 minutes and at 1 hour following the turn. In evaluating the effects of the interaction between turn-frequency and position on SvO_2, subjects who were turned every 2 hours demonstrated significantly lower SvO_2 in three positions including the supine with 45-degree backrest elevation position, the left lateral with 20-degree backrest elevation position, and the supine 20-degree backrest elevation position ($\rho = .0324$). Results of simple effects and cell mean comparisons to isolate the differences were not reported. In subgroup analyses of patients with documented unilateral pulmonary disease, SvO_2 was not significantly different when the non-affected lung was positioned in the dependent or non-dependent position ($\rho = .1327$).

Gawlinski and Dracup (1998) studied the effects of lateral positioning on SvO_2 in 42 critically ill patients who had a low left ventricular ejection fraction (LVEF). Similar to the findings of Shively, the researchers observed the lowest SvO_2 immediately following lateral positioning (i.e., minute 1 post-turn) when subjects were turned to the left lateral position. On average, when subjects were turned to the left lateral position,

SvO_2 decreased by 11.3% from baseline to minute 1 following the turn. In comparison, when subjects were turned to the right lateral position, SvO_2 decreased by 8.5% from baseline to minute 1 following the turn. When subjects were turned from the supine to left lateral position, significant differences in mean SvO_2 were observed between baseline and at each minute following the turn for 4 minutes. In comparison, when subjects were turned from the supine to right lateral position, significant differences in mean SvO_2 were observed between baseline and at minutes 1 and 2 following the turn. In comparing the supine and lateral positions over time, by minute 4 following the turn there were no significant within-subject differences between SvO_2 measured in the supine and left lateral or supine and right lateral positions. Within-subjects comparisons between the right lateral and left lateral positions, irrespective of baseline values, were not discussed.

Briones et al. (1991) evaluated the effects of lateral position on tissue oxygenation and hemodynamic variables. The purpose of the study was to determine if SvO_2, pulmonary artery pressure (PAP), and pulmonary artery occlusion pressure (PAOP) were reproducible in the 45-degree left and 45-degree right lateral positions as compared with the supine position. Eighty critically ill patients who had a systolic blood pressure $\geq$ 90 mm Hg were enrolled into the study. Subjects were randomly assigned to either the left or right lateral turn sequence. Thirty-degree backrest elevation was maintained throughout the study procedures. Measurements of SvO_2, PAP, and PAOP were obtained in the supine, left lateral and right lateral positions. Measures were taken to ensure accuracy of the measurements including instrument calibration and use of the phlebostatic axis

reference for transducer placement. Interrater reliability was reported to be 99%. Using the phlebostatic axis as a reference point, SvO_2, PAP, and PAOP were measured 15 minutes after each position change. No significant differences were observed in mean SvO_2, PAP or PAOP in any of the three positions ($\rho > .05$). The investigators concluded that SvO_2, PAP, and PAOP measurements obtained in the 45-degree left lateral and 45-degree right lateral positions are reliable and that critically ill patients demonstrate physiological adaptation to position changes within 15 minutes following the procedure. The abstract contained limited information regarding methodology and physiological measurements; therefore, conclusions were difficult to evaluate. The investigators did not discuss clinical relevancy of the findings or physiological changes associated with a particular position or sequence.

Banasik and Emerson (2001) studied the effect of supine, 45-degree right lateral, and 45-degree left lateral positions on tissue oxygenation variables including PaO_2, PvO_2, SaO_2, arterial oxygen content (CaO_2), VO_2, CO and heart rate. Serum lactate as an indicator of tissue oxygenation was also evaluated. The sample included 12 mechanically ventilated, critically ill adult patients who had either low cardiac index ≤ 2.0 L/min/m^2 ($n = 4$), low $PaO_2 \leq 70$ mm Hg ($n = 7$), or both ($n = 1$). Six subjects had unilateral lung disease and 5 subjects had bilateral lung disease as evidenced on chest radiographs. Subjects were randomized to one of six possible turn sequences. To control for turning effect, measurements were collected 15 minutes following each position change. Significant differences in mean PaO_2, SaO_2, CaO_2, lactate levels, or heart rate were not

observed between any of the three positions. PvO_2 and VO_2 were not evaluated due to missing data that resulted in insufficient statistical power. Mean cardiac output was slightly higher in the left lateral position in comparison with the supine and right lateral positions; however, the results were not statistically ($\rho = .12$) or clinically important. The authors concluded that the effect of lateral position on tissue oxygenation in critically ill patients with low CO or hypoxemia is insignificant.

The findings of these four studies suggest that the effect of position on tissue oxygenation variables may not be evident following a stabilization period that ranges from 5 to 15 minutes following the position change. Immediately following lateral positioning, SvO_2 appears to be lowest in the left lateral position, although differences between supine and left lateral position are not appreciated within 5 to 15 minutes following the turn.

Spontaneous SvO_2 Variability

Knowledge of spontaneous SvO_2 variability is important to researchers and clinicians who need to differentiate clinically relevant changes in SvO_2 related to body position effect from insignificant fluctuations related to background phenomena. Additionally, knowledge of SvO_2 normal fluctuation patterns enables the clinician to evaluate SvO_2 changes in response to activities and treatment (Noll et al., 1992). Only when study findings are compared to normally occurring physiologic variations, can clinical significance be determined.

Noll and colleagues (1992) conducted a study to define normal fluctuation patterns in SvO_2 measurements in critically ill patients during rest. Twenty critically ill adult patients (aged 19 to 85 years) who had a fiberoptic pulmonary artery catheter were enrolled into the descriptive study. The majority of subjects were diagnosed as having respiratory failure and required mechanical ventilation. Mixed-venous oxygen saturation was recorded each minute for a 2-hour period in either early morning or late afternoon hours. Minute-by-minute values obtained during a 30-minute period of rest were used to determine SvO_2 fluctuation. The lowest and highest SvO_2 values during the period were used to calculate percent change from average values (fluctuation). The investigators found that in 80% of the critically ill medical patients in this study, SvO_2 fluctuated ± 6% during periods of rest. SvO_2 fluctuation appeared to be independent of time of day, morning or evening. Furthermore, SvO_2 fluctuation was not affected by analgesics, anxiolytics, or neuromuscular blockade agents (e.g., morphine sulfate, lorazepam, pancuronium bromide). Differences in SvO_2 fluctuation were not found between subjects with high vs. low baseline values of oxygen delivery, oxygen consumption and SvO_2. In a subanalysis of four patients who were spontaneously breathing, the percentage of low fluctuation SvO_2 values was significantly lower than for subjects who were mechanically ventilated ($\rho = .02$). Because the sample represented a heterogeneous population, results are not generalizable to subgroups of critically ill patients. Additional studies, involving homogeneous subgroups of critically ill patients are needed to evaluate normal resting SvO_2 variation over time. Results of this study should be interpreted cautiously.

SvO_2 fluctuation (± 6%) observed in this sample of medical ICU patients was larger than the fluctuation (range, - 4.6% - 1.8%) observed in a sample of 30 patients following coronary artery bypass graft surgery (Noll & Fountain, 1990a). In a study that evaluated the effects of backrest elevation on SvO_2, Noll and Fountain (1990a) observed that mechanically ventilated cardiovascular surgical patients (N =30) who were enrolled into the study typically experienced SvO_2 fluctuations of -4.6% to 1.8% from baseline values. The researchers speculated that SvO_2 might have remained constant during position change because subjects received morphine sulfate prior to data collection that may have relieved pain and anxiety, thus decreasing VO_2. Measures were not taken to control for routine care procedures during the data collection. The researchers observed that SvO_2 typically decreased 8% during routine care procedures (i.e., suctioning, turning) and returned to baseline within 5 minutes.

Effect of Lateral Position on Cardiac Output

Alterations in preload, lung and chest dynamics, or vascular resistance may accompany position changes and thus affect cardiac output (Banasik & Emerson, 2001). Changes in hemodynamic indices and CO can reduce forward flow and decrease tissue perfusion and DO_2 (Gawlinski, 1993b). Three studies were reviewed that investigated the effects of lateral positions on thermodilution cardiac output measurements (Doering & Dracup, 1988; Shinners & Pease, 1993; Whitman, Howaniak, & Verga, 1982). Findings in two of these studies indicated that cardiac output, an important component of DO_2, is significantly higher in the left lateral position than in the supine or right lateral positions.

Using a within-subjects repeated measure design, Whitman et al. (1982) compared CO measurements obtained in the supine (with 20-degree backrest elevation), 20-degree left lateral recumbent, and 20-degree right lateral recumbent positions. Fifty adult cardiovascular surgical patients were randomly assigned to one of six turn sequences that included the three positions. The researchers concluded that although CO was significantly higher in the left lateral position ($\rho < .05$), the mean difference in CO observed between the three positions was clinically insignificant (0.23 L/min). Individual differences in mean CO for any position-to-position change demonstrated differences that ranged from 0.0 to 3.09 L/min ($M = 0.54$ L/min). After each position change, 15 minutes elapsed prior to data collection to allow for restabilization of hemodynamic indices. In each of the three positions, two CO measurements were obtained by the thermodilution method. Data collection was completed over a 60- to 75-minute period. The researchers concluded that valid CO measurements could be obtained in acutely ill patients in the 20-degree right or left lateral recumbent positions. The research was published in an abstract format and provided limited information regarding the collection and treatment of data.

Similarly, Doering and Dracup (1988) found significant differences in CO measurements obtained in the supine and 45-degree lateral positions ($\rho = .03$). Using random assignment to turn-sequence, 51 mechanically ventilated cardiovascular surgical patients were positioned in the supine, left lateral and right lateral positions with 20-degree backrest elevation. After each position change, 15 minutes elapsed prior to data collection to allow for reestablishment of hemodynamic indices. In each position, two CO

measurements were obtained by the thermodilution method. The largest variation occurred between CO measured in the supine (5.06 L/min) and the left lateral position (5.28 L/min) ($\rho = .01$). Stroke volume was also significantly higher in the left lateral position. Changes in mean CO were attributed to stroke volume rather than heart rate. The researchers speculated that the increase in CO and stroke volume was related to an enhancement in preload that occurs in the left lateral position as the heart shifts slightly downward toward the dependent chest wall thus producing an increase in stroke volume.

Although mean CO was not markedly different between the three positions, 45% of the subjects exhibited position-induced CO variation of greater than 10%. Subjects more likely to experience CO variation in the left or right lateral position were those who were (a) within 12 hours of surgery, (b) mechanically ventilated, (c) hypothermic (36.3°C to 37.0 °C), (d) receiving vasoactive medications, and (e) had a baseline CO of less than 2.3 L/min/m^2. Ninety-six percent of subjects who demonstrated greater than a 10% variation in CO between supine and lateral positions were mechanically ventilated. In contrast to the conclusions of Whitman et al. (1982), Doering and Dracup recommended that patients be placed in a supine position for CO measurement to avoid variation associated with lateral positions. In both studies, data collection occurred over a 50- to 70-minute period. On average, patients had undergone surgery 10.6 hours prior to being enrolled into the study (range 4 to 24 hours). Because there are frequent and rapid hemodynamic fluctuations in the postoperative period following extracorporeal circulation, secular events related to the physiological recovery from extracorporeal

circulation may partly explain the observed variation in CO that was attributed to lateral position.

Doering and Dracup (1988) speculated that the increase in cardiac performance observed in the left lateral position is related to the compression of the heart from the weight of the mediastinal structures. Using an animal model in a laboratory study, Nakao and colleagues (1986) demonstrated that a supine to lateral position change produced an increase in hydrostatic pressure and right ventricular diastolic filling (preload) that consequently accounted for an increase in stroke volume and cardiac output. However, the authors speculated that in the lateral position the liver compresses the inferior vena cava and partially diminishes the increase in hydrostatic pressure and cardiac output. Nakao et al. (1986) suggested that vena caval compression effects were more likely to occur in the left lateral position, thus resulting in a lower cardiac output in the left vs. right lateral position. The researchers' speculations were not consistent with the empirical findings of Whitman (1982) and Doering and Dracup (1988).

In a more recent study, Bein, Metz, Keyl, Pfeifer and Teager (1996) evaluated the effects of the lateral position (i.e., *position effect* vs. *turning effect*) on 12 critically ill patients requiring mechanical ventilation for respiratory failure and inotropic support. Fifteen minutes following a supine to lateral position change, the researchers measured hemodynamic parameters; intrathoracic dimensions and blood volume; and, plasma concentrations of atrial natriuretic peptide. Transesophageal echocardiography was performed in three subjects as a criterion measurement of right ventricular end-diastolic

dimensions. The researchers concluded that cardiac index ($\rho < .01$), intrathoracic blood volume ($\rho < .01$) and right ventricular end-diastolic volume ($\rho < .05$) and atrial natriuretic peptide levels increased significantly in the left lateral position compared with the supine position. In contrast, the right lateral position compared with the supine position was associated with a significant decrease in mean arterial pressure ($\rho < .01$), right ventricular end-diastolic volume ($\rho < .05$), and atrial natriuretic peptide levels, although cardiac index and intrathoracic blood volume were unchanged. The researchers concluded that the left lateral position is associated with a "hyperdynamic" state while the right lateral position produces a decrease in right ventricular preload due to an alteration in the distensibility of the right ventricle secondary to gravitational changes. Bein's findings are consistent with those of Whitman (1982) and Doering and Dracup (1988).

Shinners and Pease (1993) conducted a study to evaluate a 5-minute stabilization period following position change on hemodynamic variables. Data collection methods were similar to those used by Doering and Dracup (1988) and Whitman (1982). Thirty-one adult cardiovascular surgical patients were enrolled into the study less than 12 hours following surgery and randomly assigned to one of two turn-sequences. The researchers compared CO measurements obtained in the supine position, left and right lateral positions. The degree of lateral rotation varied from 20-degrees to 32-degrees. Using the thermodilution technique, CO measurements were obtained by averaging two individual CO measurements at baseline and at 5 and 30 minutes following each position change. The investigators concluded that CO measurements obtained in the supine, left lateral,

and right lateral positions were not significantly different. However, the study findings are difficult to interpret because statistical and physiological data for CO measurements were not provided. Similar to the conclusions of Whitman and colleagues (1982) the researchers determined that reproducible CO measurements can be obtained in the left and right lateral positions.

In two studies that evaluated the effects of lateral position on CO measurement (Doering & Dracup, 1988; Whitman et al., 1982), 50 to 70 minutes elapsed between the initial and final CO measurements. Consequently, it is possible that historical effects may have been partly responsible for the variations in CO. Another limitation of each of the studies is the use of thermodilution technique for measuring cardiac output. The spontaneous variability of CO should be considered when interpreting two or more CO determinations made at separate times. Although widely accepted in the clinical setting, thermodilution CO measurement often demonstrates appreciable variability related to measurement error associated with variation in the temperature and volume of injectate, timing of the injection during the respiratory cycle, the speed and mode of injection (Huang et al., 2000).

Spontaneous Cardiac Output Variability

Knowledge of spontaneous CO variability is important to researchers and clinicians who need to differentiate clinically relevant changes in CO related to position effect from insignificant fluctuations related to background phenomena. Sasse et al. (1994) used the intermittent bolus thermodilution method to investigate spontaneous

variability of CO in 22 non-sedated, medical ICU patients. During a 1-hour period in which no interventions were required or made, thermodilution CO was measured at baseline and every 15 minutes. The covariables of heart rate, respiration rate, mean systemic arterial pressure, mean pulmonary arterial pressure, pulmonary artery occlusion pressure, and temperature were also recorded every 15 minutes. At each measurement interval, five individual CO measurements were made and the mean CO and coefficient of variation was computed. The mean coefficient of variation between the five-thermodilution CO measurements at each 15-minute interval was 5.8%. The mean coefficient of variation during the 1-hour study period was 7.7%. In post hoc analyses, a subgroup of 15 "covariable stable" patients (±5% variability of covariable measurements) had a mean CO coefficient of variation of 6.4% during the 1-hour study period; whereas, the "covariable unstable" patients (> ±5% variability of covariable measurements) had a mean CO coefficient of variation of 9.9% during the 1-hour study period ($\rho < .05$). Patients who were spontaneously breathing demonstrated greater variability in CO than patients who were mechanically ventilated (10.1% vs. 6.3%; $\rho < .05$).

Sasse and colleagues advised clinicians to (a) consider normal spontaneous CO variability when interpreting two CO measurements made at separate time periods in both stable and non-stable populations (b) expect greater variability in CO measurements in non-sedated patients who are spontaneously breathing in comparison to sedated patients who are mechanically ventilated. Because positive pressure ventilation is a *controlled* condition, work of breathing and respiratory variation is reduced; consequently, variation

in preload and cardiac output are minimized because intrathoracic pressures fluctuate less than during spontaneous respirations. Although information regarding patient position during the study was not provided, the purpose of reviewing the study is to provide information about normal CO fluctuation that can be used when evaluating clinical differences in cardiac output related to study conditions.

In comparison, Huang and colleagues (2000) monitored CO continuously to define the magnitude of spontaneous CO variation in 22 moderately to heavily sedated, mechanically ventilated, medical ICU patients who had minimal hemodynamic fluctuations at baseline. Overall, the coefficient of variation in CO measurements was 4.6%. Patients who were ventilated by different modes of mechanical ventilation (i.e., PEEP > 15 cm H_2O, 2:1 inverse ratio ventilation) did not demonstrate significant differences in spontaneous CO variability ($\rho = .82$). The findings suggested that in critically ill, sedated medical ICU patients with stable hemodynamics, the spontaneous variability of CO over time is not significant. Therefore, Huang et al.(2000) concluded that a change in CO that exceeds 10% should be regarded as a clinically significant change and warrants further cardiorespiratory assessment and possible therapeutic intervention. Information regarding patient position during the study procedures was not provided.

Effect of Lateral Position on Hemodynamic Measurements

In critically ill patients, measurements of pulmonary artery diastolic pressure (PAD), mean pulmonary artery pressure, and pulmonary artery occlusion pressure (PAOP) normally vary by as much as 3 mm Hg; whereas, measurements of pulmonary artery systolic pressure normally fluctuate by as much as 4 mm Hg over time (Nemens & Woods, 1982). Because of the possible therapeutic implications associated with pulmonary artery pressures, clarifying the conditions under which reliable measurements can be obtained is essential (Aitken, 2000). A considerable amount of evidence exists to suggest that for most critically ill patients, intracardiac pressures (i.e., RAP, PAOP) and CO measurements do not vary significantly in the supine position with backrest elevations between 0- and 60-degrees (Chulay et al., 1982; Clochesy, Hinshaw, & Otto, 1984; Dobbin, Wallace, Ahlberg, & Chulay, 1992; Grose, Woods, & Laurent, 1981; Kleven, 1984; Laulive, 1982; Wilson, Bermingham-Mitchell, Wells, & Zachary, 1996; Woods, Grose, & Laurent-Bopp, 1982; Woods & Mansfield, 1976). However, the reliability of pulmonary artery pressure measurements obtained in the lateral position has not been clearly determined.

Several studies evaluating the effects of lateral position on the accuracy of pulmonary artery pressure measurements yielded inconsistent results (Aitken, 1995, 2000; Bridges et al., 2000; Shinners & Pease, 1993). For example, in studies by Whitman (1984) and Ross and Jones (1995) that used the supine phlebostatic axis as the reference point for hemodynamic measurements, changes in PAP in the 20- and 30-degree lateral

positions, respectively, were clinically insignificant. However, in five studies that used lateral positions of 30 degrees or more and the midsternum as the reference point, PAP and PAOP measurements obtained in the lateral position were clinically and significantly different than measurements obtained in the supine position (Cason, Holland, Lambert, & Huntsman, 1990; Groom, Frisch, & Elliott, 1990; Keating, Bolyard, Eichler, & Reed, 1986; Ross & Jones, 1995; Wild, 1983). Methodological differences may explain the inconsistencies of the findings and include (a) lack of agreement and consistency regarding the appropriate reference point for transducer placement, (b) variation in the degree of lateral position or rotation has ranged from 20 degrees to 90 degrees, (c) variation in hemodynamic stabilization time after position change has ranged from 3 minutes to 10 minutes, and (d) sample sizes have varied extensively and subjects have represented different subpopulations of critically ill patients.

Bridges and colleagues (2000) used the 30-degree left atrial reference point to evaluate the effects of a 30-degree lateral position on PAP and PAOP in cardiovascular surgical patients within the first 12 to 24 hours following surgery. The method for determining the angle-specific left atrial reference point was previously described by VanEtta and colleagues (1993) and is defined as one-half the distance between the surface of the bed and the left sternal border. Bridges et al. (2000) observed that, in comparison to the supine and 30-degree right lateral positions, PAP measurements were higher when cardiovascular surgical patients were positioned in a 30-degree left lateral position ($\rho < .05$). Because the pressure differences in the supine and lateral positions

were clinically insignificant (1 to 2 mm Hg), the researchers concluded that PAP measurements obtained in the 30-degree right and left lateral positions may be considered clinically equivalent to measurements obtained in the supine position. Similarly, other researchers who have used the angle-specific left atrial reference point to evaluate the effect of lateral position on hemodynamic measurements have also reported that reliable PAP and PAOP measurements can be obtained in the left and right lateral positions (Kennedy, Bryant, & Crawford, 1984). In comparing anatomical reference points for hemodynamic measurements obtained in the lateral position, the supine phlebostatic axis reference point results in less measurement error and more reproducible measurements than the midsternum reference point.

Shinners and Pease (1993) studied the effects of body position and time following position change on heart rate, systemic arterial pressure, systemic vascular resistance, central venous pressure (i.e., RAP), PAP, CO and SvO_2. The sample consisted of 31 cardiovascular surgical patients who were placed in three positions including the supine, 20- to 32-degree left lateral, and 20- to 32-degree right lateral positions. Data collection was performed during the first 12 hours following surgery. Backrest elevation was not specified. Subjects were consecutively assigned to either a supine-first or lateral-first group. Sequence of lateral positioning was randomly assigned. Baseline measurements were obtained following a 30-minute stabilization period. Referencing the transducer to the angle-specific, left atrial level, cardiorespiratory measurements were obtained at baseline and at minutes 5 and 30 following each position change.

With regard to the effect of turn-sequence, PAP and RAP *decreased* significantly when subjects were turned from the supine to lateral position and *increased* significantly when subjects were turned from the lateral to supine position. Mean PAP and RAP were significantly and clinically different between baseline and minute 5 regardless of turn-sequence. According to the limited descriptive information provided in a summary table, it appeared that the PAP and RAP changes observed immediately following the turn persisted throughout the 30-minute measurement period. However, results of the statistical analyses did not demonstrate significant *within-group* differences in PAP and RAP measurements between minutes 5 and 30 following positioning. The researchers reported that systemic arterial pressures were not significantly different between minutes 5 and 30 after turning and that heart rate, CO, systemic vascular resistance, and SvO_2 were not significantly different at any of the three measurement periods.

Regarding the effect of time following position change, physiological measurements obtained at 5 minutes and 30 minutes after each position change were not significantly different. Therefore, the researchers concluded that a 5-minute interval following position changes is sufficient for hemodynamic restabilization and measurements obtained 5 minutes following a position change are reliable, assuming correct technique. The authors suggested that differences between PAP measured in the supine and lateral positions were likely related to measurement error due to transducer placement.

Findings of the study were difficult to interpret because descriptive and statistical information was limited. Information and descriptive statistics about SvO_2 and CO measurements were not provided. Furthermore, the researchers did not discuss the clinical significance of the findings or differences observed between the left and right lateral positions.

Aitken (2000) found that significant differences between pulmonary artery pressure measurements obtained in the supine and 60-degree lateral positions resolved within 10 minutes following the position change. Unlike PAP measurements, significant within-subject differences were observed between PAOP measurements obtained in the supine and 60-degree left lateral positions and the supine and 60-degree right lateral positions. These clinically and statistically significant differences in PAOP measurements persisted 20 minutes following the position change. Though not explicitly stated, tabled data suggest that PAP and PAOP measurements immediately increased following a supine to lateral position change. Measurements obtained in the left lateral position were not compared to measurements obtained in the right lateral position. Despite the absence of group mean differences, 11% of the cardiovascular surgical patients demonstrated clinically significant changes from baseline PAP measurements 20 minutes after turning from the supine to lateral position. The investigators concluded that reliable measurements of PAP and PAOP cannot be obtained in the 60-degree lateral position and recommended the supine position for measuring hemodynamic variables. Researchers

used the supine phlebostatic axis to reference the transducer for hemodynamic measurements obtained in the left and right lateral positions.

Summary of Research on the Effect of Lateral *Position* On Cardiorespiratory Variables

In critically ill patients, pulmonary gas exchange, cardiac performance and the distribution of blood flow may be affected by body position. Studies that have evaluated spontaneously breathing and mechanically ventilated critically ill patients with unilateral lung disease in varying positions and in varying order suggest that PaO_2 is significantly higher when patients are positioned with the unaffected lung in the dependent position. When the non-diseased lung is in the dependent position, researchers have attributed the improvement in arterial oxygenation to a decrease in right-to-left intrapulmonary shunting and enhanced ventilation-perfusion matching (Gillespie & Rehder, 1987). Cardiovascular surgical patients are likely to demonstrate decreased PaO_2 in the left lateral position due to the high incidence of left lung atelectasis following cardiovascular surgical procedures (Banasik et al., 1987; Banasik & Emerson, 1996). However, the mean difference in PaO_2 between left and right lateral positions is usually not clinically significant. Position effect should be evaluated on an individual basis because patients with significant lung pathology or hypoxemia may experience large differences in PaO_2 with position changes. Position-induced changes in SaO_2 are usually very small and of no clinical consequence. According to the findings of two researchers, immediately following lateral positioning, SvO_2 is lower in the left lateral position, although

differences between supine and left lateral position are not appreciated within 5 to 15 minutes following the turn. In contrast, findings in three of the reviewed studies indicated that CO was significantly higher in the left lateral position (Bein et al., 1996; Doering & Dracup, 1988; Whitman et al., 1982). Doering and Dracup (1988) attributed the higher CO in the left lateral position to an increase in stroke volume; their conclusions are consistent with the findings of Chan and Jensen (1992) and Bridges et al. (2000) who observed higher PAP measurements in the left lateral position and Bein et al. (1996), who demonstrated that the left lateral position was associated with an increase in right ventricular diastolic dimensions as evidenced by transesophageal echocardiography.

Effect of Lateral *Positioning* on Tissue Oxygenation

Routine positioning at regular and frequent intervals has long been advocated to prevent the detrimental effects of prolonged bedrest and to promote comfort, skin integrity, and optimize ventilation-perfusion ratios. Two studies have documented the beneficial effects of routine positioning in cardiovascular surgical patients (Chulay et al., 1982; Gavigan et al., 1990). Chulay et al. (1982) found that, following cardiovascular surgery, patients who received lateral positioning every 2 hours experienced significantly less febrile days and spent significantly less time in ICU in comparison with patients who remained immobile for the first 24 hours following surgery. There were no differences noted between groups in terms of duration of mechanical ventilation, frequency or degree of atelectasis as demonstrated by radiographic abnormalities, or PaO_2 levels. Patients did not experience complications as a result of lateral positioning. The authors speculated

that the 32% reduction in duration of ICU stay was attributed to lateral positioning and equated to a potential savings of $150,000 annually in direct hospital (ICU) costs.

Gavigan et al. (1990) also studied the effects of regularly scheduled lateral positioning in preventing postoperative complications following CABG surgery. In comparison with patients who remained supine, those who received lateral positioning every 2 hours did not experience less atelectasis, less infection, or a reduction in ICU length of stay. The experimental group did however, experience fewer febrile episodes during the first 24 hours postoperatively. Nearly one-third of the original experimental group was disqualified because of a transient decrease in systolic blood pressure (< 100 mm Hg) following lateral positioning. Interventions to improve patient tolerance to positioning were not discussed.

Although usually tolerated, positioning is an active procedure and can increase VO_2, and thus decrease SvO_2. For this reason, positioning may have adverse physiological consequences for individuals with insufficient cardiac or oxygen reserves because they have limited ability to increase DO_2 to maintain oxygen supply and demand balance. Although backrest elevations up to 45 degrees do not produce a significant change in SvO_2 and are well tolerated (Noll & Fountain, 1990a; Shively, 1988), researchers have consistently demonstrated that critically ill patients typically experience a transient 8% to 12% decrease in SvO_2 and a 20% to 50% increase in VO_2 immediately following lateral positioning. SvO_2 returns to near baseline values within 4 to 5 minutes, whereas VO_2 may remain elevated for up to 45 minutes after turning (Weissman et al.,

1984). Compared to bed baths, back massage, and passive range-of-motion exercises, unassisted turning produces the most significant increases in VO_2 (Verderber & Gallagher, 1994). Although this amount of change in SvO_2 may not be clinically significant for the majority of patients, a 20% to 30% increase in VO_2 can be very significant for critically ill patients with limited ability to increase DO_2 as a compensatory mechanism. Research findings related to the effects of lateral positioning on SvO_2 are summarized in Table 2.

In the present study, the effects of lateral positioning on tissue oxygenation were tested at minutes 1 and 5 after the turn. These measurement intervals were selected a priori to (a) capture the maximal effects of lateral positioning that are associated with the largest increases in VO_2 and the largest decreases in SvO_2 and (b) test the effects of morphine during peak changes in tissue oxygenation variables following lateral positioning. Researchers consistently report that the largest decreases in SvO_2 occur between minutes 1 and 2 following lateral positioning and that SvO_2 returns to baseline within 4 to 5 minutes (Gawlinski & Dracup, 1998; Shively, 1988; Winslow et al., 1990). However, in the studies reviewed, researchers who obtained serial 1-minute measurements of VO_2 immediately after turning failed to report the time period associated with maximal or peak increase in VO_2 following lateral positioning. Therefore, the measurement intervals for VO_2 in the current study (i.e., minutes 1 and 5 following lateral positioning) were based on the SvO_2 literature and methodology used by other researchers who have evaluated VO_2 following positioning. Evaluation of

intermediate or long-term effects of positioning on VO_2 was not the focus of the current study.

According to Winslow et al.(1990), patients who have low hemoglobin levels and low CO are at greater risk for experiencing more dramatic SvO_2 changes and more severe complications following lateral positioning. Conditions occurring at the time of positioning such as coughing, shivering, and agitation, apparently have an additive effect and can result in greater reductions in SvO_2 than lateral positioning alone. Further research is needed to identify characteristics of patients who are likely to experience tissue oxygenation deprivation as a result of routine care procedures so nurses can make appropriate decisions about initiating or postponing activities to avoid adverse patient outcomes. Nurse scientists who have studied the effects of lateral positioning have indicated that further research is necessary to clarify inconsistencies regarding the direction or type of position change (i.e., left vs. right, supine vs. lateral, prone vs. supine) that has the greatest impact on SvO_2 (Atkins et al., 1994; Gawlinski & Dracup, 1998; Shively, 1988; Tidwell et al., 1990). Additionally, scientific investigations are needed that explore the effects of routine nursing procedures on the various components of tissue oxygenation, including VO_2, DO_2, and O_2ER, and the temporal relationships between these variables when oxygen demands change.

Effect of Lateral Positioning on Mixed-Venous Oxygen Saturation

In studies related to the effect of positioning (*turning effect*) on tissue oxygenation in critically ill adults, several researchers anecdotally reported that lateral positioning resulted in an immediate reduction of SvO_2 that was typically sustained for 10 minutes and was not associated with negative clinical outcomes. Most of the investigators qualified the decrease in SvO_2 as being *large* but did not quantify the change. Several researchers attributed the changes in SvO_2 to routine nursing care procedures including endotracheal suctioning, repositioning, and ventilator changes (Atkins et al., 1994; Baele, McMichan, Marsh, Sill, & Southorn, 1982).

Four nursing studies were examined that systematically evaluated the effect of turning from a supine to a lateral position on tissue oxygenation using continuous SvO_2 monitoring and collected data immediately after the turn (Gawlinski & Dracup, 1998; Shively, 1988; Tidwell et al., 1990; Winslow et al., 1990). Additionally, three abstracts were reviewed that studied the effects of lateral positioning on SvO_2 (Carroll, 1992; Noll et al., 1991; Pena, 1989). Two nursing studies were reviewed that systematically evaluated the effects of routine nursing procedures commonly performed in conjunction with lateral positioning (i.e., lateral positioning and bedbath, lateral positioning and backrub). Because both of the studies independently evaluated the effects of lateral positioning on tissue oxygenation using continuous SvO_2 monitoring (Atkins et al., 1994; Lewis et al., 1997), they were included in the review.

Using a prospective, experimental, repeated measures design, Shively (1988) studied 30 hemodynamically stable patients on average 9 hours following coronary artery bypass graft surgery and 3 hours following extubation. Subjects were randomly assigned to one of two groups based on frequency of positioning. Subjects in group I (n = 15) were repositioned every 1 hour, while subjects in group II (n = 15) were repositioned every 2 hours. Subjects in both groups were positioned in the same turn sequence that consisted of 4 turns for 4 series of turn sequences during the study. The turn sequence included right lateral with 20-degree backrest elevation, supine with 45-degree backrest elevation, left lateral with 20-degree backrest elevation, and supine with 20-degree backrest elevation. SvO_2 was measured at minutes 0 and 15, and 1 hour following each position change. For subjects in group II, additional measurements of SvO_2 were obtained 2 hours following positioning. The design was not counterbalanced. Mean scores rather than change scores were statistically evaluated.

Using mixed model analyses of variance (ANOVA), the between-subject factor *frequency* (of position change) and within-subjects factors *position* and *time* were examined. Main effects of *position* were interpreted despite significant two-way interactions between *Position x Group* (ρ = .03) and *Position* x *Time* (ρ = .0001). Despite the significant interactions, the investigator proceeded to interpret the main effects and concluded there were no significant differences in mean SvO_2 between groups based on *frequency* of position change nor were the repeated measurements of SvO_2 significantly different in each of the four positions. Further analyses of simple effects of the significant

interactions were not reported. However, according to the summary table of means and standard deviations, SvO_2 was noticeably lower immediately after turning (i.e., minute 0) when subjects in both groups were turned to the left lateral position. On average, the lowest SvO_2 measurements were observed in subjects assigned to group II immediately after turning to the left lateral position. The investigator suggested that the lack of *position* effect may have been attributed to the maintenance of ventilation-perfusion matching in each position or that none of the position changes caused a significant change in the DO_2 and VO_2 balance. Thirteen subjects demonstrated radiographic unilateral pulmonary pathologic changes ($n = 12$, left-sided vs. $n = 1$, right-sided). The investigator concluded that mean SvO_2 was not statistically different when subjects demonstrating unilateral pulmonary pathology were positioned with the healthy lung in a dependent or non-dependent position ($n = 13$, $\rho = .13$). However, post hoc power analysis was not performed and the conclusions may have reflected a Type II error.

Shively (1988) reported that subjects typically experienced a decrease in SvO_2 immediately after turning and SvO_2 recovery (return to baseline) occurred within 5 minutes; however, these results were not statistically examined. Findings demonstrated that SvO_2 remained stable at 15 minutes and 1 hour following lateral positioning. Shively speculated that the immediate decrease in SvO_2 following position change was related to an increase in peripheral oxygen utilization because of the muscular activity required for turning. It is not clear to what extent subjects assisted with position changes. Although cardiac output (CO) was measured at baseline and at the end of the study protocol, the

investigator did not discuss the effects of positioning on CO, DO_2, or VO_2 during the study or the contribution of these variables to the changes in SvO_2. Hemoglobin or degree of anemia within the sample was not reported. Methods of controlling for extraneous variables that may have influenced the results of the study such as vasoactive or inotropic infusions, sedation and analgesia, and administration of blood products or colloids during the study procedures were not discussed. A primary limitation of the study was the nonrandomization of turn sequences.

In a study that evaluated the effects of lateral positioning on SvO_2 and heart rate, Winslow et al. (1990) cautioned nurses to expect an immediate decrease of approximately 9% from baseline SvO_2 and a return to baseline within 4 to 5 minutes. SvO_2 changes were measured in 174 critically ill patients and heart rate responses were assessed in 183 critically ill patients who were $\geq$ 18 years. The majority of subjects were mechanically ventilated (96%) and had undergone cardiovascular surgery (61%). Subjects were turned to a 60-degree lateral position with 20-degree backrest elevation. Direction of the turn was determined by location of catheter tip in pulmonary artery. Eighty-five percent of subjects were turned to their right side. SvO_2 and heart rate measurements were recorded immediately after turning and every minute for 4 minutes thereafter. The investigators documented a significant decrease in mean SvO_2 from 67% to 61% ($\rho < .0001$) immediately after turning and a gradual return to 66% ($\rho < .002$) within 4 minutes. Significant differences in SvO_2 were not observed between the left or right lateral positions. Heart rate increased an average of 3% from the baseline and

returned to the baseline within 4 minutes after the turn. On average, physiological responses observed during the study were not interpreted to be clinically significant.

During the study procedures, two subjects became hemodynamically unstable following lateral positioning and subsequently experienced a 38% and 36% decrease in SvO_2 from baseline. These subjects were described as having low cardiac output at the time of turning. One subject experienced a 34% decrease in SvO_2 from baseline values but did not become hemodynamically unstable and appeared to tolerate positioning procedures without complications. Interestingly, this subject had a normal cardiac output during the positioning intervention. Eight subjects were disqualified during the study and the study protocol was aborted. Five of these subjects (62.5%) were disqualified because they became agitated following positioning. On average, agitation was associated with a 26% reduction in SvO_2 (range 9% to 38%). Three subjects were disqualified for clinically significant blood pressure fluctuations and cardiac rhythm changes

Based on the findings of the study, the authors provided guidelines for critical SvO_2 values during positioning procedures. The authors recommended that patients should be returned to the supine position if SvO_2 decreases more than 9% or if SvO_2 does not gradually return to baseline (within 4 to 5 minutes) following lateral positioning. Furthermore, a decrease in SvO_2 of $\geq 25\%$ following lateral positioning should be considered a critical value indicative of impending dire pathophysiological consequences. Patients with low hemoglobin and cardiac output were determined to be particularly vulnerable to the adverse effects of turning due to their limited ability to increase DO_2.

The researchers attributed the changes in SvO_2 following lateral positioning to an increase in oxygen consumption and to altered ventilation-perfusion relationships; however, VO_2, DO_2, CO, Hb, Qs/Qt, or stroke volume data were not reported.

Tidwell and colleagues (1990) investigated the effects of lateral positioning on SvO_2 in 34 patients following coronary revascularization during the first 4 to 8 postoperative hours. One subject was excluded from the data analyses (N =33). The purpose of the study was to evaluate the changes in SvO_2 associated with positional changes and to describe the mechanisms responsible for the changes in SvO_2. Measurements of the dependent variables (SvO_2, VO_2, SaO_2) were obtained at baseline, every 1 minute during the first 5 minutes following the turn, and at minutes 15 and 25 following the turn. Each subject was studied in a total of 6 positions and each position was maintained for 30 minutes following the turn. Subjects were randomized to turn-sequences. Supine to lateral and lateral to supine position changes were studied. Positions that were evaluated included supine with 30-degree backrest elevation, 45-degree right lateral, and 45-degree left lateral decubitus. Subjects did not actively assist with positioning procedures.

Compared with baseline values, mean SvO_2 was significantly lower at minute 1 after turning when subjects were turned from the supine position to right lateral ($\rho = 0$, as reported in the literature) and left lateral positions ($\rho = 0.0$, as reported in the literature) and back to the supine position ($\rho < .00$). Lateral positioning was associated with an immediate 8% to 9% decrease in SvO_2 that returned to the baseline within 5 minutes. The

largest decrease in SvO_2 was observed at minute 1 following the turn (right, $M = 6.1\%$ absolute vs. left, $M = 5.6\%$ absolute). SvO_2 changes associated with left and right lateral positions were similar. Mean SvO_2 did not drop below 60% for any patient in the study. Significant relationships were not found between SvO_2 and VO_2. Mean VO_2 was not significantly different between baseline and minute 1 following the turn or between baseline and any other time period following the turn. Average VO_2 values ranged from 0.27 to 0.32 L/m over time and position changes. The largest changes in SaO_2 were observed at minute 1 after turning from the supine to left lateral position. During this period, SaO_2 decreased by an average of 1.8%.

Individual analyses were performed on 4 outlying cases that involved a change in $SvO_2 > 10\%$ between baseline and minute 1 following position change. In these 4 cases, SvO_2 decreased by 17% to 20%, VO_2 increased by 26% to 81%, and SaO_2 decreased by 2% to 8%. Further descriptions of these subjects were not provided.

Because data collection was performed an average of 4 to 8 hours following surgery, the authors speculated that the lack of significant changes in mean VO_2 following positioning was related to residual anesthesia and heavy sedation. Thus, the researchers cautioned that the results could be misleading. Information regarding level of sedation or medications (analgesics, sedatives, paralytics) was not provided. The findings of this study offer support to the theory of oxygen consumption modulation and that analgesic or sedative agents may decrease oxygen demand in spite of conditions that would typically increase demands. The researchers concluded that cardiovascular surgical

patients were able to tolerate lateral positioning without experiencing clinically significant changes in SvO_2, SaO_2, or VO_2. DO_2, CO, and Hb were not measured and the authors did not attempt to explain the variability in SvO_2 following positioning that was attributed to oxygen delivery. Although the study has scientific merit, interpretations of the findings were limited because statistical results were either confusing or not provided.

Gawlinski and Dracup (1998) studied tissue oxygenation responses following lateral positioning in 42 critically ill, medical patients who had a left ventricular ejection fraction (LVEF) less than 30% ($M = 19.5\%$). Components of DO_2 (cardiac output, heart rate, oxygen saturation [SpO_2], Hb) and VO_2 were measured to explain the variance in SvO_2 following lateral positioning. Subjects were randomized to turn-sequence (supine to lateral) and the dependent variables were measured in the supine, left lateral and right lateral positions. SvO_2 data were collected every minute from baseline to minute 25 following the turn. To explain the variability in SvO_2 at minute 3 following the turn, VO_2, cardiac output, SpO_2, and heart rate were measured at minute 3 following the turn.

Results reflected a significant interaction between position and time ($\rho = .0001$). When subjects were turned to the right lateral position, SvO_2 was significantly lower from baseline through minute 2 following the turn ($\rho < .002$). Likewise, when subjects turned to the left lateral position, SvO_2 was significantly lower from baseline through minute 4 following the turn ($\rho < .002$). Mean changes in SvO_2 at 1 minute after turning to the right lateral position represented an 8.5% decrease from baseline values; whereas, the mean change in SvO_2 at 1 minute after turning to the left lateral position represented an

11.3% decrease from baseline. For most subjects, SvO_2 returned to baseline within 5 minutes after turning. Mean SvO_2 was not significantly different between baseline and minutes 15 and 25 after turning. Because cardiac output and SpO_2 were not significantly different from baseline to minute 3 following lateral positioning, the researchers concluded that the SvO_2 changes following lateral positioning were probably not related to ventilation-perfusion imbalance or cardiac output.

To explain the variability in the dependent variables, the contributions of DO_2 and VO_2 were examined. At minute 3 following left lateral positioning, the variability in mean SvO_2 was significantly related to DO_2 ($R^2 = .31$, $\rho = .0001$) and VO_2 ($R^2 = .54$, $\rho = .0001$); although the change in SvO_2 between baseline and minute 3 following the turn was significantly related to VO_2 ($R^2 = .46$, $\rho = .0001$) but not to DO_2 ($R^2 = .02$, $\rho = .2254$). The researchers concluded that the greatest proportion of variability in SvO_2 from baseline to minute 3 following lateral positioning is explained by an increase in oxygen consumption. Importantly, in this population of critically ill patients who had impaired myocardial function as evidenced by low LVEF, 38% of patients experienced clinically important decreases in SvO_2 after turning to the right lateral position and 48% experienced clinically important decreases in SvO_2 changes after turning to the left lateral position.

Research Abstracts

Pena (1989) studied the effect of lateral positioning on SvO_2 in 12 adult patients who were mechanically ventilated and had undergone cardiovascular surgery within the

previous 6 hours. Subjects were turned every 2 hours for a total of 2 turns. SvO_2 values were recorded continuously. On the average, subjects experienced an 8.5% decrease in SvO_2 immediately following the first-turn and a 12.3% decrease in SvO_2 immediately following the second-turn. Following both turns, SvO_2 values returned to baseline (recovery) within 3.7 minutes and SvO_2 remained at baseline 20 minutes after turning. The investigator determined that there was a significant difference in the mean SvO2 change observed following the first and second turns ($\rho = .02$), although the difference was probably not clinically significant.

Based on the findings of the study, Pena (1989) concluded that mechanically ventilated, hemodynamically stable, cardiovascular surgery patients may be turned during the first 6 hours following surgery. Immediately following a position change to the lateral position, an 8% to 12% decrease in SvO_2 should be anticipated and SvO_2 should return to baseline within 4 minutes. If SvO_2 decreases by more than 12% following lateral positioning or continues to drift downward for more than 5 minutes, the patient's cardiorespiratory profile (i.e., CO, Hb, SaO_2, DO_2, VO_2) should be reassessed, and complications commonly associated with cardiovascular surgery (i.e., bleeding, low cardiac output, etc.) should be considered and treated accordingly.

The researcher speculated that the sudden decrease in SvO_2 was related to an increase in energy expenditure and VO_2 that occurs with muscular activity during turning. However, DO_2 and VO_2 were not measured during the study. Limited information regarding methodological issues was provided in the abstract. Information

regarding the direction of the turn(s), the degree of rotation, and the randomization of the intervention was not provided. Subject participation in the turning procedures was not described. The degree of control over the extraneous variables during the study is unknown. Immediately after cardiovascular surgery, many factors may influence oxygen variables and SvO_2 due to a rapidly changing internal environment (i.e., temperature, hemoglobin, etc.). Hemoglobin levels were not reported, therefore it unknown if the subjects were anemic. Demographics were not provided; therefore, generalization of results is limited.

Carroll (1992) studied the effects of lateral positioning on SvO_2 and CO in 16 patients who had undergone CABG within the previous 2 to 4 hours of the study procedures. During a 2-hour period, subjects were turned to the flat supine, 45-degree left lateral, and 45-degree right lateral positions. Randomization to turn-sequence was not apparent. For each of the position changes, dependent measurements of SvO_2 and CO were collected at baseline before the turn, immediately following the turn, and at 15 minutes following the turn. Limited information was provided regarding the data collection procedures (i.e., time measurement intervals, frequency). Using two-way repeated measures ANOVA, the researcher found that mean CO was significantly higher when subjects were turned from the supine to left lateral position. In contrast, mean CO was not significantly different when subjects were turned from the supine to right lateral position or from the lateral to supine position. When subjects were turned from the supine to lateral position and from the lateral to supine position, SvO_2 was significantly lower

than at baseline. The decrease in SvO_2 occurred immediately following the turn. At minute 15 following position changes, mean SvO_2 was not significantly different than baseline and mean SvO_2 was not significantly different in any of the three positions. Descriptive and statistical information was not provided; therefore, generalizability of the results is limited.

Noll et al. (1991) studied the effect of routine activities on SvO_2 in critically ill patients. Twenty critically ill patients, the majority having a diagnosis of respiratory failure, were enrolled into the study. During a 2-hour observation period, SvO_2 was continuously recorded during routine care activities in the intensive care unit. On average, most subjects were exposed to 4 different routine activities within the 2-hour period. During the activities, 13 subjects (65%) experienced a 5% or larger decrease in SvO_2 from baseline. Several subjects developed clinically important symptoms related to decreased tissue oxygenation. For each activity, the researchers reported the mean decrease in SvO_2 and the time that SvO_2 remained decreased for each activity including (a) bath - 13.3% for 16 minutes; (b) turn or position change - 7.8% for 5.9 minutes; (c) weight measurement - 9.7% for 12.7 minutes; (d) supine position without head elevation - 7.0% for 4.7 minutes; and, (e) multiple procedures - 6.0% for 33.5 minutes. Three mechanically ventilated patients requiring high levels of FiO_2 and three spontaneously breathing cardiac patients experienced the greatest reductions in SvO_2 following activities. The abstract did not adequately define the activities or discuss mechanisms to control for confounding variables such as inotropic support, ventilator changes, agitation

and pain associated with routine procedures. Although statistical results were not reported, the findings that pertained to lateral positioning are similar to the findings of several other researchers.

The findings of Noll and colleagues (1991) suggest that critically ill patients may experience a clinically significant reduction in SvO_2 that is associated with routine nursing activities. The researchers speculated that patients with limited cardiac and pulmonary reserve may be more susceptible to experiencing problems with tissue oxygenation following a routine procedure such as turning, bathing, or weighing. Therefore, patient tolerance to routine activities should be evaluated using SvO_2. It may be necessary to postpone certain activities until the patient can tolerate the procedure.

Combination Interventions

Atkins and colleagues (1994) studied the effects of bathing and turning during two bedbath procedures on SvO_2 and heart rate in critically ill patients following coronary artery bypass graft surgery. The sample consisted of 26 men and 4 women who were hemodynamically stable. Subjects were randomly assigned to receive either a continuous bedbath without a rest period (n = 15) or an interrupted bedbath with a 10-minute rest period (n = 15) during the *early* postoperative period (within 2 to 5 hours following surgery) and again during the *late* postoperative period (within 16 to 20 hours following surgery). Mixed-venous oxygen saturation (SvO_2) and heart rate were recorded at 1- minute intervals 5 minutes prior to the bath, during the 13-minute bath, during the 10-minute rest period (interrupted group only), during the 2-minute turn, and for 5

minutes after each bedbath. This study is reviewed because it examined SvO_2 responses following lateral positioning. Baseline differences in cardiac index, SpO_2, hemoglobin, core temperature, SvO_2 and HR measurements between the subjects in either group were not significant. Mean hemoglobin was 10.7 (*SD* = 1.2). Researchers did not control for the effects of analgesics or sedatives. Variables that influence SvO_2 including DO_2 and VO_2 were not examined.

Because there were no significant differences in SvO_2 between the continuous or interrupted bedbath groups ($\rho > .05$), the data were combined for analyses. During the *bathing* phases of the bedbath, significant decreases in SvO_2 were observed during both the early bathing (1.6%, $\rho = .002$) and late bathing (1.9%, $\rho =< .03$) phases. Heart rate increased an average of 3.2% during early bathing and 1% during late bathing phases. During the *turning* phases of the bedbath, significant decreases in SvO_2 were observed during the early (9.2%, $\rho =< .01$) and late (12.1%, $\rho =< .01$) bedbaths. The largest decreases in SvO_2 were observed when subjects were turned from the lateral to the supine positions. On average, SvO_2 returned to baseline within 3 to 4 minutes. During the turning phase of the bedbath, the difference in SvO_2 changes from baseline during the early and late bathing phases was not significant ($\rho = .06$). In comparison, during the *turning* phase, HR increased less during late bedbath than during the early bedbaths ($\rho = .01$).

The researchers concluded that providing a 10-minute rest period between the bathing and turning phases of a bedbath is *not* beneficial. The *turning* phase, rather than

the *bathing* phase, of a bedbath is associated with clinically significant changes in SvO_2, regardless if the bedbath is given during the early or late postoperative period. During a bedbath, Atkins et al. (1994) advised clinicians to expect a 2% decrease in SvO_2 when bathing patients and a 9% to 12% decrease in SvO_2 after turning the patient. If SvO_2 decreases more than 12% for more than 5 minutes, the patient should be evaluated for other signs and symptoms of activity intolerance and physiological compromise.

During both the early and late baths, 10 subjects had very low SvO_2 (< 53%). The most severe decreases in SvO_2 were observed during the early vs. late bathing period and were usually associated with coughing, shivering and agitation. In comparison, significant decreases in SvO_2 that occurred during the late bedbath were attributed to pain. The researchers recommended that coughing, shivering, agitation, and pain should be treated prior to performing a bedbath because these conditions are associated with more clinically severe and prolonged decreases in SvO_2, especially when bedbaths are given in the early postoperative period (< 5 hours following surgery). Opiates (i.e., morphine, meperidine) are routinely administered following cardiovascular surgery to (a) treat discomfort and coughing associated with endotracheal intubation; (b) treat shivering during the emergence from anesthesia; and, (c) prevent procedural pain associated with lateral positioning, drain removal, and wound dressing change (Kruger & McRae, 1999; Pooler-Lunse & Price, 1997; Puntillo et al., 2001). Empirical findings in this study support the use of morphine during lateral positioning to attenuate increases in oxygen demand and avoid profound and sustained reductions in SvO_2.

Lewis and colleagues (1997) studied the effect of turning and backrub on SvO_2 in a sample of 57 critically ill men who were hemodynamically stable (mean cardiac index = 3.23, *SD* = 0.58), but slightly anemic (mean Hb = 8.9, *SD* = 1.2). Although eight (14%) subjects had a baseline SvO_2 of less than 60%, the majority of the sample had normal baseline SvO_2 values (mean range 66% - 67.8%). Spontaneously breathing, cardiovascular surgical patients comprised the majority of the sample. The purpose of the study was to determine the effect of left or right lateral positioning and timing of back rub (immediate or delayed) on SvO_2 in critically ill patients. Subjects were randomly assigned to the direction of position change (left or right lateral position) and timing of the backrub intervention (immediate or delayed). SvO_2 measurements were obtained each minute following the turn and back rub for 5 minutes.

Results indicated that body position ($\rho = .007$) and timing of backrub ($\rho = .000$) had a significant effect on SvO_2. Subjects turned to the left lateral position had significantly greater reductions in SvO_2 than those who were turned to the right lateral position (6.4% vs. 5.2%, $\rho = < .05$). Forty–four percent of the subjects had SvO_2 values less than 60% following the turn but SvO_2 did not remain in the 50% range for longer than 3 minutes. The lowest SvO_2 values were observed when subjects were turned to the left lateral position and immediately received a backrub.

Subjects who received a back rub immediately following the turn experienced a significant reduction in SvO_2 ($\rho < .05$). However, SvO_2 steadily increased throughout the 1-minute back rub procedure and during the 4-minute observation period following the

backrub. In contrast, subjects in the delayed back rub group experienced a significant decrease in SvO_2 following the turn and another significant, though lesser, decrease in SvO_2 when the back rub was initiated 5 minutes following the turn. On average, SvO_2 increased during the 5 minutes following the introduction of each intervention, however recovery to baseline did not occur within the 5-minute observation period following the intervention. Significant differences persisted between mean baseline SvO_2 ($M = 67.4\%$, $SD = 7.4$) and SvO_2 obtained 5 minutes after the backrub ($M = 63.4\%$, $SD = 7.2$). The researchers concluded these changes were not clinically important. Although mean SvO_2 decreased to 56.7% following the combined procedure of lateral positioning and a back rub, the researchers interpreted these findings to be clinically unimpressive because SvO_2 demonstrated a swift return towards baseline after the introduction of each intervention.

Two subjects who were in the immediate backrub group had SvO_2 values that decreased to 33% during the backrub. Both subjects had very low baseline SvO_2 values (55% and 56%). Although cardiac index and SaO_2 were within normal ranges, the subjects were anemic (mean Hb = 8.5 and 7.7 g-/dl).

The researchers concluded that SvO_2 significantly decreases following lateral rotation when a back rub is performed. SvO_2 typically remains below baseline for approximately 5 minutes after the back rub. The reductions in SvO_2 are more dramatic when a back rub is performed while the patient is in the left lateral position. Therefore, the researchers recommend monitoring SvO_2 for 10 minutes following the turn to ensure SvO_2 recovery to baseline is achieved. The two consecutive interventions (turn and back

rub) cause a greater decrease in SvO_2 than two interventions separated by a 5-minute rest period. Nevertheless, the authors recommend the standard practice of administering a back rub immediately following the turn in patients who are hemodynamically stable for the most effective use of nursing time. Information regarding analgesics or sedatives administered before or during the study was not provided.

Effect of Lateral Positioning on Tissue Oxygen Consumption

While several studies support the numerous therapeutic effects of lateral positioning on gas exchange, atelectasis, fever, psyche, and ICU length of stay in critically ill patients (Banasik et al., 1987; Banasik & Emerson, 1996; Bridges et al., 2000; Brooks-Brunn, 1995; Chulay et al., 1982; Gavigan et al., 1990; Gillespie, Didier, & Rehder, 1990; Gillespie & Rehder, 1987; Ng & McCormick, 1982), other investigators have documented the metabolic cost of lateral positioning. Specifically, researchers have demonstrated that manually placing a critically ill patient in a lateral position produces an immediate increase in VO_2 between 20% and 50% above baseline values (Cohen et al., 1996; Davis et al., 2001; Horiuchi et al., 1997; Swinamer et al., 1987; Verderber & Gallagher, 1994; Weissman et al., 1984). Following lateral positioning, VO_2 may remain elevated for up to 45 minutes (Weissman et al., 1984).

Conditions that result in profound increases in metabolic demands (i.e., 20% to 50% increase in VO_2) may be deleterious to patients compromised by cardiovascular and respiratory illnesses (Gillespie & Rehder, 1987; Remolina et al., 1981; Rivara et al., 1984; White et al., 1990). Other routine nursing procedures including endotracheal

suctioning, bathing, weighing, and chest physiotherapy are also associated with increased VO_2 and may threaten the delicate homeostatic balance of critically ill patients with altered regulatory mechanisms and impaired tissue oxygenation (Atkins et al., 1994; Clark et al., 1990; Lane & Winslow, 1987; Lane et al., 1997; Swinamer et al., 1987; Tyler et al., 1990; Verderber & Gallagher, 1994; Waite & Parsons, 1990; Weissman & Kemper, 1991; White, 1993). Knowledge of the effects and metabolic costs of routine nursing procedures on VO_2 in patients with low DO_2 can assist critical care nurses in determining when it is safe to proceed with care activities and when activities should be postponed to avoid overtaxing the oxygen reserve capacity (Jesurum, 1997).

Several researchers have anecdotally reported the effects of lateral positioning on VO_2 in critically ill patients. Weismann et al. (1984) determined that the mean resting VO_2 of postoperative, hemodynamically stable, mechanically ventilated patients was 204 (*SD* = 57) ml/min. Routine nursing interventions such as bathing and active and passive range- of-motion produced an increase in VO_2 of approximately 20%. Swinamer, Phang, Jones, Grace, and King (1987), found the average resting VO_2 of critically ill, mechanically ventilated patients to be 320 (*SD* = 47) ml/min. Nursing procedures which included repositioning and bathing resulted in average VO_2 increases of 31% (*SD* = 11) and 19% (*SD* =11), respectively. In both of these studies (Swinamer et al., 1987; Weissman et al., 1984), the investigators speculated that pain and discomfort associated with repositioning attributed to the increase in oxygen consumption observed during the study.

Verderber and Gallagher (1994) discovered that in comparison to bed baths and passive range-of-motion exercises, unassisted turning resulted in the highest VO_2 for healthy men and women. Following lateral positioning, mean VO_2 for men was 5.05 ml/kg/min (range 2.90 to 6.0) and 4.48 ml/kg/min (range 2.68 to 6.29) for women, representing an increase from baseline of nearly 20%. The authors cautioned turning patients with cardiovascular or pulmonary pathology and limited oxygen transport.

Horiuchi and colleagues (1997) systematically investigated the effects of supine to lateral positioning in 13 mechanically ventilated patients who had undergone uncomplicated coronary artery bypass graft surgery. After controlling for environmental issues that affect metabolic requirements (i.e., noise, lights, staff, visitors, temperature) and allowing a 30-minute stabilization period, subjects were turned from the supine to lateral position. After remaining in the lateral position for 2 minutes, subjects were returned to the supine position. Dependent measurements were obtained prior to and following the turn sequence. Baseline hemoglobin level was 9.5 g-/dl. Results indicated that mean VO_2 was significantly higher following lateral positioning ($M_1 = 219$, $SD = 21$, $M_2 = 324$, $SD = 58$, $\rho < .001$) and represented a 47% increase from baseline VO_2. Following the turn, O_2ER, DO_2, CO, PAD, RAP, and heart rate were significantly higher ($\rho < .001$) as was systemic arterial pressure ($\rho < .05$). The increases in oxygen demand were met by increases in both oxygen delivery ($M_1 = 852$, $SD = 238$, $M_2 = 1116$, $SD = 430$) and extraction ($M_1 = 0.27$, $SD = 0.7$, $M_2 = 0.32$, $SD = 0.09$). In review of the descriptive data, it appears that the increase in DO_2 was primarily related to an increase in

CO ($M_1 = 6.9$, $SD = 1.7$, $M_2 = 9.2$, $SD = 3.4$). Although SvO_2 was significantly lower, the findings were not clinically impressive ($M_1 = 69$, $SD = 7$, $M_2 = 65$, $SD = 9$, $\rho < .01$). Subjects were slightly anemic; however, myocardial function appeared normal. Preoperative clinical characteristics of the sample were not provided. The researchers concluded that their findings (SvO_2, heart rate) were similar to those of Winslow et al (1990). Information regarding the direction of the turn or degree of elevation was not provided.

Summary of Research on the Effect of Lateral *Positioning*

In summary, numerous researchers have systematically evaluated the effects of lateral positioning on tissue oxygenation as measured by SvO_2. Although several researchers speculated that the decreases in SvO_2 following lateral positioning were related to increases in oxygen demand and consumption, few researchers explored the components of SvO_2, including DO_2 and VO_2 to explain the variability in SvO_2 following lateral positioning. Collectively, researchers consistently have demonstrated that critically ill patients typically experience a transient 8% to 12% decrease in SvO_2 and a 20% to 50% increase in VO_2 immediately following lateral positioning. Normally, SvO_2 returns to baseline within 4 to 5 minutes, whereas VO_2 may remain elevated for up to 45 minutes following the turn. If lateral positioning is combined with another nursing procedure (i.e., bedbath, weighing, backrub), SvO_2 recovery to baseline is likely to occur within 10 minutes of the procedure (Lewis et al., 1997). In individual cases, profound decreases in SvO_2 were usually associated with low cardiac output, low hemoglobin, and agitation

during the procedure, and grouping positioning with other procedures such as backrubs and bathing.

Guidelines for practice recommend returning patients to the supine position if SvO_2 decreases by more than 9% to 12% following a lateral position change and performing a cardiorespiratory assessment (Atkins et al., 1994; Gawlinski & Dracup, 1998; Pena, 1989; Winslow et al., 1990). Although subjects in the Lewis study (1997) demonstrated a mean SvO_2 of 57% following lateral positioning, the researchers interpreted these findings to be clinically unimpressive because SvO_2 demonstrated a swift recovery towards baseline within 5 minutes following the turn. Thus, the researchers suggested that traditional guidelines that define critically low $SvO_2 < 60\%$ to be an indicator of patient intolerance of nursing procedures should be questioned (Lewis et al., 1997). Several researchers have recommended pharmaceutical interventions (i.e., analgesics, anxiolytics) prior to turning to avoid excessive increases in oxygen consumption (Gawlinski, 1993b; Tidwell et al., 1990; Winslow et al., 1990).

The generalizability of some of the studies is limited due to small sample sizes in heterogeneous populations, lack of randomization, and methodology concerns related to controlling for confounding variables (e.g., medications, analgesics, anxiolytics).

Oxygen Consumption Modulation Research

Although researchers have provided insight into the effects of specific nursing procedures on VO_2 in critically ill patients (Clark et al., 1990; Gawlinski & Dracup, 1998; Noll & Byers, 1994; Noll & Fountain, 1990a; Pena, 1989; Shively, 1988; Tyler et

al., 1990; Waite & Parsons, 1990; Weissman et al., 1984; Winslow et al., 1990), there has been little research to evaluate interventions that promote oxygen conservation during nursing care procedures (Jesurum, 1997; Stewart, 1988). Because cardiac output is the primary determinant of DO_2 and tissue perfusion (Pasquale et al., 1993a, 1993b), it is logical that the most efficient way to improve DO_2 is by manipulating preload, afterload, and contractility to augment cardiac output. However, patients who have cardiovascular disease and postoperative myocardial dysfunction may have limited response to interventions aimed at maximizing cardiac output and DO_2 (Nightingale, 1993; Smith & Steele, 1991).

Recent evidence suggests that treating anemia and augmenting DO_2 by allogenic blood transfusion does not result in increased VO_2 (Casutt et al., 1999) and may even be associated with a decrease in gastric intramucosal pH, indicating deterioration rather than improvement of tissue oxygenation (Marik & Sibbald, 1993). Storage-related alterations in blood products result in a decrease in the deformability of red blood cells and a decrease in 2, 3-diphosphoglycerate concentration (Card, Mohandas, Perkins, & Shohet, 1982; Fitzgerald et al., 1997; Surgenor, Hampers et al., 2001). Consequently, stored red blood cells have impaired ability to unload oxygen and improve tissue oxygenation. In certain populations, customary interventions intended to increase DO_2 such as inotropic support therapy and allogenic blood transfusion will have limited efficacy (Heyland et al., 1996).

In critically ill patients who have depleted cardiorespiratory reserves, research-based interventions that use VO_2I to guide interventions that support tissue oxygenation by decreasing oxygen demand and reducing oxygen deficit are desperately needed for application in the clinical setting. Approaches to modulate the extent and magnitude of the metabolic and cardiovascular responses secondary to an acute increase in oxygen demand have ranged from techniques that are global in scope (e.g., a cardiac anesthetic) to those that are mediator or cellularly focused (e.g., cytokine synthetase inhibition) (Epstein & Breslow, 1999). According to published reports, an analgesic agent is a therapeutic option that lowers metabolic rate and reduces oxygen consumption by decreasing skeletal muscle activity and relieving pain and anxiety that may be associated with lateral positioning (Alderman et al., 1972; Colonna-Romano & Horrow, 1994). Several researchers who have evaluated the effects of routine care procedures on critically ill patients have reported anecdotally that large to medium size dosages of morphine received prior to routine nursing procedures resulted in substantial reductions in mean VO_2 and carbon dioxide production (VCO_2) (Swinamer et al., 1987; Weissman et al., 1984). Swinamer and colleagues found that on average, "large" dosages of morphine resulted in a 12.7% decrease in resting energy expenditure. The researchers attributed the 31% (SD = 11%) increase in energy expenditure observed during positioning procedures to pain and discomfort associated with the procedure.

Within the medical literature, various pharmaceutical agents have been investigated to determine the effects on oxygen consumption in critically ill patients

(Cohen et al., 1996; Harding, Kemper, & Weissman, 1993; Harding et al., 1994; Horiuchi et al., 1997; Klein et al., 1988; Nimmo, Mackenzie, & Grant, 1994). Systematic attempts at attenuating the metabolic responses to multimodality physical therapy with various narcotics including fentanyl and alfentanil have resulted in conflicting findings among researchers (Harding et al., 1993; Klein et al., 1988). In studying the effects of routine intensive care procedures on 23 critically ill, mechanically ventilated patients, Weissman and colleagues (1984) discovered that lateral positioning resulted in an 20% increase in VO_2 and chest physiotherapy resulted in a 35% increase in VO_2. In comparison with other routine activities including physical examination, bathing, wound dressing changes, and positioning procedures, chest physiotherapy was associated with the most pronounced variations of cardiorespiratory parameters. Anecdotally, the researchers observed that patients who were sedated with moderate to large doses of morphine had lower VO_2 and VCO_2. The authors attributed the effects of morphine to an attenuation of metabolic responses. In a subsequent study, Klein and colleagues (1988) found that critically ill patients who received high dose fentanyl (3.0 μg/kg iv) prior to chest physiotherapy had attenuated increases in blood pressure (12% increase vs. 30%) and heart rate but VO_2 was not significantly different than responses to placebo. Responses to low dose fentanyl (1.5 μg/kg iv) during the same activity were not significantly different than response to placebo. In comparison, several researchers who have systematically evaluated the effects of morphine on tissue oxygenation and cardiorespiratory indices reported that morphine effectively attenuates the metabolic responses associated with

environmental stressors by as much as 21% (dose dependent response) while preserving or improving hemodynamic parameters in critically ill patients including cardiovascular surgical patients (Rodriguez et al., 1983; Rouby et al., 1981; Semsroth & Hiesmayr, 1990). Metabolic responses to morphine have been attributed to its analgesic and sedative properties.

Other researchers have attempted to explore other classifications of medications that have sedative and anxiolytic properties to modulate oxygen consumption during care activities. Harding (1994) found that midazolam, a short-acting benzodiazepine, in doses of 0.015 (n = 15) and 0.03 mg/kg iv (n = 13) significantly attenuated the increases in VO_2, CO, heart rate, and blood pressure during chest physiotherapy in a group of 28 critically ill patients. There were no significant differences in mean DO_2I during activity with and without midazolam; however, the change in DO_2I between baseline and measurements obtained during activity were significantly lower when subjects received midazolam. SvO_2 remained stable throughout the study regardless of treatment condition. Blood pressure was the primary hemodynamic variable attenuated in this study.

In phase 1 of a two-part study, Horiuchi and associates (1997) determined that turning critically ill surgical patients (N = 13) to a lateral position prior to performing chest physiotherapy (CPT) typically resulted in a 50% increase in VO_2 and VCO_2 ($\rho <$ .05), a 31% increase in DO_2 ($\rho <$ .05), and an 18.5% increase in O_2ER ($\rho <$ .05). Substantial increases in hemodynamic and respiratory variables including blood pressure, cardiac output and heart rate were also observed with lateral positioning.

To determine the mechanism responsible for the increase in VO_2 observed during CPT, Horiuchi et al. (1997) administered midazolam (0.15 μg/kg iv) before the initial CPT session and then, administered midazolam (0.15 μg/kg iv) and vecuronium (0.7 mg/kg iv) before a subsequent CPT session during the second phase of the study. Seven critically ill subjects were enrolled into phase 2 who were mechanically ventilated and had undergone major vascular or abdominal surgery. The researchers postulated that increased skeletal muscle activity was the major contributor to the 50% increase in VO_2 observed during chest physiotherapy. When vecuronium was received before chest physiotherapy, increases in VO_2 during the procedure were completely suppressed. However, systolic blood pressure was unaffected by vecuronium. The researchers concluded that the increase in metabolic demand that occurs during chest physiotherapy is the result of increased muscular activity as evidenced by the suppression of VO_2 following the administration of a muscle relaxant. Increases in blood pressure and cardiac output were attributed to enhanced sympathetic output. Based on the findings of the study, the researchers concluded that the increase in metabolic and hemodynamic responses produced by chest physiotherapy is secondary to both exercise-like and stress-like responses (Horiuchi et al., 1997).

Researchers have studied the effects of propofol during chest physiotherapy and suctioning in critically ill patients to determine if metabolic responses are modulated (Cohen et al., 1996). Although propofol significantly reduced increases in VO_2 typically associated with chest physiotherapy, non-desirable effects including significant decreases

in DO_2, CO and blood pressure were also observed. The researchers attributed the effects to anesthesia properties of the drug that reduced pain, anxiety, and muscular movement. These results were presented in a previous discussion (Chapter 1).

Nimmo and colleagues (1994) developed an elaborate dosing algorithm to prevent harmful hemodynamic effects of propofol while providing for a stable level of sedation in 10 critically ill patients. By adhering to the dosing guidelines, the researchers reported fewer incidences of hypotension and decreased cardiac output with propofol administration. Although the findings were not statistically significant, 3 of the 10 patients experienced hypotension, decreased cardiac output, and decreased DO_2I at hour 3 following the initiation of the propofol infusion. The subjects subsequently required fluid (volume) resuscitation to restore normal cardiovascular parameters. To avoid the negative hemodynamic and oxygen transport effects of propofol, researchers concluded that patients must be adequately resuscitated with fluid prior to initiating propofol treatment. Due to the increased permeability of capillary membranes following extracorporeal circulation, cardiovascular surgical patients are at risk of hypovolemia and typically experience extravascular fluid shifts for 24 to 48 hours following surgery (Weiland & Walker, 1986). During this time, caution is advised when using pharmaceutical therapy that decreases sympathetic activity thereby decreasing systemic vascular resistance (SVR) and arterial pressure.

Effect of Morphine Sulfate on Oxygen Consumption

Alderman, Barry, Graham, and Harrison (1972) reported an 11.6% decrease in VO_2 following the administration of 8 mg of intravenous morphine sulfate to eight patients undergoing cardiac catheterization who had significant coronary heart disease. The authors also observed an 8.6% decrease in cardiac index, a 10.6% decrease in stroke volume index, and a 20.5% decrease in left ventricular end diastolic pressure following morphine administration ($\rho < .05$). Reductions in cardiac index were not associated with changes in heart rate. Minimal reductions were observed in the left and right cardiac pressures (RAP, PAOP). These findings are similar to those of Rouby et al. (1979) who found that cardiac index remained stable when critically ill patients received a 0.15 mg/kg iv dose of morphine; however, when subjects received a 0.30 mg/kg iv dose of morphine, significant and prolonged reductions in cardiac index (~ 1 L/min/m^2) were observed during a 90-minute period along with transient decreases in heart rate, stroke volume index, left stroke work index and systemic arterial pressure during the hour following administration. Interestingly, minimal changes were observed in left and right cardiac filling pressures following morphine administration. The authors speculated that morphine-induced reductions in thoracic-pulmonary compliance were related to esophageal constriction and increased muscular rigidity. Consequently, intracardiac pressures (i.e., RAP, PAOP) may increase despite an actual reduction in cardiac index.

Rodriquez and colleagues (1983) studied the effects of morphine on cardiorespiratory parameters and VO_2 as measured by indirect calorimetry in 18

hypothermic, mechanically ventilated, surgical patients during the immediate postoperative rewarming period. Subjects were assigned to control and treatment groups based on dosages of morphine. Eight subjects in the treatment group received a continuous infusion of morphine at 0.2 mg/kg/hr iv and two subjects received a continuous infusion of morphine at 0.5 mg/kg/hr iv. Patients in the control group received morphine as needed for sedation and pain. Although the researchers implied that the control group received smaller dosages of morphine compared with the treatment groups, the actual amount of morphine received by subjects in the control group was not reported. Dependent measurements were obtained on admission to the ICU, mid-point of the study, and at the end of the study when subjects achieved normothermia. Results of the study indicated that subjects who received morphine in dosages of either 0.2 or 0.5 mg/kg/hr iv demonstrated (a) significantly less increases in mean VO_2 and VCO_2 over the rewarming period (typically 3 hours in duration), (b) 72% lower mean VO_2 compared with control group ($\rho < .05$), (c) decreased heat production and increased duration of rewarming time ($\rho < .025$), (d) fewer episodes of postoperative shivering, and (e) lower mean heart rate and systemic arterial pressure. Unlike the findings of Rouby et al. (1979) or Alderman et al. (1972), subjects in the treatment group demonstrated higher cardiac index, stroke volume index and PAOP than the control group and did not experience cardiovascular fluctuations related to morphine. The researchers attributed the lack of hemodynamic fluctuations to adequate intravascular volume (i.e., preload) secondary to high fluid requirements. Researchers concluded that the use of high-dose morphine in critically ill

patients during the dynamic phase of postoperative recovery suppresses metabolic demand and myocardial work but maintains cardiovascular function when fluid requirements are met.

Colonna-Romano and Horrow (1994) found that anesthesia induction during cardiac surgery with sufentanil, an ultrapotent opioid analgesia with properties similar to morphine, resulted in a statistically significant increase in SvO_2 and decrease in VO_2 and cardiac index. The authors attributed the decline in VO_2 to the effects of opioid analgesia, not neuromuscular blockade, on reducing the metabolic demands of organ systems, particularly the central nervous system, and to the loss of basal tone in skeletal muscle. Typically, general anesthesia in humans is associated with a 7% to 40% decrease in whole-body oxygen consumption from the measured or estimated basal rate (Brandi, Giunta, Oleggini, Mazzanti, & Fossati, 1994).

Rodriquez and colleagues (1983) suggested that morphine suppresses the body's metabolic demand by diminishing the posttetanic phase of neuromuscular transmission. Following morphine administration, evaluation of neuromuscular function using a peripheral nerve stimulator device demonstrated the absence of fade and posttetanic facilitation. Similarly, Colonna-Romano and Horrow (1994) credited a significant decrease in VO_2 to a loss of basal tone in skeletal muscle. In comparison, Swinamer et al. (1987) attributed the 12.7% reduction in resting energy expenditure following morphine administration to a reduction in pain associated with nursing care activities such as positioning. Regardless of the mechanism of action, intravenous administration of

morphine in dosages of 0.20 to 0.5 mg/kg has been shown to attenuate the stress response in cardiovascular surgical patients as evidenced by a 9% to 21% reduction in VO_2 (Alderman et al., 1972; Rouby et al., 1981; Rouby et al., 1979). The range of morphine dosages used in these studies is slightly to significantly larger than dosages typically prescribed following cardiovascular surgery for acute pain management and maintenance of sedation (Hall et al., 2001; Kruger & McRae, 1999).

In a subsequent study, Rouby and colleagues (1981) determined that 0.5 mg/kg iv of morphine resulted in a 21% decrease in VO_2 in 10 critically ill subjects who had elevated VO_2I (range 208 – 143 ml/min/m^2) and a 9% decrease in 14 subjects who had normal VO_2I (range 90 – 135 ml/min/m^2). The reductions were sustained during the 180-minute period following morphine administration. Because the decrease in VO_2 was not associated with significant changes in O_2ER, the authors attributed the changes to a reduction in oxygen demand rather than a decrease in DO_2. The researchers speculated that the decrease in oxygen demand was caused by morphine-induced sedation and analgesia secondary to attenuation of the cardiovascular adrenergic stress response. Following the administration of morphine, significant reductions were observed in heart rate (13%), cardiac index (18%), stroke volume index (17%), PAOP (21%), and systemic arterial pressure (15%). Serial measurements of the dependent variables were obtained at baseline and at multiple intervals during the 180-minute data collection period following morphine administration. Simultaneous reductions in stroke volume and transmural cardiac filling pressures, as measured by an esophageal balloon, were attributed to a

decrease in venous return and a morphine-induced increase in venous capacitance. The decrease in heart rate was attributed to a centrally mediated increase in vagal tone. The findings support the theory of oxygen consumption modulation. Interestingly, the magnitude of effect of morphine on oxygen consumption over time depended on subjects' initial status of oxygen consumption (i.e., baseline VO_2I).

Summary of Oxygen Consumption Modulation Research

Several researchers have demonstrated that various opiates or anxiolytics effectively decrease oxygen consumption in critically ill patients, thus supporting the theory of oxygen consumption modulation. Depending on the pharmaceutical actions of a particular drug, reduction in VO_2 is attributed to either an attenuation of the metabolic or cardiovascular effects (or both) associated with hypermetabolic conditions. Various researchers have also attributed reductions in oxygen consumption to the combined analgesic and sedative effects provided by the opiates. Commonly used opioids in the critical care setting include morphine, fentanyl, sufentanil and remifentanil (Mastronardi & Cafiero, 2001). Through systematic evaluation, morphine, in moderate to large dosages (0.15 – 0.5 mg/kg iv), has consistently been shown to safely attenuate the stress response to surgical recovery and reduce VO_2 in critically ill patients including those with cardiovascular disease (Alderman et al., 1972; Bernard et al., 1988; Colonna-Romano & Horrow, 1994; Rouby et al., 1981; Rouby et al., 1979). While several researchers have attributed decreases in VO_2 to morphine-induced "hemodynamic sedation" that produced significant reductions in cardiac index, stroke volume index, cardiac filling pressures, and

heart rate (Alderman et al., 1972; Rouby et al., 1981), other researchers have observed significant increases in cardiac index, stroke volume, and PAOP following morphine administration (Rodriguez et al., 1983). The initial postoperative period is associated with significant increases in metabolic demands related to adrenergic stimulation that impose a burden on the cardiovascular system and may be poorly tolerated by elderly patients or those with limited cardiorespiratory reserve. In these circumstances, morphine may be an appropriate modality to decrease VO_2 and restore tissue oxygenation balance.

Measurement of Tissue Oxygenation

Traditionally, physiologic monitoring in the critical care setting has focused on evaluation of hemodynamic parameters (i.e., PAOP, CO, SV, SVR). Although this approach is beneficial in evaluating myocardial performance, it does not address pulmonary function or tissue perfusion problems. Undoubtedly, the most important application of physiological monitoring is the evaluation of tissue perfusion and tissue oxygenation by assessing the trends of DO_2 and VO_2 (Shoemaker, 1992). Within the clinical setting, measured cardiorespiratory indices (i.e., SvO_2, CO, SV, PAOP, SpO_2) and mixed-venous blood samples are most commonly obtained from a pulmonary artery catheter. From these measurements, additional cardiorespiratory data can be calculated using the Fick equation to describe the dynamic relationship between DO_2 and VO_2 (West, 1985). The accuracy of data calculated according to the Fick method is dependent upon the accuracy of thermodilution CO measurement and the oxygen content of arterial and mixed-venous blood (Weissman & Kemper, 1991).

Patient survival may be improved when cardiorespiratory variables are comprehensively analyzed at serial intervals and used to guide the clinical management of patients at risk for tissue oxygen deprivation (Creamer et al., 1990; Edwards, 1991). Decreased DO_2 is associated with an increase in O_2ER that maintains VO_2 constant over a broad range of deliveries. When DO_2 becomes critically low, O_2ER is maximal and any further reduction in DO_2 results in a corresponding decrease in VO_2. Below a critical level of DO_2, hypoperfusion leads to tissue hypoxia and anaerobic metabolism (Vincent, 1996). To prevent tissue oxygen deprivation, therapeutic approaches are typically designed to *maximize* VO_2 by *increasing* DO_2 via augmentation of CO, hemoglobin, and SaO_2 (Matuschak, 1997; Shoemaker, 1992; Vallet, Tavernier, & Lund, 2000). In the trauma population, researchers have found that patients who survive critical illness are more likely to respond to therapies intended to "*supranormalize*" DO_2 by increasing *both* DO_2 and VO_2 (Hayes et al., 1994; Hayes et al., 1997; Vallet & Chopin, 2000; Vallet et al., 1993). Cardiorespiratory parameters that differentiate survivors from non-survivors include higher cardiac output, higher DO_2I, and higher VO_2I (Yu, 1999). In response to interventions aimed at improving tissue oxygenation, non-survivors did not demonstrate an increase in VO_2 following therapy (Bishop et al., 1995; Heyland et al., 1996). Efficacy of interventions designed to supranormalize DO_2 and correct tissue hypoxia have not been demonstrated in cardiovascular populations. Because patients with uncompensated cardiac failure have limited ability to increase DO_2 due to fixed CO, oxygen consumption is maintained by increasing O_2ER rather than increasing cardiac output (Guzman,

Lacoma, & Kruse, 1998). Studies are needed to investigate the outcomes of critically ill patients with anemia and myocardial dysfunction who are clinically managed using DO_2I, VO_2I, and O_2ER as end-points of therapy. Reliable and practical instruments are needed in the critical care setting to facilitate rapid and continuous assessment of regional and systemic tissue oxygenation and to guide treatment and evaluate responses.

Measurement of Mixed-Venous Oxygen Saturation

Over the years, many indexes have been systematically evaluated as methods of monitoring tissue oxygenation including venous PO_2, venoarterial PCO_2, gastrointestinal pH (pHi), serum lactate, and DO_2-VO_2 relationships. Other techniques, such as direct magnetic resonance or near infrared spectroscopic measurements of tissue oxygenation would probably offer valid and reliable data but these methods have not been developed to the point of clinical applicability (Dantzker, 2001). Since the introduction of mass spectrometry and oximetry into the clinical arena in the 1980s, continuous assessment of global tissue oxygenation has been accomplished primarily using the fiberoptic pulmonary artery catheter and the reversed Fick equation (Ahrens & Rutherford, 1993; Nightingale, 1990; Weissman et al., 1984). SvO_2, is a multifactorial parameter that represents global tissue oxygenation because it reflects the balance between SaO_2, hemoglobin, cardiac output and VO_2 of all organ systems (Cernaianu & Nelson, 1993; Enger & Holm, 1990; Rutherford, 1989; White et al., 1990).

The dynamic relationship between oxygen supply and oxygen demand is expressed by the rearrangement of the Fick equation (McMichan, 1986, 1987; West, 1985):

$$SvO_2 \approx \frac{SaO_2 - VO_2}{CO \times Hb \times 1.34 \times 10} \quad \langle 3 \rangle$$

SvO_2 values between 60% to 80% are usually indicative of an adequate oxygen supply and demand balance (Ahrens & Rutherford, 1993). Noll and Fountain (1992) found that under stable conditions, SvO_2 normally fluctuates between 4% to 6% in critically ill patients. Continuous SvO_2 monitoring is useful in evaluating the body's adaptation to changing tissue oxygen demands. SvO_2 would be expected to decrease in response to a (a) reduction in oxygen diffusion across the alveolar-capillary membrane, (b) decrease in oxygen transport, or (c) increase in peripheral consumption of oxygen. On the contrary, SvO_2 would be expected to increase in response to an (a) increase in oxyhemoglobin, (b) increase in CO, or (c) decrease in peripheral utilization of oxygen (Baele et al., 1982). In the cardiovascular surgical population, decreased SvO_2 (< 65%) in the immediate postoperative period has been significantly correlated with preoperative myocardial dysfunction (LVEF < 40%) ($\rho < .02$), the duration of extracorporeal circulation ($\rho = <$ .00) (Vedrinne et al., 1997), and prolonged ICU length of stay (> 24 hours) ($\rho < .05$) (Routsi et al., 1993).

Applications of SvO_2 monitoring include trending dynamic relationships of tissue oxygen supply and demand balance, early recognition of impending cardiorespiratory decompensation, and prompt evaluation of treatment efficacy (Enger & Holm, 1990). Routsi et al. (1993) reported that SvO_2 is usually decreased when CO is < 2.0 L/min/m^2. Jamieson and colleagues (1982) found that a reduction in SvO_2 of $> 10\%$ was observed prior to changes in blood pressure, heart rate, or pulmonary capillary wedge pressure. Thus, the researchers advocated the use of SvO_2 as an early indicator of hemodynamic demise. White et al. (1990) identified SvO_2 values $\leq 50\%$ as indicative of marginal DO_2 and cautioned nurses to postpone routine procedures that could increase oxygen demand and further compromise tissue oxygenation. Hence, the concept of activity management as an important nursing intervention to preserve the balance between oxygen supply and demand was generated.

While there is general agreement among researchers that a change in SvO_2 that exceeds 10% for more than 10 minutes or a sustained SvO_2 value of $< 60\%$ may be an early indicator of physiological instability and cardiorespiratory failure and warrants critical evaluation of the specific components of SvO_2 to explain tissue oxygen imbalance (Gawlinski & Dracup, 1998; Noll & Fountain, 1990a; Pena, 1989; Winslow et al., 1990), a few researchers have challenged this position (Lewis et al., 1997; Schlichtig et al., 1986; van der Hoeven, Maertzdorf, & Blanco, 1997; van der Hoeven et al., 1999). Fundamental to the concept of SvO_2 as an accurate indicator of oxygen supply and demand balance are the inherent assumptions that normal vasoregulation of blood flow is

unimpaired and that VO_2 is equivalent to oxygen demand (Enger & Holm, 1990). Variations in the distribution of blood flow and the metabolic activity of individual tissues are not reflected by SvO_2 values. Consequently, controversy has centered around the reliability of SvO_2 monitoring and the complexity of data interpretation in the presence of decreased VO_2 (i.e., *supply dependency*), hyperoxia, or compensatory cardiovascular reflexes (e.g., arteriovenous shunt) (Cernaianu & Nelson, 1993). In these situations, SvO_2 may remain stable despite inadequacies of regional and global tissue perfusion (Ahrens & Rutherford, 1993). Therefore, SvO_2 monitoring used in conjunction with serial measurements of DO_2 and VO_2 to evaluate perfusion abnormalities and treatment efficacy has been advocated in the literature as a preferable approach to patient management (Ahrens & Rutherford, 1993; Shoemaker, 1992, 1993).

Relationship Between SvO_2 and Tissue Oxygenation Variables

SvO_2 is a reliable indicator of *global* tissue oxygen balance and is not intended to reflect the oxygenation status of specific organs (Cernaianu & Nelson, 1993). Some researchers have attempted to establish correlations between SvO_2 and the components that comprise SvO_2 (i.e., CO, SpO_2, DO_2, VO_2) (Cernaianu & Nelson, 1993; Nelson, 1986; Noll & Fountain, 1990a). However, SvO_2 represents a composite of the multiple interrelating variables such that specific relationships with the determinants cannot be inferred (Enger & Holm, 1990). An alteration in SvO_2 signals a nonspecific disruption in oxygen supply and demand balance that warrants additional investigation of the individual components of DO_2 and VO_2. SvO_2 changes can be related to alterations in

DO_2 or metabolic demands (Cernaianu & Nelson, 1993). Nevertheless, critics of fiberoptic oximetry have claimed that SvO_2 is of limited value because it does not provide specific information regarding regional hypoperfusion nor does it differentiate between changes in DO_2 or VO_2. For the purpose of simplification, an increase in SvO_2 can be thought of as an enhancement of DO_2 in relation toVO_2, whereas a decrease in SvO_2 represents a reduction in DO_2 in relation to VO_2 (Cernaianu & Nelson, 1993).

Nelson (1986) conducted a prospective study to evaluate the efficacy of continuous SvO_2 monitoring to supplement traditional hemodynamic monitoring parameters including PaO_2, cardiac output, SaO_2, and oxygen extraction ratio. Thirty-eight critically ill surgical patients were enrolled in the study. Cardiorespiratory variables were calculated using standard equations including dissolved and measured oxygen contents. SvO_2 criterion values were obtained on a calibrated laboratory co-oximeter. Arterial and venous gas tensions and pH were measured on a blood gas analyzer. Results revealed a strong association between the simultaneous SvO_2 values obtained on the bedside oximeter and the laboratory co-oximeter (r = .92, $\rho < .001$) over a wide range of values (42% - 83%). Initial in-vivo SvO_2 measurements compared to in-vitro measurements were not significantly different (M = 0.694, SD = 0.095 vs. M = 0.698, SD = 0.108; $\rho > .05$). Degree of association was not significant between continuous SvO_2 and other oxygenation variables including PaO_2 (r = .09, $\rho > .05$), SaO_2 (r = .08, $\rho >$ .05) VO_2 (r = - .10, $\rho > .05$), or C (a-v) O_2 (r = -0.25, $\rho > .05$). However, the moderately positive relationship between SvO_2 and CO (r = .40, $\rho < .025$) and DO_2 (r = .49, $\rho <$

.005) was significant. There was a very strong inverse relationship between SvO_2 and O_2ER (r = - .96, $\rho < .001$).

Nelson concluded that, except for oxygen extraction ratio, the use of continuous SvO_2 as a predictor of an individual component of DO_2 or VO_2 is unreliable and not recommended. Nelson's recommendations concur with other researchers who also observed similar correlations between SvO_2 and cardiac output and have determined that SvO_2 is not a reliable predictor of cardiac output (Noll & Fountain, 1990b; Sommers, Stevenseon, & Hamlin, 1991; Wong et al., 1992). There are inconsistencies in the research literature regarding the correlation between SvO_2 and thermodilution cardiac output (Nunez & Maisel, 1998). According to published reports, correlations between SvO_2 and cardiac index range from clinically insignificant to as high as r = .90 and appear to vary greatly between different populations (Hassan, Roffman, & Applefeld, 1987; Magilligan, Teasdall, Eisinminger, & Peterson, 1987; Noll & Fountain, 1990b; Schmidt et al., 1984). Low SvO_2 does not specify the nature of the problem but is an indication that an imbalance exists between DO_2 and VO_2. Further investigation of the oxygenation components is necessary because continuous SvO_2 monitoring cannot replace cardiorespiratory profile assessment. Stable SvO_2, however, implies that the determinants of oxygen transport balance are unchanged or that two factors are changing in equal and opposite directions. From the results of this study, it may be apparent that O_2ER, CO, DO_2 and VO_2 will influence SvO_2 to a greater extent than other variables of oxygenation (i.e., PaO_2, SaO_2). The researcher did not discuss the activity level of the

patients during the study or the degree of sedation. Methods to control for confounding environmental stressors to ensure a stable baseline SvO_2 during the study period were not discussed.

Noll and Byers (1994) conducted a study to compare SvO_2, SpO_2, and clinical parameters including heart rate (HR), and respiratory rate, and mean arterial pressure (MAP) with arterial blood gas measurements during ventilatory weaning after cardiac surgery. The authors postulated that dual oximetry (SvO_2, SpO_2) monitoring in combination with hemodynamic assessment could be used to monitor the subject's physiologic response to weaning from mechanical ventilation and reduce the need for repeated arterial blood gas measurement. Fifty-seven sets of data were obtained from a sample that consisted of 30 cardiovascular surgical patients who were normothermic (i.e., euthermic), hemodynamically stable, and in the process of being weaned from mechanical ventilation. Measurements of SvO_2, SpO_2, heart rate, respiratory rate, and mean arterial pressure were obtained at baseline and every minute for the first 10 minutes following the ventilator change and then every 5 minutes for an additional 20 minutes. Thirty minutes following ventilator adjustments, arterial blood gases were collected. Data were collected after two ventilator changes and variables comprising 57 data sets were compared. Findings indicated that SvO_2, HR, and MAP were not significantly correlated with arterial blood gas variables. However, significant relationships ($p < .01$) were observed between SpO_2 and pH ($r = .65$), $PaCO_2$ ($r = -.61$), PaO_2 ($r = .51$), and SaO_2 (r

= .66). Respiratory rate was significantly correlated ($\rho < .01$) with pH ($r = .44$) and $PaCO_2$ ($r = -.41$).

Results of the study revealed that the relationship between variables were moderate and not sufficiently strong to substitute for arterial blood gas analysis while weaning from mechanical ventilation. Pulse oximetry may be useful in monitoring trends in pH, $PaCO_2$, and oxygenation, whereas measures of respiratory rate may be useful in monitoring pH and $PaCO_2$. Monitoring SpO_2 and respiratory rate may be useful to identify the need for obtaining arterial blood gas analysis. The usefulness of monitoring continuous SvO_2 during weaning was not demonstrated. Weaning from mechanical ventilation was initiated at different times during the postoperative period. Because physiological responses (i.e., hemodynamic fluctuations) are expected to be very different between the early and late postoperative period, timing of wean could potentially introduce variability into the study. Information regarding medications (analgesics, anxiolytics) received prior to or during the study was not provided and it is not clear to what extent these confounding variables were controlled (Noll & Byers, 1994).

Van der Hoeven and colleagues (1997) studied the relationships between SvO_2 and other tissue oxygenation variables (VO_2, DO_2, O_2ER) during conditions of tissue hypoxia related to anemia and hypoxemia. The tightly controlled study was conducted in a laboratory setting and utilized mechanically ventilated piglets between 10 and 14 days of age. Baseline Hb was maintained at 5 g-/dl ± 1.0 while the researchers induced varying

degrees of progressive graded hypoxemia by changing the proportion of oxygen/nitrogen in the inspiratory gas (1.0 to .01) to reduce DO_2. Linear analysis demonstrated a strong positive correlation between SvO_2 and DO_2 ($r = .87$, $\rho < .000$). A critically low DO_2 value of 11.82 ml/kg/min was associated with a significant reduction in VO_2 (2.25 ml/kg/min). Above the critical DO_2 level, a change in VO_2 was only slightly dependent on DO_2; whereas, below the critical DO_2 value, VO_2 was significantly dependent on DO_2.

Interestingly, initial reduction of SvO_2 was not associated with a reduction in VO_2 or an increase in lactate. On average, lactate, lactate/pyruvate ratio, and VO_2 remained unaltered until SvO_2 decreased below 15%. Decreases in SvO_2 corresponded to decreases in SaO_2 and maintained a stable difference between arterial and venous oxygen content ($C[a - v]O_2$) and preserved a constant VO_2 until FiO_2 was reduced to .10. Findings suggested that SvO_2 levels below 15% were very frequently associated with oxygen-restricted metabolism (i.e., anaerobic metabolism) and SvO_2 values above 40% were not associated with oxygen-restricted metabolism and can be interpreted as an indication of normal tissue oxygenation. The authors concluded that a reduction in SvO_2 is not necessarily an indicator of oxygen-restricted metabolism and lactic acidosis, and that low SvO_2 (15% to 40%) may be associated with both normal tissue oxygen metabolism and oxygen-restricted metabolism. Furthermore, a reduction in SvO_2 should be interpreted as a (a) reduction of the residual oxygen after tissue oxygen extraction without necessarily affecting VO_2, (b) change of one or more factors that determine the balance between DO_2 and VO_2, and (c) warning that with further reduction, oxygen-

restricted metabolism may develop. The authors concluded that their findings concurred with those of Schlichtig and colleagues (1986) who reported that patients with chronically low CI (range 1.10 to 1.77 L/min/m^2) were able to tolerate very low SvO_2 (range 19.5% to 40%) without increased mortality or morbidity for sustained periods. In the Schlichtig study that consisted of three subjects, there was no correlation between CO and SvO_2 and the highest VO_2 was associated with the lowest SvO_2 as a result of increased O_2ER (.56 to .80).

Summary of Research on Measurement of Tissue Oxygenation

SvO_2 is a multifactorial parameter that reflects a global balance of four variables including CO, Hb, SaO_2, and VO_2 (Jamieson et al., 1982). The dependence of SvO_2 on all of these variables emphasizes that an alteration in SvO_2 does not indicate clearly which of the principal determinants has changed, but merely implies a nonspecific disruption in dynamic oxygen balance. Thus, it is important to interpret SvO_2 in relation to the parameters of oxygen delivery (CO, Hb, SaO_2) and oxygen consumption (VO_2). Researchers generally agree that an increase in oxygen consumption or a decrease in cardiac output, hemoglobin concentration, or arterial oxygen saturation will produce a decrease in SvO_2. Collectively, researchers do not recommend substituting SvO_2 for serial assessment of individual DO_2 components and VO_2 during periods of clinically significant physiological changes.

Summary

Researchers have consistently demonstrated that PaO_2 is significantly higher when patients who have unilateral lung disease are positioned with the non-diseased lung in the dependent position. Cardiovascular surgical patients are more likely to demonstrate decreased PaO_2 in the left lateral position because of the high incidence of left lower lobe atelectasis following cardiovascular surgery; however, changes in PaO_2 related to *position* effect are not usually clinically important. Nevertheless, individual response to position changes may be significant and therefore responses should be evaluated on an individual basis.

Several researchers have demonstrated that the *left* lateral position is associated with significantly higher cardiac output that is attributed to an increase in right ventricular end-diastolic pressures and stroke volume. In a well controlled study, Bridges et al. (2000) demonstrated that PAP was higher when cardiovascular surgical patients were positioned in a 30-degree left lateral position. Research findings regarding the effects of the *right* lateral position on hemodynamic indices are inconsistent. Controversy also exists in the research literature about the reliability of hemodynamic pressure measurements obtained in the lateral position. Based on the findings of several studies, results suggest that the angle-specific left atrial reference point for referencing the transducer in the lateral positions is associated with reliable measurements.

Researchers consistently have demonstrated that critically ill patients typically experience a transient 8% to 12% decrease in SvO_2 and a 20% to 50% increase in VO_2

immediately following lateral positioning. Typically, maximal decrease in SvO_2 is observed between minutes 1 and 2 following the turn and returns to baseline within 4 to 5 minutes. In comparison, VO_2 may remain elevated for up to 45 minutes following the turn. In individual cases, SvO_2 decreased erratically in patients with a low cardiac output or low hemoglobin and in patients who became agitated during positioning (Gawlinski & Dracup, 1998; Lewis et al., 1997; Winslow et al., 1990). Researchers concluded that patients with low CO are the most vulnerable to the adverse effects of positioning because they have limited ability to increase oxygen delivery when oxygen demand increases (Gawlinski & Dracup, 1998; Winslow et al., 1990). Cardiovascular surgical patients comprised a significant proportion of the sample in most of the studies. Several researchers have demonstrated that critically ill patients experience the greatest reductions in SvO_2 immediately after turning to the left lateral position compared with the right lateral position (Gawlinski & Dracup, 1998; Lewis et al., 1997; Shively, 1988). Interestingly, other researchers have demonstrated that cardiac output, stroke volume and PAP are higher in the left lateral position (Bridges et al., 2000; Carroll, 1992; Doering & Dracup, 1988; Whitman et al., 1982).

Routsi and colleagues (1993) demonstrated that the progressive increase in VO_2 observed during the initial 24-hour period following cardiovascular surgery is primarily related to an increase in cardiac output and DO_2. When cardiac function is compromised, O_2ER increases and SvO_2 decreases. Few researchers have comprehensively explored temporal relations between tissue oxygenation variables (CO, SVI, heart rate, SaO_2,

O_2ER, and VO_2) to explain the variability in SvO_2 following lateral positioning. However, three studies demonstrated that lateral positioning is associated with an immediate increase in cardiac output, stroke volume, heart rate and O_2ER (Cohen et al., 1996; Horiuchi et al., 1997; Weissman & Kemper, 1993).

Through systematic evaluation, numerous researchers have demonstrated that morphine (0.20 – 0.5 mg/kg iv) attenuates the stress response to surgical recovery and reduces VO_2 in critically ill patients including those with cardiovascular disease (Alderman et al., 1972; Bernard et al., 1988; Colonna-Romano & Horrow, 1994; Rouby et al., 1981; Rouby et al., 1979). Several researchers have attributed these effects to morphine-induced "hemodynamic sedation" that produce significant reductions in cardiac index, stroke volume index, cardiac filling pressures, and heart rate (Rouby et al., 1981).

This study was designed to contribute to the body of knowledge on lateral positioning and tissue oxygenation. This study differs from other studies that have examined manipulations of tissue oxygen consumption and physiological adaptation to increases in VO_2 in the following ways:

1. The effect of lateral positioning on tissue oxygenation is described in critically ill patients who have low oxygen delivery. Other than one study that evaluated patients with low LVEF (Gawlinski & Dracup, 1998), the majority of studies have focused on cardiovascular surgical patients and heterogeneous critically ill populations without regard to DO_2I. It is important to study the effects of lateral positioning on tissue oxygenation in patients with low DO_2I who (a) have limited ability to increase CO as a

result of preoperative and/or postoperative myocardial depression and (b) are likely to have limited ability to increase O_2ER due to low hemoglobin levels. Critically ill patients who have low DO_2I, secondary to reduced hemoglobin and myocardial depression, have limited cardiorespiratory reserves to adapt to increases in oxygen demands. Therefore, these patients may be at risk for complications related to routine nursing procedures (i.e., lateral positioning) that increase oxygen demand.

2. The contributions of DO_2 and VO_2 to the variance in SvO_2 following lateral positioning were explored using independent instruments to calculate DO_2 and measure VO_2, thus the methodological issues pertaining to "mathematical coupling" between calculated indices that share variables was eliminated. Furthermore, VO_2 was measured through indirect calorimetry rather than derived from the Fick equation, which may reduce measurement error (Vincent, 1996). Cardiac output was measured continuously. The continuous cardiac output (CCO) measurement represented a composite of many measurements (i.e., averaged value) and was updated every 20 seconds; thus, the likelihood of measurement error was reduced. The majority of research studies have not explored the temporal relations among the components of DO_2, VO_2 and SvO_2. The studies that have explored the relations among tissue oxygenation variables have used measures of thermodilution cardiac output, SpO_2, hemoglobin, and SvO_2 to calculate VO_2.

3. There are no published research studies that have evaluated a nursing intervention to decrease oxygen demands and support adaptation in patients with

compromised tissue oxygenation. Research is needed to identify nursing interventions that support, improve, or restore tissue oxygenation and enhance physiologic adaptation to nursing care activities.

CHAPTER 3

PROCEDURE FOR COLLECTION AND TREATMENT OF DATA

A prospective, single group, quasi-experimental, repeated measures, factorial design (Cook & Campbell, 1979) was used to determine the effects of morphine sulfate (hereafter referred to as morphine) on tissue oxygenation variables following lateral positioning. Subjects served as their own controls and the effects of the independent variables were inferred from making multiple comparisons of the dependent variables before and after the introduction of the treatments. A within-subjects factorial design was used to examine the effects of the independent variables (i.e., morphine, propofol, lateral positioning) on the dependent measurements of tissue oxygenation variables that included mixed-venous oxygen saturation (SvO_2), oxygen consumption (VO_2), oxygen delivery (DO_2), and oxygen extraction ratio (O_2ER). Planned analyses of the first three hypotheses, the 2 x 2 cell structure for evaluating tissue oxygenation following lateral positioning included two levels of morphine and time (Table 3).

Design

Because of the numerous (a) complexities of the population and research phenomenon, (b) confounding variables, and (c) legitimate challenges associated with controlling physiologic processes, the practicalities associated with obtaining a control group for comparison purposes would have hindered the research process. Therefore, a *within-group design* was selected to eliminate the effects of numerous innate

confounding variables on tissue oxygenation such as gender, age, muscle mass, comorbidity, cardiorespiratory illness, and cellular metabolic rate (Leach & Treacher, 1994; Verderber & Gallagher, 1994). Collectively, cardiovascular surgery, general anesthesia and extracorporeal circulation introduce numerous confounding variables that are unique to this population and significantly alter cardiorespiratory function. Physiological derangements associated with hemolysis, hemodilution, anticoagulation, hypothermia, and hypovolemia produce significant physiologic variation in the immediate and early postoperative periods (Seifert, 1994; Weiland & Walker, 1986). Rapid temperature, pH, and hemoglobin fluctuations universally affect cardiovascular patients in the early postoperative periods (Brown, 1992; Gilski, 1993; Moreno-Cabral, Mitchell, & Miller, 1988; Seifert, 1994; Weiland & Walker, 1986). The significant impact of these factors on cardiorespiratory variables have been well described in the research literature (Casutt et al., 1999; Jamieson et al., 1982; Magilligan et al., 1987; Osguthorpe et al., 1990; Phillips, 1997; Pond et al., 1992; Schmidt et al., 1984; Vedrinne et al., 1997). A within-group design was selected because it is not possible to eliminate the influences of these physiologic processes in the human model nor was it feasible, given the available resources, to recruit a homogeneous group of subjects in whom these baseline factors were equally distributed. Because the within-subject variability is usually less than the between-subject variability, the precision of the experiment is improved when subjects serve as their own controls, thus yielding more power for within-subjects

designs (Cook & Campbell, 1979; Hulley & Cummings, 1988; Maxwell & Delaney, 1990).

Repeated measures designs are commonly used to study physiological responses (Cook & Campbell, 1979). Cardiorespiratory measurements are continuous, dynamic and respond rapidly to stimuli therefore, repeated measurements collected over a short period of time (i.e., minutes) are feasible. Use of the factorial design to guide the methodology was logical because the independent variables were rapidly administered and had almost immediate impact or causation on the dependent variables (Cook & Campbell, 1979). The onset of morphine's effect occurs within 5 to 10 minutes following intravenous administration and peak effects are achieved within 10 to 20 minutes (Hall et al., 2001). Maximal SvO_2 response following lateral positioning occurs within 1 to 2 minutes (Gawlinski & Dracup, 1998). Although researchers have not explicitly reported the time interval following lateral positioning that is associated with maximal VO_2 response, findings suggest that the maximal VO_2 response occurs within 0 to 5 minutes following the event (Gawlinski & Dracup, 1998; Horiuchi et al., 1997; Verderber & Gallagher, 1994).

Dependent and independent variables. Because it is not possible to *directly* measure cellular oxygenation in the clinical setting, physiologic adaptive responses were indirectly examined through variables that reflect tissue oxygenation including SvO_2, DO_2, O_2ER, and VO_2. Independent or treatment variables included morphine, morphine and propofol, and time following lateral positioning. To assess the immediate and short-

term effects of lateral positioning on tissue oxygenation, data were collected immediately prior to each turn (baseline) and for 10 minutes following each turn. SvO_2 and VO_2I were measured every 1 minute following the turn for 10 minutes and DO_2I and O_2ER were measured at baseline and at minutes 3, 5 and 10 following the turn. Due to continuous cardiac output (CCO) instrumentation lag times, CCO measurements obtained before 3 minutes following the turn would have introduced measurement error for calculations requiring CO/CI data (i.e., DO_2I, O_2ER). Measurement intervals were scientifically selected to capture the maximal response and early recovery of tissue oxygenation variables associated with an acute increase in oxygen demand. To account for differences related to body habitus, tissue oxygenation and cardiorespiratory variables were indexed to body surface area (BSA) according to the DuBois equation (DuBois & DuBois, 1916):

$$BSA \approx (W[\text{weight}]0.425 \times H[\text{height}]0.725) \times 0.007184 \quad \langle 4 \rangle$$

Indexed measurements were distinguished with an "I" symbol following the acronym (e.g., DO_2I, VO_2I). Cardiorespiratory data including mean, systolic, and diastolic arterial pressure (MAP, SAP, DAP); heart rate (HR); right atrial pressure (RAP); mean, systolic, and diastolic pulmonary artery pressure (PAM, PAS, PAD); pulmonary artery occlusion pressure (PAOP); cardiac index (CI); stroke volume index (SVI); left ventricular stroke work index (LVSWI); and, systemic vascular resistance index (SVRI) were collected at baseline and at serial intervals (i.e., 3, 5, and 10 minutes) during the study procedures to (a) describe the population, (b) explain the physiological responses to lateral positioning

and morphine, and (c) explore the temporal relations between tissue oxygenation variables.

During the control (phase I) and treatment (phase II) phases of the study, physiological response patterns following lateral positioning were explored through tissue oxygenation variables (SvO_2, VO_2) and temporal relationships between the variables were examined. The second phase of the study entailed administering morphine before the second turn sequence with the aim of attenuating the effects of skeletal muscle movement on metabolic and cardiorespiratory processes, thereby minimizing changes in tissue oxygenation. Because 50% of the sample had a propofol infusion during data collection, analyses were also performed to evaluate the interactions between morphine and propofol. Thus, the first phase involved quantifying the cardiorespiratory and metabolic responses to lateral positioning without the condition of morphine whereas, the second phase involved quantifying the cardiorespiratory and metabolic responses to lateral positioning with the condition of *preprocedural* morphine. Because the effects of a supine to lateral position change on tissue oxygenation in critically ill patients have been documented by many researchers (Gawlinski & Dracup, 1998; Horiuchi et al., 1997; Winslow et al., 1990), lateral positioning was selected as the *stimulus* to induce an acute increase in oxygen demand for the purpose of testing the effects of morphine during a hypermetabolic state.

Prior to obtaining baseline measurements, SvO_2 and VO_2 were recorded every 15 seconds over a 1-minute period to ensure stability of baseline measurements during both

phases of the study. During the first phase of the study, the subject was passively turned (i.e., without assisting) from the supine to lateral position and serial measurements of the dependent variables, without the effects of morphine, were obtained during a 10-minute period. Ten minutes following the first lateral position change, the subject was turned to the supine position and morphine was administered intravenously using a standard dose of 0.10 mg/kg based on ideal body weight (IBW). Twenty minutes after receiving morphine, the subject was turned from the supine to lateral position and serial measurements of the dependent variables, with the effects of morphine, were obtained during a 10-minute period. Identical positioning techniques were used for both turn sequences. The data collection period was estimated to be 50 minutes in duration. The sequence of treatment and observations is schematically represented in Table 4.

Limitations and control measures. Dependent variables were measured following a supine to 45-degree lateral positioning sequence in either the left or right lateral position during both phases of the study. To avoid placing undue stress on the subjects' delicate oxygen reserve capacity caused by multiple turning procedures, dependent variables were measured following a supine to lateral position change to either the left or the right position, but not both. Consequently, the effects of a lateral to supine position change were not explored and within-subject comparisons between the left and right lateral positions were not evaluated. To control for *position effects*, subjects were randomly assigned to either the left or right 45-degree lateral position by lottery method. Individual variation in cardiorespiratory parameters has been documented between the

left and right lateral positions (Emerson & Banasik, 1994; Gawlinski & Dracup, 1998; Shively, 1988). According to researchers, some subjects experience larger cardiorespiratory fluctuations in the right lateral position, whereas other subjects demonstrate greater changes in the left lateral position. Within-subject variation has also been observed between supine to lateral positioning and lateral to supine positioning sequences. For example, Tidwell et al. (1990) reported significantly larger reductions in SvO_2 following a supine to lateral position change compared with a lateral to supine position change ($\rho < .00$). Therefore, for the current study, measurements of the dependent variables were obtained in the same position during both phases of the study.

To reduce the effects of extracorporeal circulation and emergence from anesthesia that produce significant variability in physiological measurements during the immediate postoperative period (< 6 hours following surgery), data were collected between the 6^{th} and 24^{th} postoperative hour. Furthermore, the 18-hour period for data collection following arrival to the cardiovascular intensive care unit was used to control for progressive improvement (e.g., *maturation effects*) in tissue oxygenation that was anticipated throughout the recovery period as a result of continual therapeutic interventions aimed at maximizing physiological parameters coupled with the benefits of cardiovascular surgery. Noll and colleagues (1994; 1990b; 1991) found that in comparison with other heterogeneous populations of medical and surgical ICU patients, cardiovascular surgical patients have different *normal* variations in SvO_2 at rest. Because of the inherent differences in resting metabolic requirements and cardiorespiratory

reserves among subpopulations of critically ill patients, controlling for time following surgery facilitated homogeneity within the sample and ensured a reasonable recovery time to avoid the extreme fluctuations associated with the immediate postoperative period. During the 50-minute data collection period, extraneous variables that could confound the effects of the treatment variable such as oxygen therapy, inotropic therapy, blood replacement, or environmental stimuli were held constant.

A limitation of using the repeated measures design was the potential threat to internal validity if changes in the dependent measurements were related to *secular effects* or *historical effects* rather than treatment effects (Hulley & Cummings, 1988). Noll and Fountain (1990a) determined that under relatively stable conditions, SvO_2 normally fluctuates from - 4.6% to 1.8% around baseline values in cardiovascular surgical patients. In the current study, the probability that physiological variations were related to historical effects was minimal because the time period between the first and final measurement was less than 1 hour. To avoid the statistical phenomenon of *regression to the mean* in the absence of a control group (Bland & Altman, 1994; Hulley & Cummings, 1988), normal variation in tissue oxygenation as measured by the dependent variables (e.g., SvO_2, VO_2) was accounted for in the study by identifying within-subject changes of < 10% from baseline as clinically insignificant and unrelated to the treatment variable (e.g., morphine, propofol).

Another potential threat to internal validity was systematic bias relating to *practice effects* (Cook & Campbell, 1979) due to the subject's previous exposure to

lateral positioning in the first phase of the experiment. Pena (1989) found that cardiovascular surgical patients who were turned twice during a 2-hour period experienced an immediate decrease in SvO_2 (8.5%) during the first turn sequence and an even larger drop in SvO_2 (12.3%) following the second turn sequence ($\rho = .022$). At least 20 minutes elapsed between turn sequences. Following the first and second lateral positioning sequences, SvO_2 returned to baseline within 4 minutes following the turn and remained at baseline 20 minutes later (Pena, 1989). Regardless of the positioning sequence or the number of position changes, the effect of lateral positioning on cardiorespiratory variables (e.g., SvO_2, SpO_2, BP, HR) is of relatively short duration and equilibration with baseline values typically occurs within 5 minutes (Atkins et al., 1994; Gawlinski & Dracup, 1998; Noll & Fountain, 1990a; Pena, 1989; Shively, 1988; Tidwell et al., 1990; Winslow et al., 1990). Use of subjects as their own control is appropriate for studies involving treatments that have a short-duration effect and/or the effect of the initial treatment dissipates before the observation of a subsequent treatment or condition (Hulley & Cummings, 1988; Kirk, 1982). Therefore, practice effects associated with multiple turn sequences were unlikely to have threatened the internal validity of the study.

When intravenously administered in dosages of 2 to10 mg, morphine's onset of action occurs within 5 minutes and peak effects occur within 10 to 20 minutes. Steady-state serum concentrations occur in 20 to 40 minutes with duration of action lasting 1 to 3 hours, and elimination occurring within 1.5 to 2 hours after administration (Mason, 1993;

Turkoski, Lance, & Bonfiglio, 1999). To ensure a maximal steady state of effect of morphine, subjects were repositioned 20 minutes after receiving the morphine intervention. Counterbalancing the design by random assignment to treatment sequences (i.e., crossover design) was not possible because of the sustained or residual effects (e.g., *carry over effects*) of morphine for 1 to 3 hours following the administration time. Consequently, the sequence of the treatment remained constant and morphine was administered in the second and final phase of the study; therefore, control always preceded treatment.

To standardize the treatment intervention according to body habitus, morphine dosages (0.10 mg/kg iv) were based on the subject's *ideal* body weight (IBW) in kilograms. Based on an equation that assumes an adult medium body frame and adjusts for gender differences (Cheymol, 1988, 1993, 2000; Pai & Paloucek, 2000), ideal body weight was calculated using the formulas:

$$\begin{aligned} &\text{IBW male} = 50\text{kg} + 2.3\text{kg for each 1" inch} > 5 \text{ feet} \\ &\text{and,} \\ &\text{IBW female} = 45.5\text{kg} + 2.3\text{kg for each 1" inch} > 5 \text{ feet} \end{aligned} \qquad \langle 5 \rangle$$

The IBW formula was not adjusted for renal or liver dysfunction. The standardized morphine dose of 0.10 mg/kg was based on published clinical guidelines for acute pain and sedation management (Jacobi et al., 2002; Shapiro et al., 1995) as well as the standard of care at the research facility for treating acute postoperative pain following cardiovascular surgery. For the relief of acute postoperative pain, evidence-based clinical practice guidelines recommend intravenous morphine 2 to 10 mg every hour as needed

(Jacobi et al., 2002; Shapiro et al., 1995). Morphine dosages between 0.2 to 0.5 mg/kg have been found to attenuate metabolic responses and decrease tissue oxygen consumption (Colonna-Romano & Horrow, 1994; Rouby et al., 1981; Rouby et al., 1979).

Setting

The study was conducted in the adult cardiovascular intensive care unit (ICU) at the First Hill Campus of Swedish Medical Center in Seattle, Washington. This facility is a 697 bed, not-for-profit, private, teaching hospital that hosts the largest adult cardiovascular surgical program in the Pacific Northwest region of the United States. Approximately 65 to 80 adult patients who have undergone various cardiothoracic surgical procedures, primarily coronary artery bypass and valvular replacement, requiring extracorporeal circulation are admitted into the cardiovascular ICU monthly. The cardiovascular ICU has 16 private rooms that are fully equipped with state-of-the-art monitoring capabilities (Model M1176A, Agilent CMS Technologies, Waltham, MA) for assessing cardiorespiratory variables including a Q-Vue™ CCO Monitoring System™ (Abbott Critical Care Systems, Chicago, IL) for displaying continuous cardiac output and index, systemic vascular resistance and core blood temperature. Digital and analog data from the Q-Vue™ computer were incorporated into the bedside monitoring system through the VueLink™ interfacing module (Model M1032A, Agilent CMS Technologies) that enabled the data to be trended, recorded and inserted into hemodynamic and oxygenation calculations. The bedside monitor simultaneously and continuously displayed 16 digital numbers and 8

analog waveforms. Digital measurements were updated every 2 seconds (Hewlett Packard, 1992). The bedside monitoring system was interfaced to a computerized documentation system (Continuum 2000, Eclipsys Corporation, Delray Beach, FL) that stored the measured and calculated physiological data, laboratory test results, medication records, and nursing documentation records indefinitely.

A laboratory co-oximeter (Model IL 482, Instrumentation Laboratory, Lexington, MA) was available in the main laboratory to measure criterion reference values for instrument calibration and to obtain measured hemoglobin values. A blood gas analyzer (Model 288, CIBA-Corning Diagnostic Corporation, Medfield, MA) was also available in the main laboratory for obtaining baseline clinical characteristics. The instruments were maintained by the laboratory staff and were recalibrated every 8 hours according to the manufacturer's specifications and in compliance with hospital-laboratory accreditation standards. Point-of-care blood analysis instruments (Model M1022A, Agilent CMS Technologies) used in conjunction with I-Stat® cartridges (I-Stat® Corporation, Princeton, NJ) were also available at each patient bedside for simultaneous quantitative determination of arterial blood gas, hemoglobin, and chemistries.

Population and Sample

The accessible population included patients $\geq$ 18 years of age, admitted to the cardiovascular ICU, who had undergone cardiovascular surgery with extracorporeal circulation within the past 6- to 24-hour period, were mechanically ventilated and had low oxygen delivery as evidenced by repeated measurements of $DO_2I < 500$ ml/min/m^2.

Although there are differences in metabolic requirements between pediatric and adult populations (Pannemans & Westerterp, 1995; Shimokata & Kuzuya, 1993), the sample was limited to adults primarily because of legal issues pertaining to research involving minors (i.e., < 18 years of age) that would have required additional resources for informed consent. Additional resources would have also been required for obtaining informed consent for non-English speaking patients. Because of limited resources, the sample was limited to English-speaking adults.

Eligibility Criteria

For the purposes of efficacy research in determining the probability that an intervention is beneficial within a specified population, sampling criteria must be stringent to minimize confounding variables and to maximize the interpretation of the intervention effect (Whittemore & Grey, 2002). In addition to ensuring hemodynamic stability and a low DO_2I state, inclusion criteria were designed to control for extraneous variables within the sample that contributed to physiologic variability and affected the oxygen transport system, basal metabolic demands, or treatment response such as age, pulmonary disease, amount of respiratory support, temperature extremes, degree of anemia, and physiological fluctuations relating to extracorporeal circulation (Ahrens & Rutherford, 1993; West, 1985). Eligibility criteria for subject inclusion were:

1. Greater than or equal to 18 years of age.
2. Ability to read and speak English.

3. Status- post cardiovascular surgery with extracorporeal circulation within the past 6 to 24 hours.
4. Mechanical ventilation with positive end-expiratory pressure (PEEP) $\leq$ 10 cm H_2O and $FiO_2 < .80$.
5. Functional intra-arterial catheter defined as presence of blood return.
6. Functional fiberoptic pulmonary artery catheter verified to be in the pulmonary artery by radiographic confirmation and waveform analysis.
7. Sustained low oxygen delivery defined as two or more calculations of $DO_2I < 500ml/min/m^2$ within the hour prior to the start of study procedures.
8. Hemodynamic stability defined as a baseline systolic blood pressure $\geq$ 90 mm Hg and heart rate between 60 to 125 beats per minute.
9. No documented or known contraindications to receiving morphine (e.g., allergy, intolerance).
10. Written physician order to receive intravenous morphine.
11. Hemoglobin value $\geq$ 7.0 g-/dl (gram/deciliter) at time of enrollment.
12. Normothermia as evidenced by pulmonary artery blood temperature 36.5°C to 38.0°C.
13. Hemostasis as evidenced by chest drainage < 100 ml/hr during the 2-hour period preceeding the start of study procedures.
14. No mediastinal or pleural air leak observed in the chest drainage system.

15. Absence of shivering as evidenced by no repetitive involuntary skeletal muscle contractions.

16. No contraindications to lateral positioning (i.e., open sternum).

Energy expenditure and VO_2 is significantly affected by the intensity of work of breathing, especially in patients with impaired pulmonary function (Kanak, Fahey, & Vanderwarf, 1985; Kersten, 1989; Noll & Byers, 1995). VO_2 may increase by as much as 40% as the result of an increase in work of breathing (Kanak et al., 1985). Increased VO_2 of the respiratory muscles reflects an increase in the amount of work required to ventilate the lungs and is associated with alterations in airway resistance and compliance (Kanak et al., 1985; West, 1985). To minimize differences in spontaneous respiratory effort, strength and fatigue, subjects who qualified for enrollment into the study were mechanically ventilated. Positive end-expiratory pressure that exceeds 10 cm H_2O may decrease cardiac output, DO_2 and impair pulmonary blood flow (Copel & Stolarik, 1991; Ng & McCormick, 1982). Therefore, patients who required PEEP > 10 cm H_2O were not eligible to participate in the study. According to the Puritan-Bennett® 7250 Metabolic Monitor Operator's Manual (Puritan-Bennett, 1995), metabolic measurements obtained through indirect calorimetry are less reliable and accurate if (a) FiO_2 exceeds 0.8%, or (b) a system air leak is present. Therefore, patients who required FiO2 > .80 or those who had a visible mediastinal or pleural air leak evidenced by continuous bubbling in the water seal chamber of the closed chest drainage system were not enrolled into the study.

According to clinical practice guidelines, routine lateral positioning and activity progression following cardiovascular surgery are not initiated until hemodynamic stability is achieved (Ng & Nuckols, 1986; Winslow et al., 1995; Zevola et al., 1997). Because transient reductions in cardiac output, left ventricular end-diastolic pressure, and arterial blood pressure may be associated with morphine due to histamine release and peripheral vasodilation (Alderman et al., 1972; Mason, 1993), minimum blood pressure parameters were defined to avoid enrolling patients who had increased risks for cardiovascular instability following treatment procedures. Hemodynamic requirements for study participation included a minimum systolic blood pressure of 90 mm Hg and a heart rate between 60 and 125 beats per minute that was indicative of "hemodynamic stability."

Temperature and shivering have a profound impact on energy expenditure and VO_2 (Osguthorpe et al., 1990; Phillips, 1997). Theoretically, temperature affects peripheral vascular resistance and may alter the circulation and response time of intravenous morphine (Rodriguez et al., 1983). For every 1° C increase in temperature, VO_2 increases by 10% (Ahrens & Rutherford, 1993). Shivering, an iatrogenic complication of induced hypothermia and sympathetic stimulation, is frequently observed in the immediate period following cardiovascular surgery and can increase VO_2 three to fivefold over baseline (Phillips & Skov, 1988; Phillips, 1997). Therefore, only patients who were normothermic (e.g., euthermic) and demonstrated no signs of shivering were eligible to participate in the study.

Hemoglobin, a primary component of DO_2 and VO_2, is unstable during acute blood loss and may fluctuate during blood or fluid replacement therapy. To eliminate discrepancies related to degree of anemia and the influence of significantly reduced oxygen-carrying capacity on tissue oxygenation and gas exchange, subjects who had a hemoglobin value of < 7.0 g-/dl were not eligible to participate in the study. According to the cardiovascular surgery blood transfusion guidelines used at Swedish Medical Center, cardiovascular surgical patients who have persistently low SvO_2 are eligible to receive a blood transfusion when the hemoglobin is less than 8 or 9 g-/dl to optimize oxygen-carrying capacity, while those with normal SvO_2 are eligible to receive a blood transfusion when the hemoglobin level drops below 7.5 g-/dl. Therefore, subjects admitted into the study were expected to have higher hemoglobin levels. To ensure hemoglobin stability and hemostasis during the data collection period, subjects who had significant blood loss defined as mediastinal or pleural drainage > 100 ml/hr for the 2-hour period preceding data collection were not eligible to participate in the study.

Exclusion Criteria

Exclusion criteria were used to decrease the threats to internal validity by minimizing or eliminating factors that may influence tissue oxygenation or metabolic requirements other than lateral positioning and morphine. Following an extensive review of the literature, pathological diseases and conditions have been identified that may account for differences in the dependent variables. Accordingly, potential subjects who

were designated as eligible to participate in the study were not enrolled into the study if one or more of the following conditions existed:

1. Documented infection or sepsis in the medical record and substantiated by complete blood count (CBC) with differential analysis, persistent temperature elevation > 38.5° C, pulmonary infiltrates on chest radiograph, and positive blood, sputum, urine, or wound cultures documenting organism (Mandell, 2000) .

2. Preexisting documented pulmonary disease requiring home treatment including asthma, chronic obstructive lung disease, or restrictive lung disease.

3. Unrepaired or palliative repair congenital cardiac anomaly.

4. Documented acute respiratory failure with refractory hypoxia.

Chronic obstructive pulmonary disease, interstitial lung disease, asthma, and acute respiratory failure are pathological conditions that alter ventilation-perfusion distribution and interfere with gas exchange and DO_2 (Ng & McCormick, 1982). Researchers have observed significant differences in oxygenation values (e.g., PaO_2) following lateral positioning when subjects have unilateral or bilateral pulmonary disease (Brooks-Brunn, 1995; Ng & McCormick, 1982; Zack et al., 1974). Furthermore, morphine may trigger histamine-release causing bronchospasm in patients who have asthma (Mason, 1993). Therefore, patients with a documented history of chronic obstructive pulmonary disease,

interstitial lung disease, asthma, and acute respiratory failure were excluded from participating in the study. Pulmonary and cardiac shunting may be associated with congenital cardiac anomalies and may affect cardiac output and produce mixing of arterial and venous blood. For that reason, patients with unrepaired or palliatively repaired congenital cardiac abnormalities were excluded from participating in the study.

Disqualification Crteria

To ensure patient safety and to control for the effects of extraneous variables on cardiorespiratory measurements introduced during data collection procedures, conditions and criteria were identified that mandated subject disqualification and study abortment. Disquaification criteria incuded:

1. Hemodynamic instability defined as systolic blood pressure < 90 mm Hg for more than 1 minute or the development of lethal dysrhythmias.
2. Bleeding as evidenced by pleural or mediastinal drainage in chest drainage system ≥ 100 cc during data collection period.
3. Administration of a blood transfusion.
4. Administration of fluid (i.e., volume, normal saline, 5% albumin) ≥ 200ml delivered in ≤ 30 minutes for the purpose of supporting blood pressure.
5. Administration of an analgesic, anxiolytic, anesthetic or paralytic agent.
6. Administration of a diuretic or cardiac medication

7. Titration of the dosage of a vasoactive or inotrope drug infusion.

8. Titration of propofol infusion.

9. Adjustments in ventilator settings (i.e., FiO_2, rate, volume, or PEEP).

10. Procedure or treatment that required patient movement or acknowledgement other than study procedures (i.e., endotracheal suctioning).

5. Shivering as observed by repetitive involuntary skeletal muscle contraction.

11. Disruption of study protocol by patient care activities/procedures.

12. Subject or family request to withdraw from study.

To decrease the risks of cardiorespiratory demise during study procedures, a reduction in systolic blood pressure below < 90 mm Hg for more than 1 minute was used to signal physiologic intolerance and prompted study termination. According to Guyton (1986), if systolic blood pressure decreases below 80 or 90 mm Hg in the presence of coronary heart disease, cardiac deterioration may occur. Intravascular fluid shifts and diuretic therapy may trigger hemoglobin fluctuations and preload changes, resulting in CO fluctuations. Because of the effects on DO_2 and oxygenation variables, subjects who required blood replacement therapy, fluid resuscitation, or diuretic therapy during the study procedures would be disqualified and the study would be terminated. For reasons

previously discussed, evidence of shivering during the data collection period mandated disqualification and study termination.

Prospective Power Analysis

Statistical power was estimated using *maximal* VO_2 response to lateral positioning as the primary outcome. Prospective power analysis was conducted using data obtained during the pilot study on a sample of five subjects (Jesurum, 1996) and compared to the data of Swinamer et al.(1987), Verderber and Gallagher (1994) and Weissman et al. (1984) who demonstrated that lateral positioning was associated with a 20% to 31% maximal increase in VO_2 from baseline. Based on the results of the pilot study, mean VO_2I increased by 18.4% from baseline ($M_1 = 121$, $SD = 33.06$) to minutes 1 through 5 ($M_2 = 141$, $SD = 34.72$; $d = 20.84$ ml/min/m^2, $SD = 19.54$) and 10.3% from baseline to minutes 6 through 10 ($M_2 = 132$, $SD = 37.94$; $d = 11.44$, $SD = 26.70$) following lateral positioning, without the effects of morphine. Results from the pilot study are comparable to those of Swinamer et al.(1987) and Verderber and Gallagher (1994), but less than Weissman's (1984) findings.

Morphine in dosages of 0.20 mg/kg iv to 0.50 mg/kg iv has been shown to attenuate the stress response in cardiovascular surgical patients as evidenced by a 9% to 21% reduction in mean VO_2 (Alderman et al., 1972; Rouby et al., 1981; Rouby et al., 1979). Thus, according to the research literature, lateral positioning and morphine have approximately equal and opposite effects on VO_2. Because the morphine dosage used in the pilot study (0.07 mg/kg) was *less* than the dosage used in the main study (0.10

mg/kg), effect size observed during the treatment phase (phase II) of the pilot study was not used to calculate sample size for the main study. Rather, an interest was assumed to detect a 50% relative reduction in the maximal increase in mean VO_2 from baseline that was associated with lateral positioning during the 10 minute observation period following the procedure (beta = .2, α = .05, two-tailed). Attenuating maximal VO_2 response to lateral positioning by 50% was determined to be the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical significance. It was also assumed that this effect size was reasonable, in the sense that an effect of this magnitude could be anticipated, based on previous findings, in the clinical setting. According to Cohen (1983), an effect size of .50 is a medium to large size effect for a within-subjects design.

Power analysis was calculated according to the methods and tables provided by Maxwell and Delaney (1990) that are specific for a within-subjects repeated measure design. Assuming a minimum correlation of approximately .4 to .6 between mean VO_2 during the treatment and control phases, between 28 to 40 subjects would be required to detect an effect size (*d*) of .50 with a power of .80 (Table 13.10, Maxwell & Delaney, 1990). By using a within-subjects design to reduce underlying variability, the same power can be achieved with a smaller number of subjects (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983).

Sampling Technique

Consecutive sampling technique was used to enroll eligible subjects into the study. Of the nonprobability sampling techniques (Pedhazur & Schmelkin, 1991), the consecutive sampling method is the least biased because each patient admitted into the cardiovascular ICU who met inclusion criteria was given equal opportunity to participate in the study; consequently, sampling bias selection was reduced (Hulley & Cummings, 1988). Because the sampling frame was limited by the numerous eligibility criteria, nonprobability sampling was necessary in order to obtain an adequate sample size within a reasonable period of time. Using the Eligibility Criteria Tool (Appendix A), all patients consecutively admitted into the cardiovascular ICU who had agreed to participate in the study were screened for inclusion into the study until the sample was obtained.

Protection of Human Subjects

Permission to conduct the study was obtained from the Investigational Review Board (IRB), the Chairman of the Department of Cardiothoracic Surgery, and the Director of Clinical Services of Swedish Medical Center in Seattle, Washington where the research was conducted. Permission to conduct the study was also obtained from the Texas Woman's University Human Subjects Protection Committee. The study was discussed and the protocol was reviewed with the medical and nursing staff and with the respiratory therapists involved in the care of the subjects. Prior to inclusion into the study, verbal informed consent was obtained from the subject, the subject's family member, or legal guardian. Because the study procedures did not deviate from standard care

procedures or clinical protocols, the risks to subjects who participated in the study were determined to be no greater than risks normally associated with routine care and no greater than risks normally encountered by this population. Consequently, the IRB determined that verbal rather than written consent was appropriate for subject enrollment (Appendix F). An oral explanation of the study, proposed risks and benefits, and time involvement was provided to all potential subjects and their family members the family member or legal guardian as well as a written description of the research study (Appendix G). Each subject or their legal guardian received a copy of the consent form, written information about the study, and the investigator's contact information.

Instrumentation

The instruments that were used to measure cardiorespiratory variables included the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter (Model 52510, Abbott Critical Care Systems, Chicago, IL), Q-Vue CCO Monitoring System™ (Abbott Critical Care, Chicago, IL), and SvO_2 module (Model M1175, Agilent CMS Technologies). The Puritan-Bennett® 7250 Metabolic Monitor (Puritan-Bennett Corporation, Carlsbad, CA) was used to measure VO_2.

Fiberoptic Pulmonary Artery Catheter

SvO_2, the amount of oxygen attached to hemoglobin (Hb) in pulmonary arterial blood, reflects the relationship between DO_2, oxygen demand, and VO_2 and is expressed by the rearrangement of the Fick equation (McMichan, 1987):

$$SvO_2 \approx \frac{SaO_2 - VO_2}{CO \times Hb \times 1.34 \times 10} \quad \langle 3 \rangle$$

where, SaO_2 = arterial oxygen saturation, 1.34 = the maximum amount of oxygen (ml) carried by 1-gram of hemoglobin, and 10 = the conversion factor for deciliters to milliliters/min (Aberman, 1987; McMichan, 1986). Normal SvO_2 is between 60% and 80% (Ahrens & Rutherford, 1993). SvO_2 was continuously measured using the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter through reflectance spectrophotometry.

Through reflectance spectrometry technology, continuous SvO_2 monitoring systems differentiate oxygenated blood from deoxygenated blood in the pulmonary artery. The SvO_2 monitoring system has three components. The first component, the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter has conventional hemodynamic monitoring capabilities (i.e., RAP, PAP, CO) in addition to fiberoptics (Oximetrix® Oximetry System, Abbott Critical Care Systems, Chicago, IL) for light transmission. The second component, the optical module, contains three light-emitting diodes to illuminate blood at the tip of the catheter and a photodetector that converts light intensity levels into

electrical signals for transmission to the processor. The third component, the processor (SvO_2 Plug-In Module, Model M1175, Agilent CMS Technologies), analyzes reflected light and displays the oxygen saturation on the bedside monitor. The processor calculates oxygen saturation based on the following equation:

$$SO_2 \approx \frac{HbO_2}{Hb + HbO_2} \times 100 \qquad \langle 6 \rangle$$

where, HbO_2 represents the amount of oxygenated hemoglobin concentration and Hb denotes the amount of deoxygenated hemoglobin (Abbott Critical Care, 1989; Aberman, 1987). The SvO_2 value that is displayed on the oscilloscope represents a composite of measurements of multiple samples and is updated every few seconds. Additionally, the OPTI-Q™ pulmonary artery catheter provides an indirect, but practical method of measuring DO_2, VO_2, and O_2ER variables.

In 1982, Baele and colleagues (1982) reported that the validity of the Oximetrix® 3 Oximetry System had an acceptable accuracy ($r = .95$) and the mean difference between in vitro and in vivo SvO_2 measurements ($\pm$ 4%) was not statistically significant ($\rho = .472$). Since Baele's study, the accuracy and precision of the Oximetrix® 3 Oximetry System has been documented by numerous researchers (Gettinger et al., 1987; Hecker et al., 1989; Karis & Lumb, 1988; Rouby et al., 1990). Following pre-insertion calibration, acceptable correlation coefficients with laboratory co-oximeter values were obtained ($r =$

.994, .92, .97, and .97) in each of the studies, respectively. Chulay et al. (1992) reported that the Oximetrix® 3 Oximetry System in vivo values ranged from +1.4% to -0.4% of the reference value obtained on a co-oximeter (r = .91). Noll and Fountain (1990a; 1990b) determined the inaccuracy of the system to be $\pm$ 2% for SvO_2 values of 40% to 100%. Body temperature, hemoglobin level, cardiac index, and calibration method do not affect the accuracy of the system (Shively, 1988). Stability of the system has been demonstrated for up to 102 hours of continuous use with an observed drift of 1% (Divertie & McMichan, 1984). Reliability is enhanced by a feature that monitors the optical intensity of the reflected light signal to guard against abnormal signal conditions (e.g., a kink in the catheter, an occlusion or blood clot on the end of the catheter) and interference (Clark et al., 1990).

Concurrent criterion validity of the Oximetrix 3 System® was established during a previous biometric evaluation (Jesurum, 1996) by comparing SvO_2 values to those simultaneously obtained on the laboratory co-oximeter (Model IL 482®, Instrumentation Laboratory, Lexington, MA) (r = .99, $\rho < .00$). The sample was comprised of cardiovascular surgical patients with impaired cardiac function defined as a cardiac index < 2.4 L/min/m^2 (N = 11). One subject was disqualified because pre-insertion in vitro calibration had not been performed according to the manufacturer's recommendations; consequently, the displayed value was > 4% different (*bias*) than the co-oximeter value. Mean SvO_2 measured by the IL 482® co-oximeter (M = 61.21%, SD = 8.14%, range

49.3% - 74.8%) was similar to the mean SvO_2 measured by the Oximetrix 3 System® (M = 60.36%, SD = 8.42%, range 49% - 74%).

Using a Pearson product-moment correlation, a strong association ($r = .98$, $\rho < .00$) was assessed between paired SvO_2 measurements obtained simultaneously on the IL 482® co-oximeter and Oximetrix 3 System® in patients with a cardiac index < 2.4 L/min/m^2. A large portion (97%) of the variance in the SvO_2 measure obtained on the IL 482® co-oximeter could be explained or predicted by the Oximetrix 3 System ® SvO_2 value (adjusted $r^2 = .97$). A paired t-test indicated that there was not a significant difference between the SvO_2 values obtained on the IL 482® co-oximeter and Oximetrix 3 System® ($t = -1.84$, $df = 10$, $\rho = .096$).

The amount of agreement between SvO_2 measurements obtained on the Optimetrix 3 System® and IL 482® co-oximeter was calculated according to statistical methods outlined by Bland and Altman (1986; 1995a; 1999; Liehr, Dedo, Torres, & Meininger, 1995; 1996). Level of significance was set at $\alpha = .05$ (two-tailed). To obtain the best estimate of the true score, the mean of the paired SvO_2 values was calculated ($M_{xy} = 60.79$, $SD = 2.48$) and plotted against the mean difference (d) of the paired SvO_2 values ($M\text{-}d_{x\text{-}y} = 0.85$, $SD = 0.46$). Kolmogorov-Smirnov and Shapiro-Wilk's tests of normality were performed on the difference scores and the results were not significant for violations of the assumption ($\rho = .20$). On average, the Oximetrix 3 System® rendered a SvO_2 value that was 0.85% *less* than the SvO_2 value obtained on the co-oximeter which represented the amount of *systematic error* or *bias* associated with the Oximetrix 3

System®. Within the population, the true value of bias would fall between –1.89% and 0.18%, 95% of the time. The degree of random error between the two methods (*imprecision*), determined by calculating the standard deviation (*SD*) of the difference scores, was 1.54%. Based on the limits of agreement estimated by the mean difference ± 1.96 standard deviation ($d \pm 2_{SD}$) between SvO_2 measurements on each subject, 95% of the differences between the two methods are expected to lie between –3.86% and 2.16%.

Except for the findings of Baele et al. (1982) who reported a higher degree of imprecision, results of the pilot study concurred with the findings of Noll and Fountain (1990a; 1990b) and Chulay et al. (1992) and with the manufacturer reports that the inaccuracy (*bias*) is ± 2%. Inconsistencies associated with Baele's findings may have been related to earlier technology that had a higher degree of imprecision than the more modern technology that has been significantly improved and refined. The limits of agreement observed during the methods comparison study were clinically unimportant and within the acceptable limits as defined by hospital policy. Therefore, the Oximetrix 3 System® was substituted for the co-oximeter in clinical practice to measure SvO_2 in patients with low cardiac output.

To enhance the accuracy and reliability of SvO_2 measurements in the study, the position of the catheter in the pulmonary artery was evaluated independently by both the investigator and research assistant using waveform morphology assessment criteria detailed in the research protocol and radiographic confirmation (Appendix H). Immediately prior to data collection, an in vivo calibration procedure was performed on

the SvO_2 monitoring system using a SO_2 criterion reference obtained on the laboratory co-oximeter. Procedures for the in vivo calibration procedure are outlined in the study protocol (Appendix H). After the catheter and processor were calibrated, SvO_2 was continuously displayed as a percentage on the bedside monitor and was recorded at each 1-minute measurement interval. Data were collected only if the SvO_2 light intensity signal was indicative of an acceptable quality signal as defined by criteria established by the manufacturer (Abbott Critical Care, 1989) and described in the study protocol (Appendix H).

Continuous Cardiac Output Monitor

The Q-Vue™ Continuous Cardiac Output (CCO) Monitoring System was used to monitor cardiac output (CO) continuously. The Q-Vue™ CCO Monitoring System consists of the Q-Vue™ computer, a thermal coil cable, a CO cable, and a pulmonary artery catheter. In addition to SvO_2 monitoring, the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter has conventional hemodynamic monitoring capabilities (e.g., RAP, PAP) and was used to measure hemodynamic variables.

The Q-Vue™ CCO Monitoring System measures cardiac output continuously by periodically warming the blood in the right ventricle in a pseudorandom, binary sequence through a heated thermal coil located within the wall of the catheter. The thermal coil or filament is approximately 10 to 15 cm in length and is located 14 cm from the catheter's distal tip near the level of the right atrium or caval atrial junction in the right ventricle.

The Q-Vue™ CCO Monitoring System powers the thermal coil by sending thermal (i.e., heat) signals to the thermal coil every 20 seconds followed by a 20 second period of low energy. Thus, one thermal cycle is 40 seconds in duration. A thermistor temperature sensor located at the distal tip of the catheter in the pulmonary artery detects blood temperature changes continuously. The Q-Vue™ CCO Monitoring System computer measures the transfer of heat from the coil to the blood by interpreting the changes in blood temperature and duration of time. Using this information, a thermodilution washout curve is constructed and cardiac output is computed from a conservation of heat equation that inputs the area under the curve.

Continuous cardiac output (CCO) is averaged in a manufacturer- specific time averaging algorithm and the CCO value is digitally displayed on the monitor and updated every 10 seconds. Thus, a *sliding* window of data is continuously analyzed, combining the last 10 seconds of data with 30 seconds of previously analyzed data. CCO trend data are graphically displayed on the monitor as well as a quality signal indicator that reflects the strength of the thermal cardiac output signal in relation to the thermal background noise (Abbott Critical Care, 1989, 1997; Gawlinski & Dracup, 1998). Because the process is fully automated, the Q-Vue™ CCO Monitoring System eliminates the need for bolus fluid injections used during traditional thermodilution cardiac output measurements, thus reducing the patient risk of fluid overload and decreasing the potential for catheter contamination and measurement error. Furthermore, initial or intermittent calibration is not recommended nor required.

The Q-Vue™ CCO Monitoring System offers four different averaging modes for trending CCO data (i.e., Normal, Fast, Urgent, Fast Filtered) with different response times and differing abilities to reject artifact. The Fast, Urgent, and Fast Filtered modes were designed to improve the response time of trend CCO to acute changes in cardiac output. The "Fast" mode was used during the study to provide a moderate amount of artifact (i.e., background noise) rejection and had an approximate response time of 3 minutes to detect a 90% change in flow (Abbott Critical Care, 1997). CCO values displayed in the Fast mode reflect an average of the previous 1 to 3 minutes of data. In comparison to the Normal or Fast Filtered modes, the Fast mode uses less data to obtain an average CCO, has a shorter averaging time and provides less artifact rejection (Hughes, 1997). The Fast Mode was selected for the study to rapidly detect changes in cardiac output related to the independent variables.

Due to the lag time associated with the CCO measurements, more frequent and earlier measurements of CCO were not obtained during the study to avoid issues related to measurement error and bias. As illustrated in Table 4, CCO measurements were obtained during the study procedures at baseline and at minutes 3, 5, and 10 following lateral positioning and were entered into the formulas to calculate DO_2I and O_2ER. Measurements obtained at baseline and at minutes 5 and 10 were used for descriptive purposes only and to explore the trends in the temporal relations between oxygenation variables before and following the introduction of the treatment variables. For the purposes of evaluating the hypotheses, only minute 3 CCO measurements were

statistically analyzed; therefore, measurement error associated with instrumentation lag-time was reduced. Despite the lag time limitations, CCO monitoring was determined to offer numerous clinical and scientific advantages over thermodilution CO measurement (TDCO).

The Q-Vue™ CCO Monitoring System is reported to function reliably within a blood temperature range of 30° C to 40° C. Reported range of continuous CO measurement is 1 to 20 L. The average coefficient of variation as reported by the manufacturer is ± 3% (Abbott Critical Care, 1997).

Correlational coefficients for CCO values compared to TDCO values range from r = .84 to .97 (for r = .84, bias = - 0.008 L/min ± 1.18 L/min, precision = 0.59 L/min) (Lichtenthal & Wade, 1994; Yelderman et al., 1992). Yelderman and colleagues (1992) compared CCO to TDCO in 54 critically ill patients and obtained a correlational coefficient of r = .94 and a mean bias of 0.02 L/min with 95% confidence intervals (*CI* 95%) of -1.03 to 1.07. Ditmyer et al. (1995) reported the intraclass correlation between TDCO and CCO to be .89 and the 95% limits of agreement to be between –1.34 and 1.18 L/min. The researchers also reported a bias of – 0.10 L/min and a precision of .64 L/min, with a 95% confidence interval of ± 1.28 L/min. In comparing TDCO and CCO measurements, Burchell et al. (1997) reported the bias and precision of CO data were 0.49 and 1.01 L/min, respectively, with 95% limits of agreement between – 1.53 and 2.51 L/min. In comparing CCO to the gold standard indocyanine green dye dilution technique (i.e., Fick calculated method) for measuring CO, Haller et al. (1995) reported the bias and

precision to be 0.34 and ± 1.01 L/min, respectively. In patients who had a low CO (i.e., < 4.5 L/min), Boldt et al. (1994) reported a bias of – 0.17 ± 0.50 L/min between TDCO and CCO methods. Similarly, Albert and colleagues (1999) reported a median bias of – 0.10 L/min ($\rho = .79$) between TDCO and CCO measurements in patients with low cardiac output.

Rapid response CCO modes (i.e., Fast, STAT) have been proposed to capture acute hemodynamic changes while maintaining accuracy at steady state (Abbott Critical Care, 1997). Like the normal or trend mode of CCO, rapid response CCO is based on an averaging process to minimize the effects of baseline drift, respiratory artifact, and cardiac irregularities; however, the "moving average filter" is removed from the algorithm (Lazor et al., 1997). In examining 108 CO data sets, Lazor and colleagues (1997) determined that rapid response averaging modes for measuring CCO were accurate and precise and correlated well with TDCO ($r = .94$) in critically ill surgical patients experiencing acute hemodynamic changes (Lazor et al., 1997). Compared to TDCO, rapid response and trend CCO demonstrated similar bias and precision. The mean bias between rapid response CCO and TDCO was 0.06 L/min (*CI 95%*, -0.08 – 0.18) and the precision was 0.61 L/min. The investigators reported similar results for the comparisons between the *trend* or normal mode of CCO and TDCO. Between these two methods, mean bias was 0.06 L/min (*CI 95%*, -0.04 – 0.16) and the precision was 0.49 L/min (Lazor et al., 1997). There were no significant differences between paired CCO measurements (mean difference = 0.016 L/min, SD = 0.246 L/min, $\rho = .508$) and TDCO

measurements (mean difference = 0.008 L/min, SD = 0.352 L/min, $\rho = .808$). The investigators concluded that there was close agreement between TDCO and CCO methods over a wide range of CO measurements.

Although the majority of researchers concluded that CCO measurement is reasonably accurate in critically ill patients, is reliable and applicable to clinical practice and may facilitate patient safety, the findings in the literature regarding agreement between CCO and TDCO are variable and inconsistent. Measurement error associated with TDCO has been well documented and is associated with differences in injection technique, loss of indicator, and effects of respiratory variation. Researchers have reported that even in maximally controlled situations using proper technique, measurement error associated with TDCO is a minimum of 4% to 9% (Nishikawa & Dohi, 1993). Rapid response CCO offers advantages over trend CCO and TDCO during periods of acute hemodynamic fluctuation, without compromising accuracy in measurement.

To ensure reliability of CCO data during the study procedures, the position of the catheter in the pulmonary artery was evaluated independently by both the investigator and research assistant using waveform morphology assessment criteria detailed in the research protocol and radiographic confirmation (Appendix H). Additionally, the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter RV/Distal Thermal Positioning Port (DTPP™) was temporarily connected to the RAP transducer to verify that the heating element was distal

to the tricuspid valve as evidenced by right ventricular (RV) waveform. CCO data was not collected unless the Q-Vue CCO Monitoring System™ "Quality Signal Indicator" displayed 4 or 5 bars indicating there was acceptable signal to noise ratio (Appendix H) (Abbott Critical Care, 1997).

Metabolic Monitor

Measurement of VO_2 via the gas analysis technique is based on the theoretical principles that (a) oxygen is consumed to facilitate mitochondrial production of adenosine triphosphate through oxidative phosphorylation, (b) carbon dioxide and water are the byproducts of oxidative phosphorylation and can be quantitatively measured, and (c) measurement of oxygen and carbon dioxide concentrations via inhaled and exhaled gases yields the amount of oxygen consumed (VO_2) and carbon dioxide produced (VCO_2) (Gawlinski, 1993a). According to Epstein et al. (2000), scientific research on oxygen transport variables require indirect calorimetry measurements, especially when results will direct prospective interventions. Several researchers have demonstrated that in comparison studies, VO_2 calculated by the Fick equation underestimates VO_2 as measured by indirect calorimetry (Brandi, Bertolini, & Santini, 1999; Epstein et al., 2000).

Oxygen consumption was measured noninvasively by indirect calorimetry methods using an open system metabolic monitor (Puritan-Bennett® Model 7250™, Puritan-Bennett Corporation, Carlsbad, CA) that directly and continuously measures the oxygen difference between inspired and expired gases in patients mechanically ventilated

by a Puritan-Bennett® 7200ae Ventilator. The metabolic monitor includes an oxygen analyzer, a cylinder of calibration gas (95% oxygen, 5% carbon dioxide), a pump, a two-line light emitting diode display, and a microprocessor to aid in data acquisition and calculations. Inspiratory gas is sampled distal to the humidifier, while expired gas is sampled distal to the expiratory valve. Inspired and expired gases are sampled at 100 and 350 ml/min, respectively. Fraction of inspired oxygen (FiO_2) is measured at 5-minute intervals. Flow and volume measurements are corrected for barometric pressure and relative humidity. Measurement of VO_2 through exhaled gas analysis is expressed by the formula:

$$VO_2 \approx VE \times (FiO_2 - FeO_2) \qquad \langle 7 \rangle$$

where, VE = minute ventilation, FiO_2 = fraction of inspired oxygen, and FeO_2 = fraction of expired oxygen (Ahrens & Rutherford, 1993). Normal resting VO_2 is approximately 3.5ml/kg/min or 110 to 140ml/min/m^2 (Ahrens & Rutherford, 1993). For the study, the difference between inspired and expired oxygen concentrations was directly measured on a continuous, breath-by-breath interval, and averaged on a 1-minute interval. An underlying assumption of metabolic monitoring is that oxygen uptake or the amount of oxygen removed from the delivered gas reflects oxygen consumed for the demands of the patient's tissues and metabolic processes. In a methods comparison, in vitro evaluation,

Weissman and colleagues (1994) reported that VO_2 as measured by the Puritan-Bennett® 7250™ metabolic monitor was within $\pm$ 6% of predicted values and accuracy was not altered by FiO_2 levels, flow-by ventilation mode, PEEP levels $\geq$ 20 cm H_2O, or increased inspiratory airway pressures $\geq$ 60 cm H_2O.

For the main study, the metabolic monitor (i.e., O_2 sensors, inspiratory and expiratory lines) was calibrated immediately prior to data collection using calibration gases according to the manufacturer-recommended calibration procedures (Puritan-Bennett, 1995). After the oxygen sensors and inspiratory and expiratory lines were calibrated, continuous VO_2 (ml/min) was digitally displayed on the metabolic monitor and was recorded at each 1-minute measurement interval.

Data Collection Records

Five data collection instruments were developed by the principal investigator to describe the subjects and to identify confounding variables that may influence the dependent measures. These instruments included the (a) Eligibility Criteria Tool (Appendix A), (b) Demographic Profile Tool (Appendix B), (c) Cardiorespiratory Parameters Tool (Appendix C), (d) Interrater Reliability Tool (Appendix D), and (e) Criterion Validation Tool (Appendix E).

The Eligibility Criteria Tool was used to screen potential subjects according to inclusion and exclusion criteria. Because there were numerous eligibility criteria, the screening tool was developed to assist the investigator in determining if a patient met criteria to participate in the study. The investigator completed the screening tool by

reviewing patient medical records and assessing the patient. Descriptive data that was recorded on the Eligibility Criteria Tool included the presence of instruments such as arterial and fiberoptic pulmonary artery catheters; type of surgical procedure; presence of comorbidities; and presence of conditions such as shivering, hypothermia, hyperthermia, hemorrhage, and hemodynamic instability that can independently influence tissue oxygenation. If all eligibility criteria were satisfied and oral consent was obtained, the subject was enrolled into the study.

Information transcribed on the Demographic Profile Tool was collected from the patient medical records. Descriptive information including age, gender, preoperative morbidity, medical diagnoses, surgical procedure, and left ventricular ejection fraction were collected for the purpose of describing the sample and generalizing the results of the study. Because of the association between duration of intraoperative hypoperfusion or ischemia and postoperative complications (e.g., respiratory failure, myocardial depression, renal insufficiency, coagulopathy) (Moreno-Cabral et al., 1988; Seifert, 1994; Weiland & Walker, 1986), information regarding the duration of aortic cross clamp time and extracorporeal circulation time were collected. In addition, medications known to affect tissue oxygenation (e.g., analgesics, anxiolytics, cardiac and vasoactive medications) were recorded if administered within 6 hours preceding the study. At the end of the study, information recorded on the Demographic Profile Tool was numerically coded for entry into a computer for data analysis.

Measurements of the dependent variables (i.e., SvO_2, VO_2) that were digitally displayed on the bedside monitors were recorded on the Cardiorespiratory Parameters Tool. Additional baseline physiological measurements including heart rate, arterial and pulmonary pressures, RAP, SVRI, SVI, LVSWI, and SpO_2 were recorded from the monitor to describe patient characteristics and to explain changes in the tissue oxygenation variables and physiologic response to the treatment variables. Psychometric evaluation (Lynn, 1986; Slocumb & Cole, 1991; Tilden, Nelson, & May, 1990) of the instrument protocol by a nursing panel of nationally recognized clinical experts revealed an overall content validity index of .98 for the 43 items, thus supporting the validity of the data collection methods for measuring tissue oxygenation (Jesurum, 1996).

Data recorded on the Interrater Reliability Tool were used to evaluate consistency between the investigator and the research assistant in verifying the location of the pulmonary artery catheter by waveform analysis (Part A) and to measure error between the principal investigator and research assistant during the transcription of data (Part B). Location of the pulmonary artery catheter in the pulmonary artery represented a potential source of measurement error and bias. In order to obtain accurate and reliable SvO_2 and CCO measurements, the heating element of the pulmonary artery catheter must be located distal to the tricuspid valve and the tip of the catheter positioned within the left or right branch of the pulmonary artery, without being too proximal or distal. The first two questions on Part A of the Interrater Reliability Tool required the rater to evaluate the light intensity signal on the Oximetrix® 3 Computer monitor and the Quality Signal

Indicator on the Q-Vue CCO Monitoring System™. The remaining five questions pertained to right ventricular and pulmonary artery waveform morphology and assessment according to methods outlined in the study protocol (Appendix H) for verifying catheter position. Affirmative responses (i.e., "yes") to each of the seven questions by both raters provided evidence of correct pulmonary artery catheter location. The amount of agreement between raters in verifying the location of the pulmonary artery catheter was tested on every subject enrolled into the study. A kappa coefficient of $K \geq .90$ ($\alpha = .05$) was used to indicate acceptable agreement between the raters (Siegel & Castellan, 1988; Waltz, Strickland, & Lenz, 1991).

For the purposes of determining interrater reliability, the duplicate measurements method was used to evaluate postanalytic variability or bias between raters (Waltz et al., 1991). According to Waltz et al. (1991) the major source of postanalytic variability is transcription error onto data collection records. Interrater reliability, a type of duplicate measurement method, was tested to determine the consistency of performance between the investigator and research assistant. For each subject enrolled into the study, a Pearson's correlation coefficient was computed between six pairs of SvO_2 measurements recorded by the two investigators at 15-second intervals over a 1-minute period. A correlation coefficient of $r \geq .95$ obtained on Part B of the Interrater Reliability Tool suggested that acceptable agreement existed between raters for data transcription (Waltz et al., 1991).

Data Collection

Prior to the main study, a pilot study was conducted by the investigator to (a) field test the data collection records, the instruments and the study protocol, and (b) obtain data to determine the magnitude of the effect of morphine (0.07 mg/kg iv) on VO_2 following lateral positioning and to calculate sample size for the main study (Jesurum, 1996). Opportunities to strengthen the instrumentation protocol were identified through content validation and the pilot study and the protocol for the main study was revised accordingly. Results of the pilot study and revisions to the original study protocol are discussed.

Pilot Study Results

For the pilot study, a single group, repeated measures, factorial design was used to guide the methodology (Tabachnick & Fidell, 1983). The Roy Adaptation Model served as the conceptual framework to guide the pilot study (Andrews & Roy, 1991; Roy, 1984). Using nonprobability sampling technique (Hulley & Cummings, 1988) five patients (N = 5) were enrolled into the study from a population of mechanically ventilated adult cardiovascular surgical patients with low cardiac output. Data were collected from September 1995 to January 1996 in the cardiovascular recovery unit at a 946 bed, private, not-for-profit, teaching hospital located in Houston, Texas. Written permission to conduct the study was obtained from the IRB of the research facility and from the Human Subjects Review Committee at Texas Woman's University. Written family consent was obtained for all patients who met eligibility criteria and were enrolled in the study. All

five subjects were able to complete the study without experiencing complications. Continuous SvO_2 monitoring with a fiberoptic pulmonary artery catheter was used to assess tissue oxygenation variables prior to and following lateral positioning, with and without the effects of morphine. Dependent variables included measured (SvO_2) and calculated (VO_2I, DO_2I, O_2ER) cardiorespiratory variables. Using SPSS for Windows 95® Release 7.5 (SPSS, 1996), preliminary data were analyzed for exemplary purposes by descriptive and inferential statistics including analyses of variance obtained through SPSS MANOVA procedures.

The purpose of the pilot study was to (a) verify that VO_2 response to lateral positioning differed when 0.07 mg/kg of morphine was administered 20 minutes prior to the turn, (b) identify problems associated with the data collection tools, database and planned approach for statistical analyses, and (c) identify opportunities to refine the instruments and methodology. Five primary concerns were identified during the pilot study and each issue is addressed separately in the following discussion.

1. *Magnitude of effect of morphine (0.07 mg/kg).* Similar to the findings of other researchers, lateral positioning was associated with an immediate increase in VO_2 by approximately 20%. The pilot sample demonstrated adaptation responses to lateral positioning that were similar to the responses of critically ill patients without impaired cardiac function or low DO_2I. Following lateral positioning, the relative changes in SvO_2 and VO_2I as well as SvO_2 recovery patterns were consistent with the findings of other researchers. Clinical differences in SvO_2, VO_2I, and O_2ER following lateral positioning

were not observed when morphine 0.07 mg/kg was administered intravenously 20 minutes prior to positioning. The lack of effect of morphine 0.07 mg/kg observed in the pilot study prompted the reevaluation of morphine dosing as prescribed by the research protocol to attenuate oxygen demand-induced VO_2 response.

At low doses, opioids provide analgesia but not anxiolysis, whereas at higher doses opioids also have sedative effects (Jacobi et al., 2002). At the time of the pilot study, the treatment dose (0.07 mg/kg iv) was representative of routine treatment used in the immediate postoperative period following cardiovascular surgery to control acute postoperative pain and discomfort without causing unnecessary sedation or hemodynamic fluctuations. For managing acute postoperative pain in critically ill adults, practice guidelines published in 1995 advocated a loading dose (0.05 mg/kg iv) of morphine administered over 5 to 15 minutes with bolus therapy dosing every 1 to 2 hours (Shapiro et al., 1995). In comparison, recently published clinical practice guidelines for the use of sedatives and analgesics in the critically ill population recommend intermittent dosages (0.01- 0.15 mg/kg iv) of morphine every 1 to 2 hours or a continuous infusion (0.07 - 0.50 mg/kg/hr iv) (Jacobi et al., 2002). In consideration of the pilot study results and current pain and sedation guidelines, the treatment dose of morphine that was prescribed by the research protocol was increased to 0.10 mg/kg and was based on ideal body weight.

2. *Overly restricted inclusion criteria.* During the pilot study, the target population included subjects who (a) had undergone cardiovascular surgery with

extracorporeal circulation during the previous 12 to 24 hours, (b) were mechanically ventilated with PEEP < 10 cm H_2O, and (c) had impaired cardiac function as defined by a cardiac index < 2.5 L/min/m^2. Patients who had low cardiac output were initially targeted for the pilot study because they were likely to have persistently low DO_2, particularly during periods of increased oxygen demand (Winslow et al., 1990). Members of the expert panel who assisted with content validation expressed concern that the eligibility criteria were too stringent and excluded subpopulations with limited cardiorespiratory reserves and impaired tissue oxygenation who were vulnerable to tissue hypoxia and may benefit from the treatment prescribed in the research protocol. Therefore, based on recommendations from the expert panel, eligibility criteria for the main study were revised to include critically ill patients who had low DO_2 rather than low cardiac output. The revised eligibility criteria were consistent with the original intent of the study to test a nursing intervention aimed at restoring the balance between DO_2 and VO_2 in critically ill patients with impaired tissue oxygenation.

3. *Calculated VO_2I.* During the pilot study, VO_2I was calculated using the Fick equation:

$$\begin{aligned} VO_2I &\approx CI \times \{CaO_2 - CvO_2\} \times 10, \\ \text{and, } CaO_2 &\approx SaO_2 \times 1.34 \times Hb \times 10 + [0.0031 \times PaO_2] \\ \text{and, } CvO_2 &\approx SvO_2 \times 1.34 \times Hb \times 10 + [0.0031 \times PvO_2] \end{aligned} \quad \langle 8 \rangle$$

where, CI = cardiac index; 1.34 = the maximum amount of oxygen in milliliters (ml) carried by 1-gram of hemoglobin; 0.0031 = the solubility coefficient of oxygen in blood; 10 = the conversion factor from deciliters to ml/min., and, assuming $SpO_2 \approx SaO_2$ (Ahrens & Rutherford, 1993). Even in tightly controlled laboratory research, VO_2 calculated by the Fick equation has been demonstrated to systematically underestimate measured VO_2 via spirometry, (i.e., direct calorimetry) and is associated with approximately 20% random error ($VO_{2\ M}$ = 273 ml/min, SD = 70, vs. $VO_{2\ Fick}$ = 178, SD = 58, $\rho < .01$) (Stock & Ryan, 1996). Actual oxygen consumption is most likely underestimated by calculated VO_2 because the Fick equation *excludes* intrapulmonary VO_2, which may account for as much as 15% of total body VO_2 in metabolically active lung disease states (Light, 1988; Myburgh, 1992). The imprecision associated with calculated VO_2 via the Fick method has led some researchers to discredit its use for research purposes (Myburgh, Webb, & Worthley, 1992; Stock & Ryan, 1996). Measurement variability associated with calculated VO_2 was identified during the pilot study; therefore, the instrumentation protocol for the main study was revised to improve precision and reliability of VO_2 measurements.

For the main study, VO_2 was *measured* noninvasively by indirect calorimetry methods using a closed system metabolic monitor that directly and continuously measured the oxygen difference between inspired and expired gases in mechanically ventilated subjects. Thus, concerns related to measurement error and mathematical coupling associated with the Fick equation were eliminated. Concerns of *mathematical*

coupling and measurement error have been well described in the tissue oxygenation literature and relate to the use of shared variables (SvO_2, CO) for performing DO_2I and VO_2I calculations. If measurement error is associated with the common *measured* variable, mathematical coupling may distort the relationship among the calculated variables and result in incorrect conclusions (Moreno, Stratton, Newell, & Feustel, 1986; Nightingale, 1990).

4. *Thermodilution cardiac output measurement.* Cardiac output can be measured by (a) the direct Fick method, (b) indicator dilution methods, or (c) angiographic techniques. The indicator dilution method (e.g., thermodilution) involves injecting a substance that can be measured in the blood into a proximal site and sampling at a more distal site. Thermodilution techniques are most commonly used to measure cardiac output in the clinical setting and have traditionally involved injecting either room temperature or iced injectate solution into the proximal site. Using thermodilution methods, temperature *is* the indicator and the mean change in temperature is the indicator concentration that is measured distally (Faxon, 2000).

Thermodilution cardiac output measurements were obtained during the pilot study using the Hewlett Packard® Cardiac Output Module (M1012A, Hewlett Packard, Waltham, MA) and fiberoptic pulmonary artery catheter (Model P7110 EP-H 7.5F, Opticath, Abbott Critical Care Corporation).

Calculation of cardiac output by thermodilution uses the Stewart-Hamilton equation:

$$CO \approx \frac{I \times 60}{cm \times \tau} \quad \langle 9 \rangle$$

where, I = amount of indicator injected, 60 = seconds, cm = mean indicator concentration (mg/L), and t = total indicator circulatory time in seconds (Faxon, 2000; Nightingale, 1990). Using a closed-injectate delivery system (CO-Set, Baxter Healthcare, Edwards Critical Care Division, Santa Ana, CA) and 5ml of iced 5% dextrose solution, serial CO measurements were obtained at baseline and at minutes 1 and 5 following lateral positioning, with and without morphine. At each measurement time, three consecutive thermodilution CO measurements were performed which equated to each subject receiving a total of 90 ml of fluid over a 50-minute period. To avoid the risk of fluid overload, maintenance fluids were discontinued during the 50-minute data collection period and CO measurements were obtained in either the left or right lateral position, but not both. Nevertheless, the Human Subjects Review Committee expressed concerns about the potential for fluid overload in patients with myocardial depression and consequently, this issue was identified as a risk factor on the informed consent form for the pilot study.

Within the past decade, technology was introduced into the clinical setting for measuring CO that does not require fluid administration and provides continuous rather than intermittent CO measurement. After determining the reliability and feasibility of the new technology, the instrumentation protocol was revised for the main study to include the Q-Vue™ CCO Monitoring System and the OPTI-Q™ SvO_2/CCO Flow-Directed

Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter for obtaining continuous cardiac output measurement. In the clinical setting, CCO monitoring facilitates rapid assessment of meaningful deteriorations of cardiac output and instantaneous evaluation of therapeutic measures. In comparison to TDCO measurement, patient safety concerns related to fluid overload and the risk of possible catheter contamination are eliminated as are reliability issues related to TDCO measurement error including variation in the temperature and volume of injectate, timing of the injectate during the respiratory cycle, and the speed of injection (Huang et al., 2000).

5. *Cardiorespiratory calculations.* During the pilot study, derived oxygenation variables (i.e., DO_2I, VO_2I, and O_2ER) were calculated using the Hewlett Packard® Oxygen Calc computer program (Hewlett Packard, Waltham, MA) according to the Fick equations:

$$
\begin{aligned}
&DO_2I \approx CI \times CaO_2 \times 10, \\
&\text{where,} \quad CaO_2 \approx SaO_2 \times 1.34 \times Hb \times 10 + \left[0.0031 \times PaO_2\right] \\
&\text{and,} \\
&VO_2I \approx CI \times \left\{CaO_2 - CvO_2\right\} \times 10, \\
&\text{where,} \quad CvO_2 \approx SvO_2 \times 1.34 \times Hb \times 10 + \left[0.0031 \times PvO_2\right] \\
&\text{and,} \quad O_2ER \approx \frac{VO_2I}{DO_2I}
\end{aligned}
\qquad \langle 10 \rangle
$$

where, CI = cardiac index; 1.34 = the maximum amount of oxygen in milliliters (ml) carried by 1-gram of hemoglobin; 0.0031 = the solubility coefficient of oxygen in blood; 10 = the conversion factor from deciliters to ml/min., and, assuming $SpO_2 \approx SaO_2$.

In order to compute DO_2I, VO_2I, and O_2ER, the computer program required PaO_2 and PvO_2 data for each series of calculations (i.e., baseline, minutes 1 and 5 following turning). However, PaO_2 and PvO_2 measurements were obtained only once during the study procedures (e.g., baseline during phase I). To avoid prohibitive laboratory expenses and impractical timing issues associated with serial blood gas analyses, a method described by Severginghaus (1979) for approximating oxygen tensions (PaO_2, PvO_2) from oxygen saturations (SpO_2, SvO_2) was used for the serial cardiorespiratory calculations during the pilot study. Extrapolated computations from the oxyhemoglobin dissociation curve have been described in the literature (Ahrens & Rutherford, 1993; Severinghaus, 1979) for the purpose of *estimating* O_2 tension using O_2 saturation values. Using continuously displayed SpO_2 and SvO_2 data to extrapolate *estimated* PaO_2 and PvO_2 data permitted serial calculations of DO_2I, VO_2I, and O_2ER using the Hewlett Packard® Oxygen Calc computer program. This method was used for the pilot study.

For the main study, DO_2I and O_2ER were manually calculated. Calculations were modified by deleting the amount of oxygen dissolved in the plasma from the arterial blood oxygen content (CaO_2) formula(Ahrens & Rutherford, 1993):

$$CaO_2 \approx 1.34 \times Hb \times SaO_2 \left[\text{minus}\,(0.0031 \times PaO_2)\right] \qquad \langle 2 \rangle$$

Accordingly, for the main study, DO_2I was calculated using the following formula:

$$DO_2I \approx CI \times CaO_2 \times 10$$
$$\text{where, } CaO_2 \approx 1.34 \times Hb \times SaO_2 \left[\text{minus}\left(0.0031 \times PaO_2\right)\right]$$
$$\text{and, } SpO_2 \cong SaO_2 \qquad \langle 11 \rangle$$

where, CI = cardiac index; 1.34 = the maximum amount of oxygen in milliliters (ml) carried by 1-gram of hemoglobin; 10 = the conversion factor from deciliters to ml/min., and, assuming $SpO_2 \approx SaO_2$ (Ahrens & Rutherford, 1993).

Under normal circumstances, approximately 0.24 to 0.29 of available oxygen that is delivered to the tissues is consumed (Leach & Treacher, 1994). O_2ER was calculated using the formula:

$$O_2ER \approx \frac{VO_2}{DO_2} \qquad \langle 12 \rangle$$

Arterial oxygen saturation (SaO_2) is the ratio of oxygenated hemoglobin to total hemoglobin (Rutherford, 1993; Rutherford, 1989) and is expressed by the formula:

$$SO_2 \approx \frac{HbO_2}{Hb + HbO_2} \times 100 \qquad \langle 6 \rangle$$

The initial SaO_2 used to calculate baseline CaO_2 was measured on a laboratory co-oximeter (Model IL 482, Instrumentation Laboratory, Lexington, MA) and if the value was within ± 3% of the SpO_2 value displayed on the Hewlett Packard® monitor, SpO_2 was used as a substitute for SaO_2 in subsequent calculations of CaO_2. However, if the initial difference between SaO_2 and SpO_2 exceeded 3%, the protocol mandated study termination to avoid the risk of significant systematic measurement error or bias. Oxygen saturation by pulse oximetry (SpO_2) is a noninvasive monitoring technique used to estimate the measurement of arterial oxygen saturation of hemoglobin. SpO_2 will routinely overestimate SaO_2 because of the inability of the pulse oximeter to measure all types of hemoglobin, specifically carboxyhemoglobin and methemoglobin (Ahrens & Rutherford, 1993). However, according to the manufacturer's guidelines (Hewlett Packard, 1992), the difference should not exceed ± 3. The formula for comparing SpO_2 and SaO_2 measurements is:

$$SpO_2 \approx \frac{SaO_2}{1-(COHb-MetHb)} \qquad \langle 13 \rangle$$

where, COHb = carboxyhemoglobin and MetHb = methemoglobin (Ahrens & Rutherford, 1993).

Numerous studies have examined the accuracy of pulse oximeters, with fair consistency in findings. In general, manufacturers presently report pulse oximeter accuracy to one standard deviation of $< \pm 3\%$ when arterial oxygen saturation is $> 70\%$

(Sinex, 1999). These claims are largely supported in the most recent reviews of studies addressing accuracy. It should be recognized, however, that this bias or error is reported at one standard deviation only, and so must be doubled or tripled to express a 95% or 99% confidence interval, respectively. Researchers have consistently have found that SpO_2 measured with finger and ear transducer probes have a strong correlation with SaO_2 (Tittle & Flynn, 1997). Recently, researchers who studied the accuracy of SpO_2 in critically ill patients reported the bias between SpO_2 and SaO_2 via co-oximetry is generally between ±1% to 1.5% with precision ranging from ±0.5% to 2.25% in critically ill patients (Haessler, Brandl, Zeller, Briegel, & Finsterer, 1991; Norreslet, Ahlburg, Knage, & Rasmussen, 1990). SpO_2 response time is typically between 2 to 30 seconds depending on the quality of the signal to noise ratio and pulse-signal (Hewlett Packard, 1992).

Simultaneous measurements of SaO_2 and SpO_2 were recorded on the Criterion Validation Tool (Appendix E) and agreement between the two methods of measurement was determined using methods described by Bland and Altman (Bland & Altman, 1999). The study protocol was designed to control for extraneous variables to ensure a constant SaO_2 and hemoglobin level throughout the study procedures. Therefore, any observed SvO_2 fluctuations would most likely be related to changes in CO or VO_2.

Although the deletion of PaO_2 from the DO_2I equation represents a limitation of the study, the amount of oxygen dissolved in the blood contributes an insignificant amount to overall tissue oxygenation (Ahrens & Rutherford, 1993). Because there is

excessive financial burden and time involvement associated with blood gas analysis to obtain PaO_2 measurements, the modified DO_2I formula is frequently used in research and clinical practice (Aberman, 1987; Ahrens & Rutherford, 1993; Gawlinski & Dracup, 1998; Hayden, 1992; McGee et al., 1988; Winslow et al., 1990). Because of the insignificant contribution to overall tissue oxygenation (usually < 2% or 3%) and the excessive financial burden and time involvement associated with serial blood gas analyses, the revised methods were justified for the main study (Aberman, 1987; Ahrens & Rutherford, 1993; Hayden, 1992; McGee et al., 1988). According to Ahrens and Rutherford (Ahrens & Rutherford, 1993), if CO is low, PaO_2 would have to be enormously high (> 300 mm Hg) to significantly increase oxygen transport. None of the subjects in the sample had a PaO_2 > 300 mm Hg. The study protocol was designed to control for extraneous variables to ensure a constant SaO_2 and hemoglobin level throughout the study procedures. Therefore, any observed SvO_2 fluctuations were attributed to changes in CO or VO_2.

In summary, opportunities for improving and strengthening the instrumentation and research protocol were identified during the pilot study and psychometric evaluation. Five primary concerns were identified during the pilot study including (a) magnitude of effect of morphine, (b) restrictive inclusion criteria, (c) calculated VO_2, (d) thermodilution cardiac output measurement, and (e) estimated oxygenation values. Each issue has been presented and included a discussion of the methodology and protocol revisions for the main study.

Abbreviated Research Protocol

The following steps provide a brief description of the study procedures according to the sequence of events. The research protocol that includes an itemized detailed description of how the study was conducted is presented in Appendix H.

1. All patients > 18 years of age who were mechanically ventilated and had undergone cardiovascular surgery with extracorporeal circulation during the previous 6 to 24 hours were screened for admission into the study by the investigator using the Eligibility Criteria Tool (Appendix A). Prior to enrolling the patient into the study, either verbal consent was obtained from the patient preoperatively or from the family or legal guardian during the postoperative period. Patients who had provided verbal consent and met all of the eligibility criteria were enrolled into the study. Study procedures were reviewed with the subject immediately prior to data collection.

2. Prior to beginning data collection, study procedures were reviewed with the staff and a time for data collection was mutually determined that did not interfere with care routines. Procedures and activities known to increase energy expenditure and VO_2 such as dressing changes, bathing, and linen changes were deferred if possible until data collection had been completed. To control for the effects of environmental stimuli, measures were taken to reduce noise, lighting, and extreme ambient temperatures. Access into the subject's room was monitored and restricted during study procedures.

3. The subject was turned to the supine position with 20-degree backrest elevation and one standard foam pillow was placed under the subject's head.

4. For baseline measurements of cardiorespiratory variables obtained in the supine position, the atmospheric ports of the hemodynamic lines were referenced to the subject's supine phlebostatic axis using external landmarks previously described by Bridges and Woods (1993). Disposable pressure transducers (Ohmeda, DTX Plus Pressure Transducer Set) were mounted on a manifold holder and zeroed to atmospheric pressure. Dynamic frequency response assessment was performed on transduced pressures using the square wave test to identify overdampened or underdampened pressures (Lynn-McHale & Carson, 2001). Electronic calibration verification procedures were performed on the Hewlett Packard invasive pressure modules according to the manufacturer's guidelines (Hewlett Packard, 1992).

5. Interrater reliability was performed between the investigator and research assistant to verify the location of the pulmonary artery catheter in the pulmonary artery through interpreting signal indicators, chest radiograph and waveform morphology.

6. Thirty minutes after the subject was turned to the supine position with 20-degree backrest elevation, arterial and mixed-venous blood gases and hemoglobin samples were collected for clinical analysis and for in vivo calibration of the OPTI-Q™/Q-Vue Computer System and Hewlett Packard SvO_2 Module instrumentation. The 30-minute stabilization period between positioning the subject and collecting the laboratory samples allowed sufficient time for oxygenation variables to equilibrate to

baseline (Briones et al., 1991; Gawlinski, 1997). The OPTI-Q™/Q-Vue Computer System and Hewlett Packard SvO_2 Module were calibrated according to the manufacturer's guidelines using the SO_2 criterion obtained form the laboratory co-oximeter.

7. Using calibration gases, O_2 sensor and line calibration procedures were performed on the Puritan-Bennett® Metabolic Monitor Model 7250™ according to the manufacturer's guidelines (Puritan-Bennett, 1995).

8. To ensure a stable baseline and to control for the effects of medication adjustments on cardiorespiratory variables, data collection did not begin until the following conditions were satisfied: (a) 6 hours had elapsed since a paralytic agent was administered, (b) 1 hour had elapsed since the last administered dose of an analgesic, anxiolytic, diuretic, blood transfusion, or fluid therapy ($\geq$ 200ml over $\leq$ 30 minutes to support blood pressure), (c) 30 minutes had elapsed since titration of a vasoactive/inotropic infusion or propofol infusion, and (d) 30 minutes had elapsed since routine care procedures including suctioning, positioning, or ventilator changes. Data collection began after a steady rest state had been achieved for a minimum of 30 minutes.

9. Baseline measurements of the dependent variables (i.e., VO_2, SvO_2, O_2ER, and DO_2) were obtained with the subject in the supine position prior to receiving morphine. Additional physiological measurements were also obtained to describe the subject's baseline cardiorespiratory profile (i.e., heart rate, blood pressure, RAP, PAP, PAOP, CI, SI, LVSWI, SVRI, and SpO_2) without the effects of morphine. To ensure

reliability of measurements, RAP, PAP, and PAOP were measured during end-expiration as determined by waveform analysis and the level of the transducer was referenced to the subject's phlebostatic axis.

10. After a complete set of baseline measurements had been obtained, the subject was passively turned to the left or right 45-degree lateral position. Turn sequence was randomly assigned by lottery method. The 45-degree lateral position was verified by measuring the vertical distance from the nondependent shoulder to the bed and the horizontal distance between the acromial processes of the shoulders. After the subject was turned to the lateral position, a 45-degree foam wedge support pillow (Model 3000, Hudson Medical Industries, San Diego, CA) was placed behind the subject's back to maintain the position throughout the procedure. For comfort measures, one standard foam pillow was placed beneath the subject's head and one standard foam pillow was placed between the subject's flexed legs. The investigator and the research assistant performed all positioning procedures without assistance from the subject. The 20-degree backrest elevation was maintained throughout the procedure. With every lateral position change, a protractor was used to verify the 45-degree lateral position.

11. SvO_2 and VO_2 measurements were obtained each 1-minute interval following lateral positioning for 10 consecutive minutes. DO_2 and O_2ER were calculated at 3, 5, and 10 minutes following lateral positioning. Additional cardiorespiratory variables were measured at 3, 5, and 10 minutes from the data digitally displayed on the bedside monitor.

12. At the end of the 10-minute observation period following, the subject was turned to the supine position with 20-degree backrest elevation and one standard foam pillow was placed under the subject's head.

13. To determine the standard weight-based dose of morphine, the subject's ideal body weight was calculated according to formula that adjusted for gender and height (Cheymol, 2000; Pai & Paloucek, 2000). Morphine 0.10 mg/kg/ibw was diluted with 10ml of normal saline and administered intravenously in a syringe infusion device over a 5-minute period. After the morphine infusion was completed, 10ml of normal saline was injected into the same intravenous catheter to flush the line. Following morphine administration, an additional 15 minutes elapsed prior to resuming data collection to allow for the maximum effects of the medication. The total time between the start of the morphine infusion and the time that baseline measurements were obtained during phase II was 20 minutes.

14. Twenty minutes after receiving morphine, baseline measurements of the dependent variables (i.e., VO_2, SvO_2, O_2ER, and DO_2) were taken with the subject in the supine position with 20-degree backrest elevation. Additional physiological measurements were also obtained to describe the subject's baseline cardiorespiratory profile (i.e., heart rate, blood pressure, RAP, PAP, PAOP, CI, SI, LVSWI, SVRI, and SpO_2) with the effects of morphine. To ensure reliability of measurements, RAP, PAP, and PAOP were measured during end-expiration as determined by waveform analysis and the level of the transducer was referenced to the subject's phlebostatic axis.

15. The subject was passively turned to the same lateral position following the procedures described in step #10.

16. To determine the effects of morphine on tissue oxygenation, SvO_2 and VO_2 measurements were obtained each 1-minute interval following lateral positioning for 10 consecutive minutes. DO_2 and O_2ER were calculated at 3, 5, and 10 minutes following lateral positioning. Additional cardiorespiratory variables were also measured at 3, 5, and 10 minutes following lateral positioning from the data digitally displayed on the bedside monitor.

17. At this point, the study procedures were concluded and the subject was returned to the supine position.

Treatment of Data

Data obtained from the Demographic Profile Tool, Cardiorespiratory Parameters Tool, Interrater Reliability Tool, and Criterion Validation Tool were coded, entered into a computer, and examined for accuracy. Statistical analyses was performed using Statistical Package for the Social Sciences for Microsoft Windows Release 9.0.1 (SPSS, 1999). Data obtained on the Demographic Profile Tool in addition to the baseline cardiorespiratory measurements were analyzed by descriptive statistics and displayed in a frequency distribution table. Nominal and categorical descriptors such as gender, medical diagnoses, type of surgical procedure, and use of mechanical assistance were analyzed using frequencies and percentages. Interval-ratio data such as age, ejection fraction, hemoglobin, and baseline cardiorespiratory parameters (i.e., CI, SvO_2, DO_2I, VO_2I, and

O_2ER) were reported using the mean, range, and standard deviation as measures of central tendency and variability to describe the characteristics and acuity of the sample. Baseline data were graphically screened for outliers and departures from normality using frequency histograms and normal probability plots. Assumptions of normality for interval-ratio level data were statistically evaluated using Kolmogorov-Smirnov and Shapiro-Wilk's tests (Gibbons, 1993).

Changes in SvO_2 and VO_2I between baseline to minute 1, baseline to minute 3, and baseline to minute 5 following lateral positioning, with and without morphine, were calculated. Changes in DO_2I and O_2ER between baseline and minute 3, with and without morphine, were also calculated. Descriptive statistics of the change scores were examined to help explain the findings; however, statistical analyses were not conducted on the change scores. Actual scores and change scores of the repeated dependent variables were examined using the mean, standard deviation, and range to evaluate within-subject differences as a result of treatment variables. Additional physiological measurements (i.e., heart rate, blood pressure, RAP, PAP, PAOP, CI, SI, SVRI, and SpO_2) were analyzed using means and standard deviations to explain changes in the dependent variables. Measures of skewness, histograms and normal probability plots of actual scores and change scores were examined to identify outliers and to determine the distribution of the data. Assumptions of normality were statistically determined using Kolmogorov-Smirnov and Shapiro-Wilk's tests. For between group comparisons (i.e., propofol groups, right vs. left lateral position), homogeneity of variance assumption was

statistically tested using Levene's Test. The level of significance for all tests of assumptions was set at $\alpha < .05$.

Inferential statistics were used to test the five hypotheses. For the first hypothesis, mean VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning were analyzed using separate three-way, repeated measures, split plot analyses of variance (ANOVA) to evaluate the main effects (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983) of propofol and possible interactions between propofol, morphine and time. In order to appreciate the synergistic interactions with morphine, it was necessary to evaluate propofol independently. Therefore, the analyses were performed over both conditions of morphine (i.e., phase I and II). Because the primary interest of the first hypothesis was to identify confounding synergistic effects between propofol and morphine, particular emphasis was placed on the avoidance of a Type II error to protect the internal validity of the study (i.e., not detecting a true difference related to the effect of propofol). To reduce the risk of a Type II error, the familywise alpha level (α_{FW}) for each type of major effect was adjusted to $\alpha < .10$ to enhance power (Huck & Cormier, 1996).

For the second and third hypotheses, planned simple effects analyses were used to test the effects of morphine on VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning. To determine if mean VO_2I was lower and if mean SvO_2 was higher following lateral positioning when morphine was received before the turn, planned comparisons of the interaction between *morphine* and *time* following lateral positioning were conducted using an *F* statistic to test the effect of *morphine* at minute 1 and minute

5 following lateral positioning (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983). By using planned comparisons to test the hypotheses, statistical power was reserved for priority tests of primary interest. Consequently, the Omnibus *F* tests for the main effects of *morphine* and *time* and the *Morphine* x *Time* interaction was avoided as this would have increased the probability of a Type II error (Huck & Cormier, 1996). Because there were only two levels of the repeated factor (morphine) at each level of time, only one correlation coefficient was produced. Therefore, the sphericity assumption was automatically satisfied and statistical evaluation of the homogeneity of treatment-difference variance assumption was unnecessary (Maxwell & Delaney, 1990). Using a separate error term and a mixed-model approach (i.e., univariate), analyses were conducted on the mean scores of the dependent variables rather than change scores. Results were based upon a conservative *F* test. Consequently, the power of the test was reduced to avoid a Type I error (Huck & Cormier, 1996; Maxwell & Delaney, 1990). To control the α_{FW}, the level of significance was adjusted using the Bonferroni technique and alpha was set at 0.05/2 or $\alpha = .025$ for the second and third (df = a-1, n-1) (Bland & Altman, 1995b; Maxwell & Delaney, 1990). To decrease the possibility of a Type I error, a more stringent alpha level was used since the results of the study may influence decisions regarding the medical treatment of individuals. Contrasts or post-hoc investigations of the simple effects were unnecessary because there were only two levels of the repeated factor (Maxwell & Delaney, 1990). Post hoc estimation of power and

magnitude of effect were calculated using methods described by Maxwell and Delaney (1990).

For the fourth hypothesis, simple standard regression was performed using the Logistic Regression procedures in the SPSS™ Regression Models 9.0 computer program (SPSS, 1999) to evaluate whether the proportion of variance in SvO_2 that was accounted for by VO_2I following lateral positioning was significantly different when morphine was received before the turn (Glass & Hopkins, 1984; Maxwell & Delaney, 1990). For the analyses, VO_2I measured at minute 3 following lateral positioning (i.e., the independent variable), was regressed on SvO_2 measured at minute 3 following lateral positioning (i.e., the dependent variable) under both conditions of morphine. To determine if there was a significant difference between the proportion of variance in SvO_2 accounted for by VO_2 at minute 3 following lateral positioning, with and without morphine, planned comparisons of the standardized correlation coefficients (β), with and without morphine, were evaluated using a z test. The level of significance was set at $\alpha = .25$ ($df = n - 2$, two-tailed). To evaluate the assumptions of normality, linearity and equal variance or homoscedasticity, bivariate scatterplots were examined for outliers and nonlinearity.

For the fifth and final hypothesis, Kaplan Meier survival analysis was used to evaluate SvO_2 recovery following lateral positioning, with and without the effects of morphine (Bland, 1997). Statistical analyses were performed using the SPSS™ Advanced Models 9.0 statistical program.

Summary

A prospective, single group, quasi-experimental, repeated measures, factorial design was used to determine the effects of morphine on tissue oxygenation variables following lateral positioning in cardiovascular surgical patients with low oxygen delivery. Prospective power analysis was calculated using data obtained from the pilot study (Jesurum, 1996) and from other researchers (Rodriguez et al., 1983; Rouby et al., 1979) to determine the magnitude of effect of morphine (0.10 mg/kg iv) on maximal VO_2 response following lateral positioning. Using methods described by Maxwell and Delaney (1990) for a within-subjects repeated measures design, between 28 and 40 subjects were needed to detect a significant difference in VO_2 response related to morphine ($d = 0.5$; $r = .4$ to .6) with a power of .80 ($\alpha = .05$; 2-levels of the repeated factor). Subjects who met the eligibility criteria and provided verbal consent were enrolled into the study using nonprobability sampling technique from a population of mechanically ventilated, adult cardiovascular surgical patients with low oxygen delivery. Continuous SvO_2 and CO were measured using the OPTI-Q™ SvO_2/CCO pulmonary artery catheter that has conventional hemodynamic monitoring capabilities in addition to fiberoptics for light transmission. VO_2 was measured noninvasively by indirect calorimetry methods using a closed system metabolic monitor that directly and continuously measured the oxygen difference between inspired and expired gases in mechanically ventilated patients. These instruments were used to assess the immediate and short-term effects of lateral positioning on cardiorespiratory variables (SvO_2, DO_2I,

VO_2I, and O_2ER) with and without the effects of morphine. Using SPSS for Windows® Release 9.0.1, the data were analyzed using descriptive and inferential statistics through the SPSS MANOVA procedures (SPSS, 1999) to statistically test the five hypotheses and to validate the selected assumptions of the Roy Adaptation Model. Opportunities to strengthen the instrumentation protocol and increase internal validity were identified through content validation and the pilot study; and, the protocol was revised accordingly. Revisions to the protocol regarding the collection and treatment of data were also presented in this discussion.

CHAPTER 4

ANALYSIS OF DATA

Critically ill patients frequently undergo routine nursing and medical procedures that substantially increase the consumption of oxygen (VO_2) (Weissman & Kemper, 1991). Positioning patients to a side-lying or to a lateral position every 1 to 2 hours is standard nursing practice in the intensive care unit (ICU) (Bridges, 2001; Bridges et al., 2000). Previous studies have shown that immediately following lateral positioning, VO_2 increases by 20% to 50% and SvO_2 decreases by 8% to 10% (Atkins et al., 1994; Cohen et al., 1996; Horiuchi et al., 1997; Verderber & Gallagher, 1994; Winslow et al., 1990). Additional oxygen requirements are usually made available to the tissues by increasing the cardiac output (CO) and by increasing the percentage of oxygen extracted from the oxyhemoglobin molecule (O_2ER). However, critically ill patients who have decreased myocardial function and decreased hemoglobin levels may lack the normal compensatory mechanisms to adapt to situations that increase metabolic demands. Thus, nursing interventions that increase metabolic demands may overly stress critically ill patients already compromised by cardiorespiratory dysfunction.

The purpose of the first phase of the study was (a) to describe the physiological response patterns of tissue oxygenation variables in critically ill patients with low oxygen delivery (DO_2) following lateral positioning, and (b) to examine the hypothesis that the

decrease in mixed-venous oxygen saturation (SvO_2) observed following lateral positioning is primarily related to an increase inVO_2. This phase involved quantifying the cardiorespiratory and metabolic responses to positional changes. The second phase of the study entailed administering an opioid agonist, morphine sulfate (hereafter referred to as morphine), 20 minutes before turning subjects to a 45-degree lateral position. The investigator hypothesized that the preprocedural morphine intervention would attenuate the effects of skeletal muscle movement on metabolic and cardiorespiratory processes, thereby decreasing VO_2I and minimizing changes in other tissue oxygenation variables (SvO_2, O_2ER). Five research hypotheses were statistically examined.

Description of the Sample

Between April and June 2002, data were collected in the cardiovascular intensive care unit of a 697 bed, not-for-profit, private, teaching hospital located in Seattle, Washington. During this period, 137 adult cardiovascular surgical patients were evaluated to determine if they met the criteria to participate in the study. According to the eligibility criteria, thirty-two patients (23%) qualified to participate in the study. However, one patient who met inclusion criteria was not enrolled into the study due to scheduling conflicts. Therefore, using consecutive sampling technique, 31 subjects were enrolled into the study. Before study enrollment, either the patient, family member or legal guardian provided verbal informed consent. Subjects were able to complete the study procedures and there was no attrition related to hemodynamic fluctuations or treatment adjustments. However, as mandated by the disqualification criteria, one subject

was disqualified during the second phase of the study due to persistent shivering. Data analyses were completed on 30 subjects. On average, data collection was begun 14.5 (*SD* = 6.1) hours following the surgical procedure. The total length of time of the study procedures was approximately 53 (*SD* = 4.7) minutes per subject.

Data obtained on the Demographic Profile Tool in addition to baseline cardiorespiratory measurements were analyzed by descriptive statistics and displayed in a frequency distribution table. Cardiorespiratory parameters including DO_2, VO_2, cardiac output, and stroke volume were indexed to body surface area (i.e., DO_2I, VO_2I, CI, and SI). Mean body surface area (BSA) for the sample was 1.90 (n = 30, SD = 0.3, range 1.41 – 2.48). Baseline data were graphically screened for outliers and departures from normality through frequency histograms and normal probability plots. Normal probability plots of the baseline physiologic measurements demonstrated relative proximity to the diagonal. Neither patterns nor clustering of data points were apparent. Statistical significance of skewness and kurtosis was evaluated by calculating the ratio of each statistic to its standard error (SPSS, 1996). Although some of the physiological variables used to describe the sample appeared to be skewed upon inspection of the histograms, none of the variables had a ratio greater than ± 2.0 that would have been indicative of a departure from normality. Normality of the interval-ratio level data was assessed using the Shapiro-Wilk's test. Results of data inspection suggested that the sample's baseline physiologic measurements were normally distributed ($\rho > .05$) (Gibbons, 1993).

Age, gender and ethnic origin. Caucasians composed 93.5% (n = 28) of the sample; with the other two participants being of Asian descent (6.7%). Although the sample lacked ethnic diversity, the ethnic distribution of the sample was representative of the patient population at the facility where the research took place. Men (n = 15, 50%) and women (n = 15, 50%) were equally represented in the sample. The mean age of the sample was 68.4 years (SD = 9.9, range 46 - 87).

Medical diagnoses. Admitting medical diagnoses and preexisting comorbidities for the sample included ischemic coronary heart disease (n = 26, 86.7%), hypertension (n = 20, 66.7%), prior myocardial infarction (n = 15, 50%), heart failure (n = 14, 46.7%), valvular disease (n = 13, 43%), diabetes mellitus (n = 13, 43.3%), renal insufficiency or failure (n = 5, 16.7%), and pulmonary hypertension (n = 3, 10%). According to the medical records, 50% (n = 15) of the sample was diagnosed preoperatively as having left ventricular dysfunction (i.e., diagnosed by attending cardiologist as having left ventricular ejection fraction (LVEF $\leq$ .50). However, documentation of preoperative LVEF was available for only 18 subjects. For these subjects, mean LVEF was 49.8% (n = 18, SD = 15.4, range 42.1 – 57.4). Additional information about specific cardiovascular diagnoses for the sample is presented in Table 5.

Surgical procedures. During their hospitalization, 43% (n = 13) of the sample had a coronary artery bypass graft procedure, 33% (n = 10) had a valve replacement, 20% (n = 6) had a combination coronary artery bypass graft (CABG) procedure with valve replacement, and one subject (3.3%) had an aneurysm repair with coronary artery

reimplantation. Of the 16 (53.3%) subjects who underwent valvular surgery, either in isolation (n = 10, 33.3%) or as a combination procedure with CABG (n = 6, 20%), 20% (n = 6) had an aortic valve replacement, 20% (n = 6) had a mitral valve repair or replacement, 1 (3.3%) had a tricuspid valve replacement, and the remaining 3 (9.9%) subjects had multiple valvular replacements involving the aortic, mitral, and tricuspid valves.

For the majority of the sample, the urgency of surgical treatment was classified as emergent, within 0 to 5 hours of presentation (n = 12, 40%), or urgent, within 5 to 48 hours of presentation (n = 8, 27%). Twenty-three percent (n = 7) of the procedures were classified as reoperations, which indicated that the subject had previously undergone cardiovascular surgery via a median sternotomy approach. Predictably, extracorporeal circulation and aortic cross-clamp times were prolonged and reflected the complexity of the procedures and difficulty in separating from extracorporeal circulation (extracorporeal circulation time, M = 151 minutes, SD = 64; aortic cross-clamp time, M = 117 minutes, SD = 54). Emergent mediastinal reexploration was indicated for four (13%) subjects who developed early postoperative complications including coagulopathy and cardiac tamponade. Additionally, four subjects (13%) experienced cardiac arrest during the perioperative period prior to study enrollment and nine (30%) subjects required intra-aortic balloon counterpulsation therapy postoperatively for treatment of cardiogenic shock or failure to separate from extracorporeal circulation. Surgical intervention and perioperative data are summarized in Table 6.

Mortality. To illustrate the severity of illness in the sample, discharge disposition was evaluated. As a group, the sample had a higher inhospital mortality rate (16.7%) in comparison with the overall inhospital mortality rate for the cardiovascular surgery population at the facility where the research took place (2% - 6%). Higher mortality of the sample was anticipated due to the large number of subjects who were elderly and had multiple preexisting comorbidities, advanced cardiovascular disease, and complex surgical procedures. Five (16.7%) subjects died as a result of postoperative complications, 14 (46.7%) were discharged home, and eleven (36.7%) were discharged to a long-term care facility.

Clinical characteristics. Baseline cardiorespiratory assessment revealed decreased myocardial performance as evidenced by elevated pulmonary artery occlusion pressure (PAOP) (M =16, SD = 5.2), decreased left ventricular stroke work index (LVSWI) (M = 23 g/min/m^2, SD = 5.7), decreased stroke volume index (SVI) (M = 28 ml/m^2, SD = 5.0), and low to normal cardiac index (CI) (M = 2.6 L/min/m^2, SD = 0.41). Tissue oxygenation disturbances were substantiated by baseline parameters that demonstrated increased oxygen extraction ratio (O_2ER) (M = .41, SD = .11), a predictable response associated with elevated VO_2I (M = 139 ml/min/m^2, SD = 22) and low DO_2I (M = 355 ml/min/m^2, SD = 71). Although many subjects exhibited normal SvO_2 values (M = 64%, SD = 8.3) at the beginning of the study procedures, all subjects were noted to have persistent low oxygen delivery defined as $DO_2I < 500$ ml/min/m^2. Although arterial oxygen saturation (SaO_2) was adequate (M = 98, SD = 1.06), the combination of low cardiac index, low

hemoglobin (Hb) (M = 10.38 g-/dl, *CI 95%*, 9.9 – 10.8, SD = 1.2), and low arterial oxygen content (CaO_2) (M = 13.9, SD = 1.53) resulted in low DO_2I at baseline. Clinical characteristics of the sample are summarized in Table 7.

Treatment modalities. During the study procedures, most of the subjects (n = 28, 93%) received multiple vasoactive or inotropic infusions (M = 2.4, SD = 1.1, range 0 - 4) for treatment of low cardiac output syndrome (LCOS) and/or hypotension related to low systemic vascular resistance. Information regarding pharmacological interventions for the sample is presented in Table 8.

Acute blood loss, hemodilution, and hemolysis resulted in significant anemia, an anticipated complication associated with cardiovascular surgery, despite a high blood transfusion rate (n = 26, 86.7%). Mean number of allogeneic red blood cell (RBC) transfusions received was 2.7 units (SD = 4.86) during the intraoperative period and 2.4 units (SD = 2.86) in the early postoperative period before data collection.

Subjects (N =30) were mechanically ventilated using traditional modes of ventilation (synchronized intermittent mandatory ventilation [SIMV], n = 26, 86.7%; assist-control [AC], n = 4, 13.3%) and settings, including fraction of inspired oxygen (FiO_2) (M = .50, SD = .07, range .40 - .70), tidal volume (M = 10 ml/kg, SD = 1.8, range 6 - 14), positive end-expiratory pressure (PEEP) (M = 5.5 cm H_2O, SD = 1.3, range 5 - 10), and pressure support (M = 5.6 cm H_2O, SD = 2.4, range 0 – 15). The investigator and research assistant evaluated *work of breathing* by using a four-point scale to subjectively qualify each subject's breathing effort immediately prior to study

procedures. Numerical ratings ranged from 1 (*non-labored breathing*) to 4 (*very labored breathing*). All subjects (N =30) received a score of 1, implying that breathing effort appeared to be non-labored.

Analgesia and sedation. Within 2-hours of beginning data collection, all subjects (N =30) received an anxiolytic (n = 28, 93%), an analgesic (n = 25, 83%), or both (n = 24, 80%). For the management of acute postoperative pain, 24 (80%) subjects received fentanyl via intermittent dosing (i.e., nurse-controlled analgesia) or continuous infusion and one subject received a continuous infusion of morphine (2.0 mg/hr iv). Five subjects (17%) did not receive an analgesic agent within the 2-hour period before data collection. Analgesic dosages were not weight-based and the average dose of fentanyl (M = 20.0 µg/hr iv, *CI 95%*, 16.0 – 25.0, SD = 17.3) was significantly *lower* than therapeutic dosages recommended in the literature (0.70 – 10.0 µg/kg/hr iv) (Jacobi et al., 2002; Shapiro et al., 1995). As mandated by the study protocol, data collection did not begin until at least 1-hour following the last administered dose of an analgesic, which on average was 74 minutes (*CI 95%*, 65 – 84, SD = 24).

At the time of enrollment, 50% (n = 15) of the sample was receiving a continuous infusion of propofol (Diprivan®) that was maintained at a constant dose throughout the study procedures. The average dose of propofol during data collection was 23.5 µg/kg/min iv (*CI 95%*, 14.0 – 33.0, SD = 17.64). For comparison purposes, this equated to a dose of 1.4 mg/kg/hr iv. Dosages were not adjusted during the 30-minute period before beginning the study protocol or during the data collection period. In addition to the

15 subjects who received propofol during the study procedure, 11 other subjects had also received a continuous infusion of either propofol (n = 9) or midazolam (n = 1) prior to enrollment; however, these medications were discontinued an average of 46 minutes (*SD* = 21) before beginning data collection. Immediately prior to the start of data collection, level of sedation scores were obtained by the investigator and research assistant using the Modified Ramsay Sedation Scale that quantifies degrees of sedation according to stimulus response (Barr et al., 2001; Ramsay, Savege, Simpson, & Goodwin, 1974; Robinson, Ebert, O'Brien, Colinco, & Muzi, 1997). The majority of the sample was classified as lightly sedated and easily arousable (n = 15, 50%) or moderately sedated and sleeping but responsive to normal auditory stimulus (n = 8, 26.7%). Five subjects (16.7%) were classified as awake and responsive to commands, while only two (6.7%) subjects were classified as deeply sedated. Spearman's Rho correlational analyses revealed that propofol dosages (n = 28, r_s = -.11), time since receiving an analgesic (n = 25, r_s = -.013), and previous fentanyl dose (n = 22, r_s = -.19), had essentially no relationship with sedation scores ($\rho > .05$). Sedation scores for the sample and for subjects with and without propofol are summarized in Table 9.

Propofol groups. To assess baseline differences between subjects with and without a propofol infusion, physiological measurements and tissue oxygenation variables were evaluated between subgroups using independent samples t tests. To control for an inflated Type I error risk attributable to multiple comparisons (Huck & Cormier, 1996), the level of significance for baseline comparisons between propofol

groups was set at $\alpha = .01$ (two-tailed). Equality of variance assumption was statistically evaluated using the Levene's Test ($\rho < .05$). Because the assumption of homogeneity of variance was rejected, group comparisons between mean VO_2I was based on the more conservative unequal-variance *t* test. No significant baseline differences were identified between propofol groups ($\rho > .20$). Baseline physiological data and clinical characteristics of subjects who received propofol and those who did not are presented in Table 10.

Body position. To control for the effect of body position (left vs. right), 15 (50%) subjects were randomized to the 45-degree left lateral position and 15 (50%) subjects were randomized to the 45-degree right lateral position. To test the randomization process, baseline physiological data including cardiorespiratory parameters were evaluated between subjects turned to the left and those turned to the right. Differences related to propofol dosages and amount of time (minutes) since receiving an analgesic were also examined between subjects turned to the left and right position. Baseline comparisons were evaluating using independent samples *t* tests ($\alpha = .01$; two-tailed). To control for an inflated Type I error risk attributable to multiple comparisons (Huck & Cormier, 1996), the level of significance was set at $\alpha = .01$. Equality of variance assumption was statistically evaluated using the Levene's Test ($\rho < .05$). Because the assumption of homogeneity of variance was rejected ($\rho < .05$), conclusions for CaO_2 and LVSWI were based on the more conservative unequal-variance *t* test. Baseline

physiological data and clinical characteristics of subjects positioned in the left and right lateral positions are presented in Table 11.

Of the 24 baseline characteristics that were statistically and clinically evaluated, no statistically significant differences were found between group means ($\rho > .01$). Because group differences on measures of hemoglobin, heart rate, left ventricular stroke work index, and mean arterial pressure *approached* the level of significance ($\rho = .02 - .05$), these variables were critically evaluated. Most outstanding was an approximate 1g-/dl difference in hemoglobin between the groups (left, $M = 10.91$, $SD = 1.31$ vs. right, $M = 9.85$, $SD = 0.88$). In addition to lower hemoglobin levels, subjects randomized to the right lateral position had marginally higher O_2ER (left, $M = .38$ vs. right, $M = .43$), VO_2I (left, $M = 133$ ml/min/m^2 vs. right, $M = 146$ ml/min/m^2), cardiac index (left, $M = 2.44$ L/min/m^2 vs. right, $M = 2.70$ L/min/m^2), and heart rate (left, $M = 90$ vs. right, $M = 98$). Although group differences between cardiorespiratory variables did not exceed 10%, results suggested that subjects randomized to the right lateral position were more anemic and had a higher heart rate and O_2ER. Importantly, differences in mean SvO_2, DO_2I, arterial oxygen saturation (SpO_2), and stroke index were not observed between groups.

Findings

Data obtained from the Cardiorespiratory Parameters Tool were coded, entered into a computer, and examined for accuracy of data entry and missing cases. Statistical analyses were performed using the Statistical Package for the Social Sciences ™ (SPSS) for Microsoft Windows ® Release 9.0.1 (SPSS, 1999). Measures of skewness,

histograms and normal probability plots were graphically examined for outliers and departures from normality. Normal probability plots of the dependent measurements demonstrated relative proximity to the diagonal. Neither patterns nor clustering of data points was apparent. Assumptions of normality were statistically evaluated using Kolmogorov-Smirnov and Shapiro-Wilk's tests (Siegel & Castellan, 1986). Results indicated that the dependent measurements were normally distributed ($\rho > .05$) (Gibbons, 1993; SPSS, 1999). Pairwise linearity and homoscedasticity were graphically assessed through bivariate scatterplots of the dependent measurements. Assumptions appeared to be satisfied and transformations of the dependent variables were not indicated. Independence of observations was assumed because all treatments were individually administered (Glass & Hopkins, 1984). All 30 cases were included in the analyses.

Interrater reliability. For each subject enrolled into the study, interrater reliability was evaluated by assessing the consistency between SvO_2 measurements recorded by the investigator and research assistant at designated time intervals during baseline measurements as specified in the research protocol. Results indicated that there was acceptable interrater reliability between the investigator and research assistant (N =120 pairs, r = 1.00) (Waltz et al., 1991). Prior to collection of baseline data, the investigator and research assistant independently conducted pulmonary artery waveform analyses according to established criteria (Appendix D) to ensure that the fiberoptic catheter was correctly positioned in the pulmonary artery, a necessary condition for obtaining reliable data. As part of the instrumentation calibration procedures to ensure reliability of

measurement and reduce measurement error, the raters independently interpreted the quality of the signal to noise indicator of the CCO instrumentation and the SvO_2 light intensity signal as displayed on the bedside monitors. Results indicated that raters were in agreement 100% of the time (N =30) regarding the anatomical location of the pulmonary artery catheter and quality of instrumentation signals.

SaO_2 vs. SpO_2: Methods comparison. Clinically significant differences (M = .072, SD = 1.22) were not observed between paired measurements of SaO_2 obtained on the laboratory co-oximeter (M = 98.34, SD = 1.06) and SpO_2 obtained via a finger transducer probe and displayed on the bedside monitor (M = 98.27, SD = 1.51). On average, SpO_2 rendered oxygen saturation (SO_2) that was .07% *less* than the SaO_2 obtained on the co-oximeter and represented the amount of systematic error or *bias* of SpO_2. Within the population, the true value of bias would fall between -.39% and .54%, 95% of the time (t_{28} = .319, ρ = .752). The degree of random error or imprecision, determined by calculating the standard deviation (SD) of the difference scores between SaO_2 and SpO_2, was 1.22%. Thus, for approximately 95% of the population, it was expected that pulse oximetry would provide a mean SpO_2 value that was within ± 3% of the SaO_2 value obtained on the co-oximeter (95% limits of agreement = -2.3% and 2.4%). These limits of agreement were determined to be clinically unimportant and within the acceptable limits established for the research protocol. Therefore, for each subject, the initial measurement of SaO_2 was obtained on a co-oximeter and for the following measurements, SpO_2 was obtained from the bedside monitor. These findings are similar

to those of other researchers who have evaluated pulse oximetry and determined the instrument to be accurate and precise in comparison to co-oximetry (Clayton, Webb, Ralston, Duthie, & Runciman, 1991; Haessler et al., 1991; Nickerson, Sarkisian, & Tremper, 1988; Norreslet et al., 1990). Results of the method comparisons between SaO_2 and SpO_2 are represented in the Bland-Altman plot presented in Figure 5.

Hypothesis 1

Planned Analyses

Hypothesis 1 stated that there are significant differences in mean VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning between groups of cardiovascular surgical patients with low DO_2I who receive morphine before turning and those who receive morphine and propofol (H_0: $\mu 1_{MS} = \mu 1_{MS+P}$; $\mu 5_{MS} = \mu 5_{MS+P}$; $\alpha = .10$, two-tailed). The two dependent measures, VO_2I and SvO_2, were analyzed in separate analyses of variances (ANOVA) (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983). To evaluate the main effects of propofol and possible interactions between propofol, morphine, and time, a three-way (Propofol x Morphine x Time), repeated measures, split plot ANOVA was performed using the General Linear Model Repeated Measures procedure in the SPSS™ Advanced Models 9.0 statistical program (SPSS, 1999). A custom model, rather than a full factorial model, was specified to test the main effects and interactions of interest (e.g., main effects of within-subjects factors were not evaluated). In order to appreciate synergistic interactions between morphine and propofol, it was necessary to evaluate propofol independently (phase I) as well as in

combination with morphine (phase II). Therefore, the analyses were performed over both conditions of morphine. The within-subjects repeated factor *time* had two levels (minute 1 and minute 5) and the within-subjects repeated factor *morphine* had two levels (with and without morphine). *Propofol*, the between-subjects factor, had two levels that included the group who received propofol (n = 15) and the group who did not receive propofol (n = 15).

Because there were only two levels of the repeated factor (*morphine*) at minutes 1 and 5 following positioning, only one correlation coefficient was produced. Hence, the sphericity assumption was automatically satisfied (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983). Error terms and F tests were identical in the univariate and multivariate models (i.e., df = 1). For the between-subjects factor, the assumption of homogeneity of variance was evaluated using the Levene's Test (SPSS, 1999). Although mean VO_2I at minute 1 following lateral positioning with morphine demonstrated unequal variance between groups (ρ = .014), the ANOVA was determined to be robust to violations of homogeneity of variance because the design was balanced and orthogonal (i.e., equal ns across cells), (Glass & Hopkins, 1984). An estimation of the proportion of total variability in the dependent measurements related to propofol was calculated using the eta-squared statistic (η^2) (Maxwell & Delaney, 1990).

For the first hypothesis that evaluated the synergistic effects of propofol and morphine on tissue oxygenation variables, particular emphasis was placed on the avoidance of a Type II error to protect the internal validity of the study (i.e., not detecting

a true difference related to the effect of propofol). To reduce the risk of a Type II error, the familywise alpha level (α_{FW}) for each type of major effect was adjusted to $\alpha < .10$ to enhance power (Huck & Cormier, 1996; Maxwell & Delaney, 1990). Summarized tissue oxygenation and hemodynamic data of propofol groups at baseline, and minutes 1 and 5 following lateral positioning are presented in Tables 12 and 13, respectively. Summary tables of the planned separate three-way ANOVAs are presented in Tables 14 and 15.

Main effect of propofol. Results *inferred* that there were no significant differences in mean VO_2I ($F_{1, 28} = 0.37$, $\rho = .54$) or SvO_2 ($F_{1, 28} = .01$, $\rho = .94$) at minutes 1 and 5 following lateral positioning between subjects who received propofol during study procedures and those who did not. Regardless of time or morphine, subjects who received propofol had slightly *higher* VO_2I ($M_{MS+P} = 143$ vs. $M_{MS} = 139$, $\rho = .54$). For the sample data, the estimated proportion of variance in VO_2I accounted for by the levels of propofol was less than 1%. Essentially, no differences were observed in mean SvO_2 between subjects who received propofol and those who did not ($M_{MS+P} = 61.8$ vs. $M_{MS} = 62.0$, $\rho = .94$).

Propofol x Morphine interaction. Results of the two-way interaction analyses suggested that the overall pattern among the means of VO_2I ($F_{1, 28} = 0.25$, $\rho = .62$) and SvO_2 ($F_{1, 28} = 0.37$, $\rho = .55$) on the repeated factor of morphine were consistent across both levels of propofol. Effects of morphine on VO_2I and SvO_2 did not vary depending on propofol. Simple effect analyses were not indicated.

Propofol x Time interaction. Results of the two-way interaction analyses suggested that the overall pattern among the means of VO_2I ($F_{1, 28} = 0.28$, $\rho = .60$) and SvO_2 ($F_{1, 28} = 0.38$, $\rho = .54$) on the repeated factor of time were consistent across both levels of propofol. Effects of time on VO_2I and SvO_2 did not vary depending on propofol. Simple effects analyses were not indicated.

Propofol x Morphine x Time interaction. Results of the three-way interaction analysis suggested that the effects of the interaction between time and morphine on the means of VO_2I ($F_{1, 28} = .19$, $\rho = .67$) and SvO_2 ($F_{1, 28} = .16$, $\rho = .69$) were not significantly affected by propofol. Therefore, the interaction between time and morphine does not need to be qualified based on the level of propofol. Simple effect analyses were not indicated.

Conclusion. The *F* tests for the main effects of *propofol* and the interactions of propofol with *morphine* and *time* (following lateral positioning) were not sufficiently large to permit an absolute rejection of the null hypothesis. Therefore, the null hypothesis was not rejected and Hypothesis 1 was not supported (H_0: $\mu_{MS} = \mu_{MS+P}$). Results inferred that there were no significant differences in mean VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning between subjects who received morphine and those who received morphine and propofol. Based on these findings, the decision was made to proceed with data analyses of Hypotheses 2 through 5, collapsing over both levels of propofol. Mean VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning, with and without morphine, for both groups are graphically presented in Figures 6 and 7.

Additional Analyses – Post Hoc

As detailed in the original study protocol (Appendix H), additional measurements of VO_2I and SvO_2 were obtained every minute from baseline through minute10 following lateral positioning, during the first and second phase of the study. Because Hypothesis 4 and 5 involved time periods other than minutes 1 and 5 following lateral positioning, additional analyses were indicated to evaluate the effects of propofol on VO_2I and SvO_2 lateral positioning that were not evaluated in the planned analyses of Hypothesis 1.

Separate three-way (*Propofol x Morphine* x *Time*), repeated measures, split plot ANOVAs were performed on the dependent measurements VO_2I and SvO_2 (H_0: all $\alpha\beta jk = 0$; $\alpha = .10$, two-tailed) (Glass & Hopkins, 1984). For this test series, the within-subjects repeated factor *time* had 11 levels (i.e., baseline through minute 10) and *morphine* had two levels (phase I = without morphine; phase II = with morphine). Homogeneity of treatment–difference variances was evaluated using Mauchly's Test of Sphericity. As anticipated, the assumption was rejected due to the high correlation between pairs of measures within the repeated factor that were closest in time (i.e., 1-minute interval). Because the multivariate approach is not robust to violations of homogeneity, analyses involving the repeated within-subjects factor *time* (i.e., Propofol x Time, Propofol x Morphine x Time) were performed using a univariate approach. For the interactions involving *time*, the *df*s were adjusted with the Greenhouse-Geisser procedure to produce a more conservative *F* statistic (Maxwell & Delaney, 1990). For the first hypothesis, particular emphasis was placed on avoidance of a Type II error to protect the internal

validity of the study. Therefore, a less conservative alpha was selected ($\alpha_{FW} < .10$) to enhance the power of detecting a true difference in mean VO_2I related to the effect of propofol (Tabachnick & Fidell, 1983).

Similar to the findings at minutes 1 and 5 after turning, there were no significant differences in mean VO_2I ($F_{1, 28} = .78$, $\rho = .39$) or SvO_2 ($F_{1, 28} = .00$, $\rho = .99$) from baseline through minute 10 following positioning procedures that were related to the main effects of propofol when both phases of the study were evaluated together. Effects of the two-way and three-way interactions involving propofol (Propofol x Time, Propofol x Morphine, Propofol x Morphine x Time) on the means of VO_2I and SvO_2 were not significant. Summary tables of the additional three-way ANOVAs for VO_2I and SvO_2 from baseline through minute 10 following lateral positioning are presented in Tables 16 and 17, respectively. Mean VO_2I and SvO_2 from baseline to minute 10 following lateral positioning, with and without morphine, are graphically presented in Figures 8 and 9, respectively, for both groups.

Conclusions. Results of the additional analyses concurred with the results of the planned analyses that mean VO_2I and SvO_2 following lateral positioning, with and without morphine, was not significantly different between the propofol groups. Therefore, for minutes 1 through 10 following lateral positioning, data were collapsed over levels of propofol rather than incorporating propofol into the analyses and risk sacrificing statistical power.

Power Analysis

The primary concern related to propofol was the potential for a synergistic effect with morphine such that an intervention consisting of morphine *plus* propofol would be more effective at reducing oxygen consumption than an intervention of morphine *without* propofol. If morphine and propofol worked synergistically, subjects who received propofol may demonstrate *lower* VO_2I throughout the study procedures. Consequently, the internal validity of the study would be compromised. To avoid a Type II error, power analysis was conducted to determine whether the available sample size was sufficiently sensitive to detect a statistically significant difference in VO_2I between the propofol groups. Observed statistical power, or the probability of detecting a significant difference between groups and rejecting a false null hypothesis, was calculated using the SamplePower™ 1.0 statistical software program (SPSS, 1997). To test the null hypothesis that the means of VO_2I were equal between groups with morphine and those with morphine and propofol (H_0: $\mu_{MS} = \mu_{MS+P}$), a two-tail test was specified with an alpha level of .10.

An estimated magnitude of effect of propofol was computed on the sample data of mean VO_2I (marginal means, baseline – minute 10, $M_{MS+P} = 144.5$, $SD = 27.3$; $M_{MS} = 134.5$, $SD = 14.4$) using the common within-group standard deviation of 21.8. Results revealed a standardized mean difference (d) of .46 that according to Cohen (1983) is a medium size effect for between-subjects designs. With a sample size of 15 subjects per group, the study yielded a power of .34 to detect a statistically significant result. Based on

the effect size observed in the sample, 60 subjects per group would be required to achieve a power of .80 ($\alpha = .10$, two-tailed). Although the power of the study was limited due to an insufficient number of subjects per group, the *direction* of the observed effect (i.e., *higher* mean VO_2I in subjects who received propofol) *refuted* the notion that propofol at a constant infusion rate of 24 μg/kg/min worked synergistically with morphine (0.10 mg/kg/ibw iv) to augment the treatment effect of reducing oxygen consumption. Thus, the decision to not reject the null hypothesis was retained. Further analyses on the effects of morphine on tissue oxygenation variables did not include propofol as a between-subjects factor.

Statistical power analysis was performed only on the means of VO_2I. The decision to exclude SvO_2 from the power analysis was based on the rationale that the primary intention of the treatment variable was to directly effect oxygen consumption. SvO_2 is a multifaceted variable that globally represents the balance between oxygen delivery and oxygen demand. The treatment variable indirectly affects SvO_2 through a direct influence on oxygen delivery and oxygen consumption simultaneously, thus the observed response may be less readily apparent and require complex interpretations to explain the findings.

Hypothesis 2

Hypothesis 2 stated that mean VO_2I would be significantly lower at minutes 1 and 5 following lateral positioning when cardiovascular surgical patients with low DO_2I receive morphine before turning (H_0: $\mu 1 = \mu 1_{MS}$; $\mu 5 = \mu 5_{MS}$; $\alpha = .025$, two-tailed). To

evaluate whether VO_2I was significantly lower following lateral positioning when morphine was received prior to turning, planned comparisons of the interaction between morphine and time were performed using an *F* statistic to test the effect of morphine (*A*) at minute 1 (B_1) and at minute 5 (B_2) following lateral positioning. Minute 1 post-turn comparisons were methodically selected in anticipation of testing the power of the treatment variable (morphine) at the time interval following lateral positioning when VO_2I was expected to peak. Minute 5 post-turn comparisons were selected for examining the recovery of VO_2I following lateral positioning, with and without the effects of morphine.

To minimize the risks of a Type II error, analyses of the main effects and interactions of morphine and time were not performed. Through the SPSS™ MANOVA Syntax procedures, *morphine* was treated as a within-subjects factor with two levels (A_1 = with morphine; A_2 = without morphine). Two planned simple effects of the morphine (*A*) within time (*B*) interaction were conducted on mean VO_2I at minute 1 (*A* within B_1) and at minute 5 (*A* within B_2) following lateral positioning. Separate error terms were used for each contrast, which provided a more conservative *F* statistic to decrease the possibility of a Type I error. Using the Bonferroni adjustment to control the Type I error rate, the level of significance for each *A* within *B* planned comparison was $\alpha_{PC} = .05/2$ (two-tailed) (Tabachnick & Fidell, 1983).

Simple effects: Morphine within Minute 1 Post-turn (A within B_1). Although mean VO_2I was slightly lower at minute 1 following lateral positioning when morphine was

received prior to turning, the results were not clinically or statistically significant (M_1 =139.90, SD = 23.20; M_2 = 137.86, SD = 25.60; $F_{1,29}$ = 0.22, ρ = .64). During both phases of the study, VO_2I increased from baseline to minute 1 following positioning, however, the increase was greater when morphine was received prior to turning (M_1 = 1.15%, SD = 11.55; M_2 = 4.11%, SD = 8.99).

Simple effects: Morphine within Minute 5 Post-turn (A within B_2). At minute 5 following lateral positioning, VO_2I was slightly lower when morphine was received before the turn, however the results were not clinically or statistically impressive (M_1 = 145.43, SD = 21.81; M_2 = 141.40, SD = 20.95; $F_{1,29}$ = 0.70, ρ = .41). During both phases of the study, VO_2I increased from baseline to minute 5 following lateral positioning. Similar to the findings at minute 1 following the turn, the average increase in VO_2I from baseline to minute 5 following lateral positioning was slightly higher when morphine was received prior to turning (M_1 = 6.07%, SD = 18.32; M_2 = 7.69%, SD = 12.65).

Conclusion. According to the eta-squared statistic (η^2), the variability in mean VO_2I following lateral positioning that was attributable to morphine was less than 1% at minute 1 after the turn and less than 2% at minute 5 after the turn. The null hypothesis was not rejected; therefore, Hypothesis 2 was not supported. Although cardiovascular surgical patients with low DO_2I demonstrated lower mean VO_2I scores at minutes 1 and 5 following lateral positioning when morphine was received before turning, the differences were not statistically or clinically different from turning without morphine. Mean VO_2I at minutes 1 and 5 following lateral positioning, with and without the effects of morphine, is

graphically represented in Figure 10. Details of the statistical results for the simple effect comparisons of *A* within *B* for VO_2I are presented in the ANOVA summary table presented in Table 18. Summarized tissue oxygenation and hemodynamic data that correspond to Hypotheses 2 through 5 are presented in Tables 19 and 20, respectively.

Hypothesis 3

Hypothesis 3 stated that mean SvO_2 would be significantly higher at minutes 1 and 5 following lateral positioning when cardiovascular surgical patients with low DO_2I receive morphine before turning (H_0: $\mu 1 = \mu 1_{MS}$; $\mu 5 = \mu 5_{MS}$; $\alpha = .025$, two-tailed). To determine if SvO_2 was significantly higher following lateral positioning when morphine was received prior to turning, planned comparisons of the interaction between morphine and time were conducted using an *F* statistic to test the effect of morphine (*A*) at minute 1 (B_1) and at minute 5 (B_2) after turning. Minute 1 post-turn comparisons were scientifically chosen to test the power of the treatment variable (morphine) at the time interval following lateral positioning when SvO_2 is expected to be the lowest (Gawlinski & Dracup, 1998). Minute 5 post-turn comparisons were selected for examining the effects of morphine on SvO_2 recovery following lateral positioning.

Analyses of the main effects and interactions of morphine and time were not performed to minimize the risks of a Type II error. Through the SPSS™ MANOVA Syntax procedures, *morphine* was treated as a within-subjects factor with two levels (A_1 = with morphine; A_2 = without morphine). Two planned simple effects of the morphine (*A*) within time (*B*) interaction were conducted on mean SvO_2 at minute 1 (*A* within B_1) and

at minute 5 (A within B_2) following lateral positioning. Separate error terms were used for each contrast, which provided a more conservative *F* statistic to decrease the possibility of a Type I error. Using the Bonferroni adjustment to control the Type I error rate, the level of significance for each *A* within *B* planned comparison was $\alpha_{PC} < .05/2 = .025$ (two-tailed) (Tabachnick & Fidell, 1983).

Simple effects: Morphine within Minute 1 Post-turn (A within B_1). At minute 1 following lateral positioning, mean SvO_2 was significantly higher when morphine was received before turning ($M_1 = 59.27$, $SD = 7.99$; $M_2 = 62.9$, $SD = 7.20$; $F_{1, 29} = 16.82$, $p = .000$). During both phases of the study, SvO_2 decreased from baseline to minute 1 following lateral positioning (CI_1 97.5%, -4.48 - -9.95; CI_2 97.5%, -2.1 - -6.77). However, the average relative decrease in SvO_2 from baseline to minute 1 following lateral positioning was 38.4% less when morphine was received before the turn ($M_1 = -7.21\%$, $SD = 6.33$; $M_2 = -4.44\%$, $SD = 5.42$). According to the eta-squared (η^2) statistic, 37% of the variability of in SvO_2 at minute 1 following lateral positioning was explained by the effects of morphine. Observed power was calculated by SPSS™ procedures using the noncentrality parameter *SD* of the *F* statistic. Power calculations using the noncentrality parameter *SD* formula have been shown to underestimate the actual power of the test in a repeated measures design (Maxwell & Delaney, 1990). Observed power of the *F* test to detect a statistically significant difference between the means of SvO_2 at minute 1 following lateral positioning, with and without the effects of morphine, was .95 ($\alpha = .025$).

Simple effects: Morphine within Minute 5 Post-turn (A within B_2). At minute 5 following lateral positioning, SvO_2 was significantly higher when morphine was received before turning ($M_1 = 61.40$, $SD = 7.89$; $M_2 = 64.13$, $SD = 6.80$; $F_{1, 29} = 13.55$, $\rho = .001$). During both phases of the study, SvO_2 decreased from baseline to minute 5 following lateral positioning (CI_1 97.5%, -0.68 - -6.85; CI_2 97.5%, -0.77 - -4.29). However, the relative decrease in SvO_2 at minute 5 following lateral positioning was 32% less when morphine was received before turning ($M_1 = -3.73$, $SD = 7.23$; $M_2 = -2.53$, $SD = 4.04$). As indicated by the eta-squared (η^2) statistic, 32% of the variability in SvO_2 at minute 5 following lateral positioning was attributed to the effects of morphine. Observed power of the F test to detect a statistically significant difference between the means of SvO_2 at minute 5 following lateral positioning, with and without the effects of morphine, was .90 ($\alpha = .025$, two-tailed).

Conclusion. The null hypothesis was rejected in favor of Hypothesis 3. Based on the analyses, cardiovascular surgical patients with low DO_2I had significantly higher SvO_2 at minutes 1 and 5 following lateral positioning when morphine was received before turning ($\rho < .00$). Results are graphically illustrated in Figure 11. During the first phase of the study, subjects on average experienced a 7.2% decrease in SvO_2 from baseline to minute 1 following lateral positioning and a 3.7% decrease from baseline to minute 5. In comparison, during the second phase of the study when morphine was received before the turn, subjects on average experienced a 4.4% decrease in SvO_2 from baseline to minute 1 following lateral positioning and a 2.5% decrease from baseline to

minute 5. When morphine was received before the turn, the decrease in SvO_2 at minutes 1 and 5 following lateral positioning was on average 38% and 32% less, respectively, than when subjects were turned without morphine. Changes in SvO_2 following lateral positioning are graphically illustrated in Figure 12. Details of the statistical results for the simple effects comparisons of *A* within *B* for SvO_2 are presented in the ANOVA summary table presented in Table 21.

Hypothesis 4

Hypothesis 4 stated that there is a significant difference in the proportion of variance in SvO_2 accounted for by VO_2I when cardiovascular surgical patients with low DO_2I receive morphine before turning (H_0: $zr1 = zr2$; $\alpha = .025$, two-tailed). To evaluate whether the proportion of variance in SvO_2 that was accounted for by VO_2I following lateral positioning was significantly different when morphine was received before the turn, simple standard regression was performed using the Logistic Regression procedures in the SPSS™ Regression Models 9.0 computer program (SPSS, 1999). For the analyses, VO_2I measured at minute 3 following lateral positioning (i.e., the independent variable), was regressed on SvO_2 measured at minute 3 following lateral positioning (i.e., the dependent variable) under both conditions of morphine. For the comparisons, minute 3 observations were selected to "*capture*" the largest changes in SvO_2 and VO_2I following lateral positioning (Gawlinski & Dracup, 1998; Horiuchi et al., 1997). To determine if there was a statistically significant difference in the proportion of variance in SvO_2 that was attributed to VO_2I, when morphine was received before turning, planned

comparisons of the standardized correlation coefficients (β), with and without morphine, were evaluated using a z test ($df = n - 2$, two-tailed) (Bland, 1997; Glass & Hopkins, 1984; Huck & Cormier, 1996). To avoid a Type I error, the level of significance for the planned comparisons was adjusted using the Holms procedure, a Bonferroni-type adjustment ($\alpha_{FW} = .025$) (Huck & Cormier, 1996).

Assumptions of normality, linearity, and homoscedasticity were examined through bivariate scatterplots of the residuals against the predicted and observed SvO_2 scores and the residuals against VO_2I. Inspection of the scatterplots suggested that normality and homoscedasticity assumptions were satisfied. However, a moderate curvilinear relationship was observed between the plotted residuals; therefore, the assumption of linearity was not satisfied (Figure 13). Seven outliers were identified as having very low ($n = 2, \leq 113$) or very high ($n = 5, \geq 157$) VO_2I scores that caused excessive variance in the distribution of residuals (≥ 2 *SD*s). Outliers were not removed from the analyses because they properly represented the target population and provided physiological measurements of primary interest. For the same reason, data were not transformed to force linearity.

Normality was statistically evaluated using Kolmogorov-Smirnov and Shapiro-Wilk's tests. Results inferred that there were no significant departures from normality ($\rho > .05$). Pearson product moment correlation coefficients (r) were calculated between SvO_2 and VO_2I to evaluate multicollinearity and singularity. Bivariate correlations revealed weak relationships between the variables. To avoid unacceptably low power of

the regression analysis, minimum requirements of case-to-independent variable ratio (20:1) were satisfied (Tabachnick & Fidell, 1983).

Regression of VO_2I on SvO_2. At minute 3 following lateral positioning, the variance accounted for in SvO_2 by VO_2I was less than 1% and was not statistically different from zero ($r = .096$, $F_{1,28} = 0.26$, $\rho = .61$). At minute 3 following lateral positioning, when morphine was received before the turn, the variance accounted for in SvO_2 by VO_2I was slightly higher (10%) but was not statistically different from zero ($r = .010$, $F_{1,28} = .28$, $\rho = .59$). Means, standard deviations, and partial correlations between the variables are presented in Table 22.

Conclusion. The null hypothesis was not rejected; therefore, Hypothesis 4 was not supported. There was no significant difference between the variance accounted for in SvO_2 by VO_2I at minute 3 following lateral positioning, when subjects received morphine before the turn ($zr^1 = .096$, $zr^2 = .100$, $z = .716$, $df_{1,28}$, $\rho > .05$). VO_2I did not explain SvO_2 during the first or second phase of the study. Results may have been distorted due to the relatively large number of outliers within a small sample causing the strength of the relationship to be understated. However, removal of the outliers would have reduced the case-to-independent variable ratio and possibly altered statistical power; therefore, outliers were not removed from the analyses.

Hypothesis 5

Hypothesis 5 stated that SvO_2 will return to baseline in a significantly shorter period of time (minutes) following lateral positioning when cardiovascular surgical patients with low DO_2I receive morphine before turning (H_0: $\mu 1 = \mu 2$; $\alpha = .05$; two-tailed). To evaluate whether SvO_2 returned to baseline (recovery) in a shorter period of time following lateral positioning when morphine was received before turning, survival analysis was performed using the Kaplan-Meier procedure (Bland, 1997). To capture the SvO_2 recovery event, a 10-minute observation period was selected based on previous research findings that have documented average SvO_2 recovery times following lateral positioning in similar populations (Gawlinski & Dracup, 1998; Pena, 1989; Tidwell et al., 1990; Winslow et al., 1990). For the purposes of the analyses, the terminal event of interest was defined as the time (minutes) following lateral positioning that SvO_2 returned to the exact or higher baseline (pre-turn) value, thus indicating SvO_2 recovery had occurred. If SvO_2 recovery occurred within the 10-minute observation period following lateral position, the data were treated as *uncensored* and the exact time of recovery was statistically analyzed. If SvO_2 recovery did not occur within the 10-minute period following lateral positioning, the data were treated as *censored* and the survival time was limited to 11 minutes for the purpose of data analyses. Cumulative survival, an estimation of the probability that SvO_2 recovery will not occur within 10 minutes following lateral positioning, was calculated for both conditions of morphine. Pairwise comparisons of the equality of survival distributions between the first and second phase of the study were

performed using the non-parametric logrank, or Mantel-Cox test that has a chi-square distribution with one degree of freedom ($\alpha = .05$, two-tailed.) (Bland, 1997). Assumptions of the logrank test including stability of the baseline measurements and exactness of survival and censoring times were satisfied by procedures outlined in the study protocol. Descriptive statistics including mean survival time (limited to 11 minutes), standard error and 95% confidence intervals were reported for the uncensored cases.

Cumulative survival. During the first phase of the study, 50% ($n = 15$) of the sample was censored, meaning SvO_2 did not return to baseline within 10 minutes following lateral positioning. When subjects ($N = 30$) did not receive morphine before turning, the estimated probability of SvO_2 not returning to baseline within 10 minutes was .50 ($SE = .09$). Limited mean survival time for SvO_2 recovery was 7.8 minutes for the 15 uncensored subjects who achieved SvO_2 recovery during phase I ($SE = .7$, *CI 95%*, 6.39 – 9.14).

During the second phase of the study, 26.7% ($n = 8$) of the sample was censored, meaning SvO_2 did not return to baseline within 10 minutes following lateral positioning when morphine was received before turning. When subjects received morphine before turning, the estimated probability of SvO_2 not returning to baseline within 10 minutes was .27 ($SE = .08$). Limited mean survival time for SvO_2 recovery was 6.1 minutes for the 22 uncensored subjects who achieved SvO_2 recovery during phase II ($SE = .73$, *CI 95%*, 4.63 – 7.50).

When morphine was received before turning, there was a significantly higher probability of achieving SvO_2 recovery within 10 minutes following lateral positioning ($U = 3.73$, $df = 1$, $\rho = .05$). Cumulative survival and hazard curves are presented in Figures 14 and 15, respectively. As graphically demonstrated by the descent of the cumulative survival curve, when morphine was received before turning, SvO_2 recovery was achieved in a shorter period.

Conclusion. The null hypothesis was rejected; therefore, Hypothesis 5 was accepted. Forty-six percent more subjects achieved SvO_2 recovery within 10 minutes following lateral positioning when morphine was received before the turn ($n = 22$ vs. $n = 15$). Additionally, for subjects who achieved SvO_2 recovery, the mean time to recovery (limited to 11 minutes) was on average 1.76 (22%) minutes less when morphine was received prior to turning ($M_1 = 7.8$, *CI 95%*, 6.39 – 9.14; $M_2 = 6.07$, *CI 95%*, 4.63 – 7.50). Results inferred clinical and statistical significance.

Summary of the Findings

Statistical analyses were completed on 30 subjects. Five research hypotheses were analyzed using a variety of inferential and non-parametric tests to study physiological response patterns of critically ill patients with impaired oxygen delivery following lateral positioning. Additionally, the effect of a preprocedural morphine intervention on attenuating the oxygen demand-induced VO_2 response associated with lateral positioning was evaluated. Statistical analyses were performed using the SPSS™ Advanced Models 9.0 statistical program.

For the first hypothesis, mean VO_2I and SvO_2 were analyzed using separate three-way, repeated measures, split plot ANOVAs to evaluate the main effects of propofol and possible interactions between propofol, morphine and time. Although subjects who received propofol demonstrated higher VO_2I during both phases of the study, the statistical results inferred that there were no significant differences in VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning between subjects who received propofol during the study procedures and those who did not receive propofol. The empirical evidence demonstrated that at minutes 1 and 5 following lateral positioning with morphine, subjects who received propofol had *higher* mean VO_2I than subjects who did not received propofol (minute 1 post-turn, $M_{MS+P} = 142$ vs. $M_{MS} = 134$; minute 5 post-turn, $M_{MS+P} = 143$ vs. $M_{MS} = 140$). Additional analyses confirmed similar trends throughout both phases of the study at each 1-minute interval from minutes 1 though 10 following lateral positioning. Because the available sample size was small ($n = 15$ per group), there was insufficient power (.34) to reject the *non-directional* null hypothesis that mean VO_2I was not significantly different between propofol groups. Based on the dosages at the time of data collection, the interactions between propofol and morphine were determined to be inconsequential to the internal validity of the study. Because there was no empirical evidence that suggested mean VO_2I was *lower* when subjects received propofol *plus* morphine, data were collapsed over levels of propofol (i.e., propofol groups were combined) for the analyses of Hypotheses 2 through 5. Further comparisons between subjects who received propofol and those who did not were not indicated.

For the second and third hypotheses, planned simple effects analyses were used to test the effects of morphine on the means of VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning. Results of the second hypothesis indicated that there were no significant differences in meanVO_2I following lateral positioning when subjects received morphine before the turn; therefore, the null hypothesis was not rejected. Although mean VO_2I following lateral positioning trended *lower* when morphine was received prior to turning (minute 1 post-turn, $M = 140$ vs. $M_{MS} = 138$; minute 5 post-turn, $M = 145$ vs. $M_{MS} = 141$), the findings were not statistically or clinically significant. In comparison, findings of the third hypothesis revealed that mean SvO_2 was significantly higher at minutes 1 and 5 following lateral positioning when subjects received morphine before turning (minute 1 post-turn, $M = 59$ vs. $M_{MS} = 63$; minute 5 post-turn, $M = 61$ vs. $M_{MS} = 64$). During both phases of the study, SvO_2 decreased (i.e., percent change from baseline) immediately following a supine to lateral turn; however, when morphine was received before the turn, the average decrease in SvO_2 from baseline at minutes 1 and 5 following the turn was 38% and 32% less, respectively, than when subjects did not receive morphine prior to turning. The null hypothesis was rejected in favor of Hypothesis 3.

For the fourth hypothesis, simple standard regression analysis was used to evaluate the proportion of variance in SvO_2 that was accounted for by VO_2I at minute 3 following lateral positioning, with and without the effects of morphine. Findings indicated that there was no significant difference in the proportion of SvO_2 accounted for by VO_2I when subjects received morphine before turning. However, the analyses were

likely distorted due to the large number of outliers in the relatively small sample and the curvilinear relationship between the residuals of the dependent and independent variables. No clinically impressive patterns emerged during either phase of the study that could explain the relationship between SvO_2 and other cardiorespiratory variables. For Hypothesis 4, the null hypothesis was not rejected.

For the fifth and final hypothesis, Kaplan Meier survival analysis was used to evaluate SvO_2 recovery following lateral positioning, with and without the effects of morphine. Results indicated that when morphine was received before turning, subjects had a 46% greater chance of achieving SvO_2 recovery (i.e., return to baseline) within a 10-minute period following lateral positioning compared with turning without morphine. During the first phase of the study (without morphine), SvO_2 returned to baseline within a 10-minute period following lateral positioning in 50% of the sample ($n = 15$). In comparison, during the second phase of the study (with morphine), SvO_2 returned to baseline within a 10-minute period following lateral positioning in 73.3% of the sample ($n = 22$). For subjects who achieved SvO_2 recovery, the mean time to recovery (i.e., return to baseline) was 22% less (1.76 minutes) when morphine was received before the turn. The null hypothesis was rejected in support of Hypothesis 5.

CHAPTER 5

SUMMARY OF THE STUDY

For critically ill patients, the predominant threat to tissue oxygenation is a primary reduction in oxygen delivery (DO_2) that is independent of a decrease in oxygen demand (Enger & Holm, 1990). When DO_2 is insufficient to satisfy metabolic requirements, oxygen demand may be temporarily supported by an increase in oxygen extraction (O_2ER); consequently, venous oxygen content (CvO_2) may decrease below minimum levels necessary to ensure adequate tissue oxygenation (McMichan, 1987; Stevens, 1987). When DO_2 is critically low, conditions or situations that increase oxygen demand may trigger tissue oxygen deprivation and alterations in cellular function (Routsi et al., 1993; Smith & Steele, 1991; Verderber & Gallagher, 1994). Cardiovascular surgical patients are a subset of critically ill patients who are at risk of having low DO_2 due to commonly occurring complications following cardiovascular surgery including decreased hemoglobin and depressed myocardial function. These patients are especially vulnerable to disruptions in oxygen supply and demand balance because they often lack compensatory mechanisms to increase DO_2 when metabolic requirements increase (Winslow et al., 1990).

Lateral positioning, a routine nursing procedure to prevent complications associated with immobility and prolonged bedrest, increases sympathetic stimulation and oxygen demand (Gawlinski & Dracup, 1998). Routine positioning to promote comfort,

skin integrity, and optimal ventilation-perfusion ratios may have adverse physiological consequences for cardiovascular surgical patients with insufficient DO_2 (Horiuchi et al., 1997; Winslow et al., 1990). Researchers have shown that morphine sulfate (hereafter referred to as morphine), an opioid agonist, decreases metabolic rate and oxygen consumption (VO_2) in patients undergoing interventional and surgical cardiovascular procedures (Colonna-Romano & Horrow, 1994; Rodriguez et al., 1983; Rouby et al., 1981). Therefore, the investigator postulated that if cardiovascular surgical patients with low DO_2 received morphine before lateral positioning, further disruption of oxygen supply and demand balance would be avoided, as evidenced by decreased VO_2 and increased mixed venous oxygen saturation (SvO_2). Furthermore, complications associated with tissue hypoxia such as cardiac arrhythmias, hypotension, and cardiac arrest may be prevented (Winslow et al., 1990).

Roy's Adaptation Model (Andrews & Roy, 1991; Roy, 1984; Roy & Andrews, 1991), which emphasizes the effects of environmental stimuli on human beings and the role of intrinsic and extrinsic factors in mediating responses to stressors, guided the conceptual framework of the study. According to Roy's model, ventilation, alveolar/capillary gas exchange, and gas transport are prerequisites of adequate tissue oxygenation (Thompson, 1991). Adaptation to lateral positioning occurs through neurochemical regulation and is manifested by physiological integrity and oxygen supply and demand balance (Andrews & Roy, 1991; Roy & Andrews, 1991). "If one's

oxygenation needs are met, then physiological integrity is achieved" (Andrews & Roy, 1986).

The twofold purpose of the clinical trial was (a) to describe the physiological adaptation patterns of severely ill patients with limited cardiorespiratory reserves following lateral positioning, and (b) to test the efficacy of preprocedural morphine on attenuating the oxygen demand-induced VO_2 responses associated with lateral positioning in critically ill patients with low DO_2. Ultimately, the goal of the study was to develop the nursing science related to oxygen modulation therapy that provides critical care nurses with research-based interventions that they can use to support tissue oxygenation and improve patient tolerance and outcomes to routine nursing procedures. Although other researchers have systematically studied oxygen consumption attenuation, the current study is the only study that has clinically evaluated oxygen consumption modulation therapy by investigating a *nurse-administered* intervention to decrease oxygen demand and prevent oxygen deficiency in critically ill patients with low DO_2. This study also extends other similar research by investigating physiological adaptation patterns of a homogenous group of critically ill patients qualified by low DO_2. Lateral positioning as well as pain and sedation management are typically nursing domains; and, therefore, it is appropriate for nurses to scientifically evaluate these phenomena.

Summary

A prospective, single group, quasi-experimental, repeated measures, factorial design (Cook & Campbell, 1979) was used as the methodological framework to determine the potential benefits of a preprocedural morphine intervention on attenuating the oxygen demand-induced VO_2 response following lateral positioning in critically ill patients with low DO_2. Five hypotheses were statistically examined. For the first hypothesis, mean VO_2I and SvO_2 was analyzed using separate three-way, repeated measures, split plot ANOVAs to evaluate the main effects of propofol (Diprivan®) and possible interactions between propofol, morphine and time. For the second and third hypotheses, planned simple effects analyses were used to test the effects of morphine on VO_2I and SvO_2 at minutes 1 and 5 following lateral positioning. For the fourth hypothesis, simple standard regression analysis was used to evaluate the proportion of variance in SvO_2 that was accounted for by VO_2I at minute 3 following lateral positioning, with and without the effects of morphine. For the fifth and final hypothesis, Kaplan Meier survival analysis was used to evaluate SvO_2 recovery following lateral positioning, with and without the effects of morphine. Statistical analyses were performed using the SPSS™ Advanced Models 9.0 statistical program.

Prospective power analysis for a repeated measures design indicated that between 28 and 40 subjects would be required to detect a large size effect ($d = 0.5$) of morphine on mean VO_2I at the .05 level of significance with a power of .80 and an estimated mean correlation among the repeated measurements of $r = .4$ to .6, when only two levels of

morphine were examined (phase I = no morphine, phase II = morphine 0.10 mg/kg/ iv) (Maxwell & Delaney, 1990). Cardiovascular surgical patients with low DO_2 (< 500 ml/min/m^2) were eligible to participate in the study if they (a) had undergone surgery requiring extracorporeal circulation within the past 6 to 24 hours, (b) were mechanically ventilated with positive end expiratory pressure ≤ 10 cm H_2O and FiO_2 < .8, (c) had a fiberoptic pulmonary artery catheter, and (d) had no contraindications to morphine or lateral positioning. The Institutional Review Board at Swedish Medical Center in Seattle, Washington approved the study. Subjects or their family member provided verbal informed consent. Eligibility was not limited by DO_2, SvO_2 or cardiac output.

Using non-probability, consecutive sampling technique, 31 of the 137 patients who were screened over a 3-month period qualified to participate in the study and were enrolled. One subject who developed shivering during the data collection period was disqualified as mandated by the research protocol. Thus, the final sample consisted of 30 cardiovascular surgical patients, fifteen men and fifteen women, who were hemodynamically stable despite having impaired tissue oxygenation. Typically, men comprise about 70% of the cardiovascular surgery population. The higher percentage of women (50%) in the sample is likely related to the severity of the disease classification associated with the target population since elderly females are known to have worse outcomes following cardiovascular surgery (American Heart Association, 2001; Beery, 1995).

Although most subjects had normal SvO_2 ($M = 64\%$, $SD = 8.3$), tissue oxygenation disturbances were substantiated by baseline parameters that revealed low DO_2I (M = 355 ml/min/m^2, $SD = 71$) and increased O_2ER ($M = .40$, $SD = .11$). Baseline cardiorespiratory assessment revealed decreased myocardial performance as evidenced by elevated pulmonary artery occlusion pressure (PAOP) ($M = 16$, $SD = 5.2$), decreased left ventricular stroke work index (LVSWI) ($M = 23$ g/min/m^2, $SD = 5.7$), decreased stroke volume index (SVI) ($M = 28$ ml/m^2, $SD = 5.0$). Although not excessively anemic according to current transfusion guidelines (Klein, 1995), subjects did have low hemoglobin ($M = 10.38$ g-/dl, *CI 95%*, 9.9 – 10.8, $SD = 1.2$) and, therefore, low arterial oxygen content (CaO_2) ($M = 13.9$, $SD = 1.53$). On average, data collection was begun 14.5 ($SD = 6.1$) hours following surgery.

During the first phase (*control phase*) and second phase (*treatment phase*) of the study, physiological response patterns following lateral positioning were explored through tissue oxygenation variables (SvO_2, VO_2) and relationships between the variables were examined. The second phase of the study entailed administering morphine 20 minutes before turning subjects in an attempt to attenuate the effects of skeletal muscle movement on metabolic and cardiorespiratory processes, thereby minimizing changes in tissue oxygenation. Thus, the first phase involved quantifying the cardiorespiratory and metabolic responses to lateral positioning without the condition of morphine, whereas the second phase involved quantifying the cardiorespiratory and metabolic responses to lateral positioning with the condition of morphine.

Physiologic adaptive responses were studied through variables that reflect tissue oxygenation including SvO_2, DO_2, O_2ER and VO_2. Independent or treatment variables included lateral positioning and morphine. Hypothesis 1 had an additional treatment variable that included propofol. To assess the immediate and short-term effects of positioning on tissue oxygenation, data were collected at baseline and for 10 minutes following the turn during both phases of the study. SvO_2 and VO_2 were measured at 1-minute intervals. DO_2 and O_2ER were measured at baseline and at 3, 5 and 10 minutes following the turn. Cardiorespiratory parameters were indexed to body surface area (BSA) (i.e., DO_2I, VO_2I, CI, LVSWI, SI). Cardiorespiratory data including blood pressure (BP), heart rate (HR), right atrial pressure (RAP), pulmonary artery pressure (PAP), CI, stroke index (SI), left ventricular stroke work index (LVSWI), and systemic vascular resistance index (SVRI) were also collected at baseline and at serial intervals (3, 5, and 10 minutes) following the turn to describe the population and explain the physiological responses to lateral positioning and morphine. Hemoglobin (Hb) and arterial oxygen saturation (SaO_2) were measured on a laboratory co-oximeter at baseline during the first phase of the study. Hemoglobin was assumed to remain stable during the 50-minute data collection period. To ensure hemoglobin stability, subjects who had an acute blood loss defined as pleural or mediastinal drainage > 100 ml/hr during the 2 hour period prior to the study were not eligible to participate in the study. Blood loss of $\geq$ 100 ml during the data collection period mandated disqualification and termination of the study.

Instruments used to measure hemodynamic pressures (RAP, PAP), CO, SI, LVSWI and SvO_2 included the (a) OPTI-Q™ SvO2/CCO fiberoptic pulmonary artery catheter, (b) Q-Vue CCO Monitoring System™, and (c) SvO_2 module (Agilent CMS Technologies). After the catheter and processor were calibrated using in vitro criterion obtained on the laboratory co-oximeter, SvO_2 was continuously displayed as a percentage on the bedside monitor. Hemodynamic (SVRI, LVSWI, SI) and oxygenation (Qs/Qt, CaO_2) variables were calculated using the Hewlett Packard® Hemo Calc and Oxygen Calc software programs. VO_2 was measured by indirect calorimetry methods using the Puritan-Bennett® Model 7250™ closed system metabolic monitor that directly and continuously measures the oxygen difference between inspired and expired gases in patients who are mechanically ventilated. The metabolic monitoring system consisted of an oxygen analyzer, a cylinder of calibration gas (95% oxygen, 5% carbon dioxide), a pump, a two-line light emitting diode display, and a microprocessor to aid in data acquisition and calculations. Differences between inspired and expired oxygen concentrations were directly measured on a continuous, breath-by-breath interval and averaged every 1 minute. Measurement of VO_2 through exhaled gas analysis is expressed by the formula:

$$VO_2 \approx VE \times (FiO_2 - FeO_2) \qquad \langle 7 \rangle$$

where, VE = minute ventilation, FiO_2 = fraction of inspired oxygen, and FeO_2 = fraction of expired oxygen (Ahrens & Rutherford, 1993). After the line and oxygen sensors were calibrated, VO_2 (ml/min) was continuously displayed on the metabolic monitor and recorded at each 1-minute measurement interval.

For the purposes of the study, DO_2I was manually calculated using the formula:

$$DO_2I \approx CI \times 1.34 \times Hb \times SaO_2 \times 10 \qquad \langle 8 \rangle$$

where, arterial oxygen saturation as measured by pulse oximetry (SpO_2) was substituted for SaO_2 (Ahrens & Rutherford, 1993). O_2ER was calculated using the formula (Ahrens & Rutherford, 1993):

$$O_2ER \approx \frac{VO_2}{DO_2} \qquad \langle 9 \rangle$$

Prior to beginning data collection, measures were taken to reduce environmental stimulation including decreasing ambient light and noise, maintaining a constant ambient temperature, and eliminating unnecessary traffic into the subject's room. To ensure a stable baseline, data collection did not begin until a 30-minute equilibration period following positioning and suctioning procedures, ventilator changes, and titration of medications. Following the 30-minute stabilization period, additional measurements of SvO_2 and VO_2 were obtained every 15 seconds over a 1-minute period and averaged to ensure that a stable baseline for comparison had been achieved prior to beginning data

collection. Interrater reliability was assessed to determine potential sources of variability or measurement error relating to locations of the pulmonary artery catheter and data transcription.

Using the lottery method, subjects were randomly assigned to the left or right 45-degree lateral position with 20-degree backrest. During the first turn sequence, measurements of the dependent variables were obtained before and after the subjects were passively turned from the supine to lateral position. A body wedge support pillow was placed between the bed and subject's back to maintain the lateral position. Following a 10-minute observation period, subjects were passively turned to the supine position and a standardized dose of morphine based on ideal body weight (0.10 mg/kg/ibw iv) was administered via an infusion device over a 5-minute period. Twenty minutes after the morphine infusion was initiated, subjects were turned again to the lateral position. Turn sequences and data collection procedures were identical during the first and second phase of the study (Appendix H). To avoid the *carry over* effects of morphine, control preceded treatment for all subjects. The average length of time for the completion of the study procedures was 53 ($SD = 4.7$) minutes per subject.

Discussion of the Findings

The following discussion focuses on the comprehensive temporal relationships between cardiorespiratory variables that were examined to address the first aim of the study.

Hypothesis 1

According to literature sources, the concomitant use of opiates may intensify the cardiorespiratory depression effects of propofol (Clinical Pharmacology Online, 2000). Due to the potential for synergistic interactions between morphine and propofol, it was postulated that an intervention consisting of morphine and propofol would be more effective at reducing oxygen consumption than an intervention of morphine without propofol. In theory, subjects who received propofol would be more likely to have *lower* VO_2I than subjects who did not receive propofol. Consequently, the internal validity of the study would be compromised if propofol confounded the effects of morphine. Therefore, analyses of variances were performed to evaluate the main effects of propofol and possible synergistic interactions between morphine and propofol over time periods following lateral positioning.

VO_2I. Results of the planned analyses at minutes 1 and 5 following lateral positioning, *inferred* there were no significant differences in mean VO_2I between subjects who received propofol and those who did not receive propofol. Although the differences were not statistically significant, subjects who received propofol had *higher* mean VO_2I at minutes 1 and 5 following lateral positioning than subjects who did not receive

propofol. Results of additional analyses that evaluated mean VO_2I from baseline through minute 10 following positioning concurred that there were no statistically significant group differences related to propofol during either phase of the study. However, despite the statistical findings, group comparisons revealed that mean VO_2I was consistently *higher* in the propofol group during the 10-minute period following lateral positioning when morphine was received before the turn. These observations were contrary to the anticipated effects of propofol on VO_2I and were inconsistent with the findings of other researchers (Cohen et al., 1996).

Although the results were not statistically significant, distinct clinical patterns emerged within the groups between the first and second phase of the study. For the 15 subjects who received propofol, mean VO_2I between minutes 1 and 10 following lateral positioning was not different when morphine was received before the turn. In comparison, when subjects without propofol received morphine, mean VO_2I was considerably *lower* during the 10-minute period following lateral.

On average, the increase (i.e., relative percent change from baseline) in VO_2I from baseline to minute 1 and from 5 following lateral positioning, with and without morphine, was comparable between groups. During phase I and II, both groups demonstrated larger increases in VO_2I from baseline to minute 5 than from baseline to minute 1 following lateral positioning; however, the largest increases were observed in phase II when morphine was received before the turn. Between baseline and minute 5 following lateral positioning with morphine, VO_2I increased an average of 6.5% in the

group with propofol and 8.9% in the group without propofol. These findings were inconsistent with the findings of other researchers who have demonstrated that mean VO_2I usually increases by 20% to 50% from baseline following lateral positioning (Cohen et al., 1996; Horiuchi et al., 1997; Swinamer et al., 1987; Weissman et al., 1984). Excessively large variances and standard deviations were associated with the change in VO_2I from baseline to each minute following the turn during the 10-minute measurement period. Compared to subjects who did not receive propofol, subjects in the propofol group demonstrated larger variances in VO_2I between baseline and minute 1 through minute 10 following positioning, although less variance was observed when morphine was received prior to the turn. Group differences were not clinically significant (i.e., > 10%) during either phase of the study.

SvO_2. In comparing mean SvO_2 between propofol groups, results of the original analyses and additional analyses inferred that mean SvO_2 at baseline and at each minute for 10 minutes following lateral positioning was not significantly different between propofol groups. These findings were consistent during phase I and II. Mean SvO_2 appeared to be clinically unaffected by propofol irrespective of morphine treatment.

Without morphine, the average decrease (i.e. change from baseline) in SvO_2 from baseline to minute 1 following lateral positioning was 8.0% for subjects with propofol and 6.4% for subjects without propofol. These findings are comparable to the results of other investigators (Gawlinski & Dracup, 1998; Winslow et al., 1990) and considered to be clinically insignificant changes (i.e., expected variability associated with lateral

positioning). At minute 5 following lateral positioning without morphine, the average decrease in SvO_2 from baseline was 5% for subjects with propofol and 2.5% for subjects without propofol. In comparison, the average decrease in SvO_2 from baseline to minute 1 (4.4% for both groups) and from baseline to minute 5 (propofol = 2.7%, no propofol = 2.4%) was essentially the same for both groups when morphine was received before turning. These findings do not concur with the findings of other researchers who have consistently demonstrated that in critically ill patients SvO_2 normally returns to baseline by minute 5 following lateral positioning (Gawlinski & Dracup, 1998; Winslow et al., 1990). In the current study, SvO_2 recovery to baseline for both groups appeared to be steady but prolonged during the 10-minute observation period following lateral positioning. In either group, differences in mean SvO_2 between baseline and minute 10 following the turn were not significantly different.

Effect of Propofol on Cardiorespiratory Variables

To explain the unanticipated findings, the effects of propofol on cardiorespiratory variables were examined. Descriptive statistics of the hemodynamic and tissue oxygenation variables were examined at baseline and at minutes 1 and 5 following lateral positioning, with and without morphine, between propofol groups.

Between-subjects comparison: Phase I. On average, subjects in the propofol group had lower SVRI and Qs/Qt at baseline although the differences did not appear to be clinically impressive. Reduced SVR observed in the propofol group was most likely related to the vasodilation properties of propofol and has been reported by other

researchers (Mosby's Drug Consult, 2002; Nimmo et al., 1994). Other variables including VO_2I, DO_2I, SvO_2, O_2ER, SpO_2, HR, CI, SVI, RAP, PAOP, hemoglobin, blood temperature, LVEF, and CaO_2 were not clinically different between groups at baseline during the first phase of the study. Characteristic of critically ill patients with low flow states, subjects in both groups had elevated O_2ER that supported VO_2I in the presence of low DO_2I.

Unlike Cohen et al. (1996) who found that propofol decreased metabolic requirements, mean VO_2I, O_2ER and DO_2I at baseline was not clinically different between groups. Nimmo and colleagues (1994) demonstrated that propofol produces a "*dose-dependent*" decrease in CO that is related to depression of myocardial contractility (i.e., negative inotropic effect) coupled with a reduction in preload due to vasodilatation properties. In the current study, clinically significant differences in mean CI, SVI, or preload (i.e., RAP, PAOP) were not apparent between groups. According to the recommended propofol dosing guidelines for maintaining sedation in critically ill patients, subjects enrolled in the study received "small" doses of propofol (Jacobi et al., 2002; Shapiro et al., 1995). Thus, it is conceivable that cardiorespiratory depression was not observed in the propofol group because the magnitude of effect related to the average dose of propofol was minimal.

Between-subjects comparisons: Phase II. There were no clinically significant differences in mean SvO_2, O_2ER, and SpO_2 between groups at baseline after receiving morphine. Comparisons of cardiorespiratory variables revealed no clinically significant

differences between groups (> 10%); however, several clinical trends emerged from the data. As reported in the analyses, VO_2I was slightly higher in the propofol group. After receiving morphine, subjects in the propofol group had slightly higher preload (i.e., PAOP, RAP) and HR compared with subjects who did not receive propofol; consequently, CI and DO_2I were marginally higher in the propofol group. Because there was a trend for subjects in the propofol group to have lower SVI, SVRI and LVSWI, the most likely explanation for higher mean DO_2I was related to higher mean heart rate. This finding is unexplainable since bradycardia is one of the most common cardiodepressive adverse reactions associated with propofol (Mosby's Drug Consult, 2002). Results of the current study are inconsistent with the findings of Nimmo et al. (1994) who investigated the effects of propofol on hemodynamic and oxygen transport variables in 10 critically ill patients and observed a reduction in CO, blood pressure, and heart rate that was not associated with a change in stroke volume or right ventricular ejection fraction. The researchers concluded that the reduction in heart rate and slight reduction in SVRI rather than a decrease in myocardial systolic function caused CO and blood pressure changes. Several investigators have attributed propofol's effect on HR to a reduction in sympathetic activity (Kowalski & Rayfield, 1999; Robinson et al., 1997). Nimmo and colleagues concluded that when dosed for sedation vs. anesthesia effects, propofol does not produce significant myocardial depression. Therefore, it is possible that the absence of cardiodepressive effects in the propofol group may be explained by the small propofol dosages.

Within-subjects comparisons: Phases I and II. For both groups, baseline measurements of mean VO_2I, O_2ER, MAP, and SVRI were lower with morphine than without morphine. However, mean CI and DO_2I were not clinically different between baseline measurements with and without morphine. Consequently, mean SvO_2 was higher at baseline during the second phase of the study although the findings were not clinically impressive. Subjects without propofol demonstrated a trend towards lower PAD, PAOP and RAP at baseline after receiving morphine, however SVI was unaffected.

Response patterns to lateral positioning. Physiological responses to lateral positioning were similar between propofol groups during the first phase of the study. Without morphine, physiological adaptation to an increase in VO_2I following lateral positioning was associated with an increase in DO_2I of approximately 3% to 6% above baseline. Interestingly, heart rate and O_2ER did not change following lateral positioning although mean arterial pressure did increase slightly. Increases in DO_2I were related to an increase in CI and SVI rather than an increase in heart rate. In the propofol group, there was a strong, positive relationship between VO_2I and SVI at minute 5 following lateral positioning ($r = .73$, $\rho = .002$). It is possible that the reduction in SVRI associated with propofol resulted in a decrease in afterload and an increase in cardiac output. When subjects were turned without morphine, SvO_2 decreased immediately following lateral positioning and partially recovered (i.e., returned to baseline) by minute 5 following the turn. SvO_2 response to lateral positioning without morphine was similar in both groups.

Both groups demonstrated similar response patterns during the second phase of the study. When morphine was received before the turn, physiological adaptation to an increase in VO_2I following lateral positioning was associated with an increase in O_2ER of approximately 5% to 8% above baseline (group with propofol, $r = .63$, $\rho = .013$; group without propofol, $r = .75$, $\rho = .001$). Heart rate, CI, SVI, and DO_2I did not increase from baseline to minute 5 following lateral positioning in either group although mean arterial pressure did increase slightly. SvO_2 response patterns were similar between propofol groups. By minute 5 following lateral positioning with morphine, SvO_2 approximated baseline values.

Cardiovascular compensatory mechanisms to an acute increase in oxygen demand appeared to be "*blunted*" during the second phase of the study following lateral positioning. Evidence suggests that morphine as well as propofol could produce similar cardiodepressive effects when administered separately. Cohen et al. (1996) found that a bolus injection of propofol (0.75 mg/kg iv) administered 2 minutes prior to activity suppressed CO and DO_2I responses to increased activity. In the current study, both groups demonstrated HR, CI, and DO_2I suppression following lateral positioning when morphine was received prior to the turn. Because these responses were not observed during the first phase of the study prior to morphine administration, cardiodepressive effects were likely related to morphine rather than propofol. Findings in this study are consistent with the findings of other researchers who have described "morphine-induced hemodynamic sedation" that results in attenuation of the cardiovascular responses

normally observed during periods of increased activity (Alderman et al., 1972; Rouby et al., 1981; Rouby et al., 1979). Attenuation of cardiovascular physiological responses can be deleterious for critically ill patients with compromised cardiorespiratory reserves when oxygen demands increase acutely. Nimmo and Grant (1994) described a pathological response pattern that consisted of a parallel reduction in DO_2 and VO_2 when severely ill patients received a sedative agent (i.e., propofol). According to the theory of pathologic oxygen supply dependency, critical reductions in DO_2I during periods of high demand may limit VO_2 and result in profound tissue oxygen deprivation (Baigorri & Russell, 1996; Leach & Treacher, 1994). The researchers concluded that in critically ill patients with low-flow states and oxygen supply dependency, sedative agents may produce reductions in VO_2 that are linked to changes (i.e., reductions) in DO_2 and not oxygen demand (Nimmo et al., 1994). The theory of pathological oxygen supply dependency may offer insight into the temporal relationships observed between tissue oxygenation variables following lateral positioning when morphine was received before the turn. It is possible that morphine's effect on the cardiovascular responses resulted in *critically* low DO_2I in relation to the oxygen demand-induced VO_2 response. Further discussion of morphine's effects independent of propofol is presented in the following section.

The combination of "*low-dose*" propofol and morphine did not appear to work synergistically to cause additional cardiorespiratory depression than the intervention of morphine without propofol. The findings are consistent with those of Nimmo et al. (1994) who concluded that propofol, when dosed according to level of sedation, does not

effect global oxygen transport. No studies were reviewed that systematically evaluated the synergistic effects of morphine and propofol on tissue oxygenation variables. For Hypothesis 1, the summarized key conclusions regarding the effects of morphine and propofol in the sample are:

1. The concurrent use of morphine and propofol did not attenuate the oxygen demand-induced VO_2I response following lateral positioning; therefore, for the subjects who received propofol during the study, the treatment variable (*morphine*) was not confounded by the effects of propofol.

2. The effects of morphine and propofol on metabolic and cardiovascular responses are dose-dependent (Cohen et al., 1996; Nimmo et al., 1994; Rouby et al., 1979). The absence of synergistic effects between morphine and propofol observed in the study is likely related to small dosages that subjects received during data collection procedures.

3. Physiological responses to lateral positioning were similar between subjects who received propofol and those who did not receive propofol. Lateral positioning without morphine was associated with an increase in CI and DO_2I. Subjects who received propofol had lower SVRI; therefore, afterload reduction may have enhanced SVI and CI. In comparison, lateral positioning with morphine was associated with an increase in O_2ER and blunted CI and DO_2I responses.

Magnitude of effect. With the available sample size of 15 subjects per group, the study yielded a low power of .34 to detect a statistically significant difference in mean

VO_2I between subjects who received propofol and those who did not receive propofol. Based on the medium size effect size observed in the sample, 60 subjects per group would be required to obtain a power of .80 (Cohen, 1983). Due to the small size of the sample, it is possible that a Type II error was made in the analyses of Hypothesis 1. A larger sample size may have resulted in a significant difference in mean VO_2I between subjects who received propofol and those who did not receive propofol. Based on the empirical evidence, the trend suggested that subjects who received propofol had *higher* mean VO_2I than subjects who did not receive propofol. Although the power of the study was limited due to an insufficient number of subjects per group, the *direction* of the observed effect (i.e., higher VO_2I in subjects who received propofol and morphine) *refuted* the notion that propofol worked synergistically with morphine to augment the treatment effect resulting in a more pronounced reduction in VO_2I. Retrospectively, stipulating a directional alternative hypothesis (i.e., H_a: $\mu_{MS} < \mu_{MS+P}$; one-tailed) would have more specifically tested the effect that was of primary interest in regards to internal validity and would have alleviated concerns regarding a Type II error. For the analyses of Hypotheses 2 through 5, data were collapsed over levels of propofol to increase the statistical power of the tests for exploring the effects of morphine on oxygen consumption modulation.

Findings in the current study do not concur with the findings of Cohen and colleagues (1996) who studied the effects of propofol in 16 critically ill, mechanically ventilated patients during chest physiotherapy. Although Cohen et al. did not control for

the effects of other analgesics or sedatives during the procedure, the findings suggested that large doses of propofol (0.75 mg/kg iv) significantly decreased VO_2I during chest physiotherapy procedures as did low doses of propofol (0.35 mg/kg iv). In Cohen's study, both low and high dose propofol regimens significantly decreased DO_2I and CO, although SvO_2 and O_2ER remained stable. Reductions in systemic arterial blood pressure and heart rate were also observed with low and high doses of propofol. The investigators attributed the reductions in blood pressure to propofol's direct effect on sympathetic vascular tone. Although intracardiac pressures (i.e., RAP, PAOP) were not significantly different between propofol and placebo groups, the difference between baseline measurements and measurements obtained during activity trended slightly lower in the propofol group. Interventions that result in further reductions in DO_2I and CO are not desirable in patient populations with compromised cardiorespiratory function. Therefore, other treatment options that result in isolated reductions in VO_2 are desirable and should be evaluated.

Several explanations of the differences between the findings of the current study and those of Cohen et al. (1996) are offered.

1. Differences in propofol dosages. In the current study, the average dose of propofol during data collection was 23.5 μg/kg/min iv (*CI 95%*, 14 – 33, *SD* = 17.64) that equated to 1.4 mg/kg/hr administered via a continuous infusion. In the Cohen study (1996), the treatment intervention consisted of either low-dose (0.35 mg/kg) or high-dose (0.75 mg/kg) propofol administered intermittently as a "bolus" over a 2-minute interval

before the activity intervention. Compared with the average propofol dose in the current study, both the low-dose and high-dose treatments represent significantly larger doses of propofol administered over a short period of time. It is possible that the differences in patient responses to propofol observed between the studies were related to an "induction" effect vs. a "maintenance" effect. This may also explain why increases in CO, heart rate, and systolic blood pressure were "suppressed," rather than attenuated, in the high-dose propofol group. One subject in the high-dose propofol group experienced hypotension immediately after propofol administration and required intravenous ephedrine for blood pressure support. Because of it's negative inotropic and cardiorespiratory effects, propofol is not the sedative of choice for patients requiring vasopressor or inotrope therapy for cardiac failure (Jacobi et al., 2002).

2. Duration of time following surgery. In 41 clinical trials that examined the use of propofol for sedation in post-CABG patients, the median dose was 11 μg/kg/min (range 0.10 – 30.0 μg/kg/min) (Mosby's Drug Consult, 2002). On average, cardiovascular surgical patients require lower maintenance doses of propofol during the early postoperative period compared with other critically ill patients related to the effects of residual anesthesia and intraoperative administration of high-dose narcotics. In critically ill medical patients or patients who have recovered from the effects of general anesthesia or deep sedation, $\geq$ 50 μg/kg/min iv of propofol may be required to achieve adequate sedation (Mosby's Drug Consult, 2002). In the current study, data collection began an average of 14.5 hours following surgery. Therefore, it is possible that some of the

subjects had residual effects of anesthesia and required lower doses of propofol to maintain sedation. Cohen et al.(1996) did not specify the time between surgery and data collection. If the time between surgery and the start of data collection was greater than 24 hours, subjects may have required larger doses of sedatives (fentanyl, midazolam, lorazepam) to maintain sedation. Accumulation of the parent drug or active metabolites resulting in prolonged sedation are associated with benzodiazepines and depend on patient-specific factors such as age, concurrent pathology, concurrent drug therapy, and duration of drug therapy (Jacobi et al., 2002).

3. Confounding medications. In the Cohen study, measures were not taken to control for the administration or titration of additional sedatives or analgesics, or for titration of vasoactive medications during the study. In fact, 75% of subjects in both the low-dose and high-dose propofol groups received either a continuous intravenous or epidural infusion of fentanyl concomitantly during the study procedures. Other subjects had also received additional doses of midazolam, lorazapam, and fentanyl prior to the study; however, information regarding dose and time of administration in relation to the study procedures was not provided.

4. Different patient populations. In the current study, eligibility requirements included sustained low $DO_2I < 500$ ml/min/m^2. Subjects in the propofol group had a baseline DO_2I of 361 ml/min/m^2 and subjects without propofol had a baseline DO_2I of 350 ml/min/m^2 for subjects without propofol. In comparison, the propofol group in the Cohen study (1996) had a mean DO_2I of 1145 ml/min/m^2 and a CO of 8.9 L/min, while

the control group had a mean DO_2I of 1123 ml/min/m^2 and a CO of 8.8 L/min. In consideration of these strikingly different patient characteristics that directly relate to the oxygen transport system, it is likely that the patients in the two studies would mount different physiological adaptation responses to acute increases in oxygen demands and to interventions designed to decrease metabolic requirements.

Although sedative agents, such as propofol, reduce the stress response and may improve patient tolerance to routine ICU procedures, an analgesic is an appropriate *initial* therapy when pain or discomfort may be associated with a procedure or is the suspected cause of acute agitation (Harding et al., 1994; Jacobi et al., 2002; Klein et al., 1988; Stanik-Hutt et al., 2001). Critically ill patients experience a significant amount of pain during positioning procedures (Puntillo et al., 2001; Stanik-Hutt et al., 2001; Swinamer et al., 1987). In a recently published study involving 6,200 acute and critically ill patients, turning was identified as the most painful and distressing procedure experienced by adults during their hospitalization, in comparison to wound dressing change, drain removal, or tracheal suction (Stanik-Hutt et al., 2001). Although positioning procedures are performed many times a day, analgesics are not routinely administered prior to lateral positioning (Puntillo et al., 2001). In fact, Puntillo et al. (2001) reported that 96.8% (n = 739) of critically ill patients did not receive opioids prior to turning.

Hypothesis 2

Results of the analyses indicated that mean VO_2I was *lower* at minute 1 and at minute 5 following lateral positioning when cardiovascular surgical patients with low DO_2I received morphine before turning however, the findings were not clinically or statistically significant. According to these findings, morphine (0.10 mg/kg iv) administered 20 minutes prior to lateral positioning resulted in less than a 3% reduction in mean VO_2I at 1 and 5 minutes compared to mean VO_2 responses following lateral positioning without morphine. Results of the study suggest that preprocedural morphine in low-dosages does not produce significant attenuation of the VO_2 response during procedures associated with an acute increase in oxygen demand. These observations were contrary to the anticipated effects of morphine on mean VO_2I and were inconsistent with the findings of several other researchers who have reported that morphine in moderate to large dosages (0.20 – 0.5 mg/kg iv) safely attenuates the stress response to surgical recovery and reduces VO_2 by approximately 9% to 21% in critically ill patients including those with cardiovascular disease (Alderman et al., 1972; Bernard et al., 1988; Colonna-Romano & Horrow, 1994; Rouby et al., 1981).

Several mechanisms are offered to explain the differences observed in the current study with those of other studies. These mechanisms include: (a) "actual" magnitude of effect of morphine on VO_2I response was not adequately evaluated by the planned analyses; (b) limited cardiorespiratory reserves attenuated basal VO_2 response and masked responses of oxygen consumption modulation therapy; (c) morphine dosages

(0.10 mg/kg/ibw iv) prescribed by the research protocol were insufficient to adequately attenuate the metabolic response associated with lateral positioning; and, (d) distinct (i.e., equal and opposite effects) VO_2I responses of subgroups within the sample distorted group means and masked the actual effects of morphine within the subgroups. Each of these mechanisms will be presented in the following discussion.

Magnitude of the Effect of Morphine on Peak VO_2I Response

Because peak (i.e., highest) VO_2I did not occur at minute 1 following lateral positioning as had been anticipated, it was possible that peak VO_2I was not "captured" in the planned analyses and therefore the "absolute" magnitude of the effect of morphine was not adequately evaluated. These findings concur with Tidwell et al. (1990) who reported that VO_2 did not significantly change from baseline to minute 1 following lateral positioning in cardiovascular surgical patients during the immediate postoperative period. Therefore, to determine the magnitude of the effect of morphine on peak VO_2I response, descriptive statistics of VO_2I data from baseline through minute 10 following lateral positioning were examined. Results indicated that during the first phase of the study, peak VO_2I (M = 161, SD = 23.9, CI 95%, = 152 - 170) typically occurred between minutes 4 and 5 (CI 95%, 3.2 – 5.5) following lateral positioning and represented a 17.3% (CI 95%, 10 – 24) increase from baseline VO_2I. During the second phase of the study, peak mean VO_2I (M_{MS} = 152, SD = 23.4, CI 95%, 143 - 161) occurred around minute 4 (CI 95%, 3 – 5.3) following lateral positioning and represented a 15.5% (CI 95%, 10 - 21) increase from baseline VO_2I.

Comparisons between mean peak VO_2I response revealed that, on average, morphine was associated with a 6% *relative* reduction in peak VO_2I response following lateral positioning ($M = 161$ - $M_{MS} = 152$). Although the magnitude of effect of morphine was larger by two-fold when peak VO_2I was evaluated, rather than VO_2I at minutes 1 and 5, the overall clinical impression was that morphine (0.10 mg/kg/ibw iv) did not significantly attenuate the oxygen demand-induced VO_2I response following lateral positioning. Excessively large variances and standard deviations were associated with changes in VO_2I between baseline and each minute following the turn during the 10-minute observation period.

An estimated magnitude of effect of morphine on *peak* VO_2I was computed from the sample data using the pooled standard deviation of 23.7. Results revealed a standardized mean difference (d) of 0.38, that according to Cohen (1983) is between a medium and large effect size for within-subjects designs ($M = 161$, $SD = 23.9$; $M_{MS} = 152$, $SD = 23.4$). Observed power, or the probability of detecting a significant difference between groups and rejecting a false null hypothesis, was calculated using SPSS™ MANOVA procedures for a within-subjects factorial design and an alpha (α) level of .10 (two-tailed) and $N = 30$. Results indicated that the study had an observed power of .55 to detect a statistically significant difference in peak VO_2I occurring within the 10 minute observation period following lateral positioning when morphine was received prior to turning. According to methods described by Maxwell and Delaney (1990) for a within-subjects repeated measures design, approximately 80 subjects would be required to detect

a significant difference in the maximal VO_2 response due to the effects morphine with power of .80 ($\alpha = .05$, two-tailed; two-levels of repeated factor) when the effect size is 0.38 and the minimum correlation between the population means is $r = .33$. With the available sample size of 30 subjects, the study was underpowered (.55) to detect a significant difference related to morphine.

Cardiorespiratory Response Patterns

During both phases of the study, subjects had a diminished VO_2 response to lateral positioning. Findings in the current study do not concur with the findings of other investigators who have consistently reported that lateral positioning is associated with a 20% to 50% increase in VO_2 above baseline values (Cohen et al., 1996; Davis et al., 2001; Horiuchi et al., 1997; Swinamer et al., 1987; Verderber & Gallagher, 1994; Weissman et al., 1984). Based on the findings of other researchers who have documented low VO_2 in critically ill patients with myocardial depression (Astiz et al., 1988; Edwards, 1991; Snell & Calvin, 1993), it is possible that morphine did not produce a significant attenuation of the VO_2 response following lateral positioning because VO_2 response was already diminished due to compromised cardiorespiratory reserves. To explain the findings, the effects of morphine on cardiorespiratory variables were examined. Descriptive statistics of the hemodynamic and tissue oxygenation variables were examined at baseline and minute 5 following lateral positioning, with and without morphine. Means and standard deviations of tissue oxygenation and hemodynamic data are summarized in Tables 19 and 20, respectively.

Results demonstrated that when subjects were positioned without morphine, the increase in VO_2I between baseline and minute 5 following lateral positioning was associated with a small (< 5%) increase in DO_2I ($r = .47$, $\rho < .00$) that was related to an increase in CI ($r = .81$, $\rho < .000$) and SVI ($r = .55$, $\rho < .00$). Heart rate and O_2ER did not change significantly between baseline and minute 5 following lateral positioning. In comparison, when subjects received morphine before turning, the increase in VO_2I between baseline and minute 5 following lateral positioning was associated with an 8% increase in O_2ER ($r = .65$, $\rho < .000$). Unlike the metabolic and cardiovascular responses demonstrated during the first phase of the study, DO_2I, SVI, CI, and heart rate did not increase between baseline and minute 5 when morphine was received prior to the turn. Between minutes 1 and 10 following lateral positioning with morphine, there was a trend for CI and DO_2I to gradually decrease over time. Although MAP and SVRI were lower following morphine administration, values were within normal parameters and preload (RAP, PAOP) was unaffected.

Phase I: Response without morphine. Empirical studies have demonstrated that normal VO_2 response to an acute increase in oxygen demand is associated with an immediate increase in cardiac output, stroke volume, heart rate and O_2ER (Cohen et al., 1996; Horiuchi et al., 1997; Weissman & Kemper, 1993). With the exception of O_2ER and heart rate changes that were not apparent, similar physiological trends were demonstrated in the current study. However, the magnitude of VO_2 response observed in the current study did not concur with previous research reports. Specifically, lateral

positioning was associated with a 17.3% increase in VO_2 from baseline whereas other researchers have consistently demonstrated that critically ill patients typically experience an increase in VO_2 by 20% to 50% following lateral positioning (Cohen et al., 1996; Horiuchi et al., 1997; Swinamer et al., 1987; Weissman et al., 1984).

Horiuchi and colleagues (1997) studied the effects of lateral positioning on VO_2I in 13 mechanically ventilated, critically ill cardiovascular surgical patients who were moderately anemic ($M = 9.5$ g-/dl, $SD = 1.2$) and had normal DO_2I, CO, SvO_2 and O_2ER at baseline. In this study, subjects were turned from the supine to lateral position. After remaining in the side-lying position for 2 minutes, subjects were passively turned to the supine position. Immediately following lateral positioning, VO_2 increased by 40% to 50% and returned to baseline by minute 10 following the turn ($M = 219$ at rest, $M = 324$ post-turn). The increase in VO_2 following lateral positioning was associated with a 31% increase in DO_2 ($M = 852$ at rest, $M = 1116$, post-turn) and an 18.5% increase in O_2ER ($M = .27$ at rest, $M = .32$ post-turn). Heart rate and systemic blood pressure also increased after the turn. The researchers attributed the 5.8% decrease in SvO_2 ($M = 69\%$ at rest, $M = 65\%$ post-turn) following turning to an increase in VO_2 (i.e., oxygen demand-induced response). The researchers concluded that an increase in muscle activity associated with lateral positioning was responsible for the increase in VO_2.

It is possible that the diminutive oxygen demand-induced VO_2 response observed in the current study may have been limited by low DO_2I and CaO_2 and maximal oxygenation extraction. Unlike other studies that have examined tissue oxygenation and

metabolic responses of critically ill patients, the focus of the current study was limited to the responses of severely compromised patients, the majority being elderly, with low DO_2 secondary to concomitant hemoglobin reduction and myocardial depression. Explanations for the inability of subjects to mount a "normal" VO_2 response to an acute increase in oxygen demands include (a) limited cardiac reserve and inability to substantially increase CO despite inotropic therapy and optimized preload (i.e., "fixed" cardiac output), (b) depletion of O_2ER reserve capacity, and (c) reduced CaO_2 secondary to low hemoglobin concentration. In studying the response patterns of critically ill patients grouped according to resting metabolic profiles, Weissman, Kemper, and Harding (1994) concluded that metabolic responses (i.e., either an increase in DO_2 or an increase in O_2ER) to an acute increase in oxygen demand will be characterized by the "*underutilized mechanism*" or reserve capacity. The researchers reported that patients who had a hyperdynamic profile at rest (i.e., high DO_2, low O_2ER) demonstrated increased O_2ER in response to an increase in oxygen demand. In comparison, patients who had an elevated O_2ER at rest increased CO when oxygen demand increased. Based on Weissman's conclusions, subjects in the current study who were characterized by low DO_2, low CO, and high O_2ER at baseline would be expected to increase CO in response to an acute increase in oxygen demand. However, Weissman's theory was based on the premise that the reserve capacity was sufficient to facilitate physiological adaptation. Because subjects in the current study had impaired cardiorespiratory function, response patterns may have differed due to the lack of reserve capacity.

Phase II: Response with morphine. In comparison, when 0.10 mg/kg/ibw of intravenous morphine was received 20 minutes before turning, physiological adaptation patterns of tissue oxygenation variables mechanisms to an acute increase in oxygen demand were not apparent. Specifically, reductions in VO_2 were associated with a decrease in CO and DO_2 and an increase in O_2ER that suggested the effects of morphine were primarily related to a *blunting* (i.e., lack of or reduction in anticipated physiological response) of cardiovascular responses rather than a reduction in metabolic demands. Interestingly, the changes were not associated with clinically significant reductions in SvO_2.

Cardiovascular response patterns observed in the current study are similar to the findings of other researchers who have attributed reductions in VO_2 to morphine-induced "*hemodynamic sedation*" that resulted in reductions in cardiac index, stroke volume index, cardiac filling pressures, and heart rate (Alderman et al., 1972; Rouby et al., 1981). Alderman and colleagues (1972) reported an 11.6% decrease in VO_2 following the administration of 8 mg of intravenous morphine sulfate to eight patients undergoing cardiac catheterization who had significant coronary artery disease. Attenuation of VO_2 was associated with an 8.6% decrease in cardiac index, a 10.6% decrease in stroke volume index, and a 20.5% decrease in left ventricular end diastolic pressure following morphine administration ($\rho < .05$). Reductions in cardiac index were not associated with changes in heart rate and minimal reductions were observed in mean RAP and PAOP measurements.

Results of the Alderman et al. (1972) study are inconsistent with those of Rouby and colleagues (1979) who demonstrated that cardiac index remained stable when critically ill patients received 0.15 mg/kg of morphine intravenously. However, when subjects received 0.30 mg/kg of morphine, significant and prolonged reductions in cardiac index ($\geq$ 1 L/min/m^2) and transient decreases in heart rate, stroke volume index, left stroke work index and systemic arterial pressure were observed during the 90-minute period hour following morphine administration. Interestingly, Alderman et al. (1972), Rodriquez et al. (1983), and Rouby et al. (1979) reported that mean RAP and PAOP changed minimally following morphine administration. The researchers speculated that morphine-induced esophageal constriction and increased muscular rigidity may have caused increases in intracardiac pressures (e.g., RAP, PAOP) despite an actual reduction in cardiac index. In the current study, small increases were observed in mean RAP and PAOP following lateral positioning; however, these changes were consistent during both phases of the study regardless of the morphine intervention. Unlike the Rouby et al. study (1979), subjects experienced a reduction in mean CI after receiving 0.10 mg/kg of morphine.

Weissman and colleagues (1994a) suggested that therapeutic interventions should be aimed at maintaining patients in a high DO_2 and low O_2ER state. Therefore, patients would have the physiological reserve capacity to respond to increases in oxygen demand by increasing oxygen extraction rather than increasing cardiac output. During the second phase of the study, mean VO_2I at rest was lower after subjects received morphine.

Despite the effects of morphine, subjects demonstrated persistent elevation of mean O_2ER at rest that was indicative of compromised tissue oxygenation related to a low-flow state and reduced hemoglobin. Normally, patients who have acute-onset anemia respond to an acute increase in oxygen demand by increasing CO and DO_2 (Woodson, Wills, & Lenfant, 1978). However, this physiological compensatory mechanism is impaired in patients who have concomitant myocardial depression. Patients who lack the ability to increase DO_2 are dependent upon a higher O_2ER to meet their needs (Routsi et al., 1993; Smith & Steele, 1991). When oxygen demand is increased, the amount of hemoglobin desaturation is able to increase from about 25% to a maximum arteriovenous saturation difference of 80% (Dantzker, 1987). However, oxygen extraction that exceeds 25% is indicative of insufficient DO_2I reserve to meet the oxygen demands of the tissues (Yu et al., 1998). Examination of the sample data suggests that O_2ER appeared to have been "fixed" between .38 to .42 despite obvious hypermetabolic demands related to critical illness (Epstein & Breslow, 1999). Furthermore, O_2ER appeared to be relatively limited in response to an acute increase in oxygen demand associated with lateral positioning. "*Fixed*" O_2ER, in the presence of hypermetabolic demand, is a hallmark indicator of pathologic supply dependency(Epstein & Breslow, 1999).

In treating patients with tissue oxygenation disturbances, Yu and associates (1998) suggested that therapeutic modalities aimed at augmenting and titrating DO_2 to maintain O_2ER between .20 and .25 may be warranted. However, in the presence of high O_2ER, treatment aimed at *decreasing* oxygen demands may be more appropriate if

critically ill patients with limited cardiorespiratory reserves do not adequately respond to therapies intended to increase DO_2. In the current study, subjects demonstrated a lower mean VO_2I following lateral positioning when morphine was received before the turn. However, metabolic responses to morphine also included larger reductions in oxyhemoglobin (i.e., higher O_2ER) following lateral positioning. Interpretation of these response patterns suggested that morphine blunted normal cardiovascular responses to lateral positioning rather than reducing metabolic demands. Further research is warranted to evaluate oxygen modulation therapies comparing VO_2 and O_2ER as end-points of therapy in subjects with low DO_2, high O_2ER, and compromised cardiac function.

"Low-Dose" Morphine

In the current study, the average dose of morphine calculated on ideal body weight (0.10 mg/kg/ibw, $M = 6.2$ mg iv, $SD = .86$, range 5 to 8) was considerably less than the dosages used by other researchers (range 0.20 to 0.5 mg/kg iv) who have reported significant reductions in VO_2 related to morphine (Alderman et al., 1972; Colonna-Romano & Horrow, 1994; Rodriguez et al., 1983). Inconsistencies between studies regarding the magnitude of morphine's effect on VO_2 attenuation may be partly explained by the differences in dosages. Findings of the current study concur with the results of other researchers (Nimmo et al., 1994; Rouby et al., 1981) who have suggested that that *low-dose* sedation or analgesia is unlikely to produce significant changes in tissue oxygenation variables. As has been suggested by Nimmo and Grant (1994), the

insufficient suppression of VO_2 response to lateral positioning observed in the current study may have been influenced by "*underdosing*" or inadequate dosages of morphine.

To avoid hemodynamic fluctuations associated with histamine response, morphine dosages were based on subject's ideal body weight (IBW) rather than actual body weight (ABW) (Hall et al., 2001). For the majority of subjects in the sample, actual body weight ($M = 82$, $SD = 24.23$) was significantly greater than ideal body weight (IBW) ($M = 61$, $SD = 8.75$). These findings were not unexpected due to the increased risks of coronary artery disease associated with obesity (American Heart Association, 2001). Even if morphine dosages had been based on *adjusted* ideal body weight (IBWa, $M = 70$ kg) vs. ideal body weight (IBW, $M = 61$ kg), the average dosage for subjects would have been larger (IBWa = [(ABW – IBW) x 0.4] + IBW) (Turkoski et al., 1999). Therefore, it is possible that morphine dosages based on adjusted ideal body weight would have resulted in further reductions in the cardiovascular responses and triggered hemodynamic fluctuations which would have been undesirable outcomes. During the study procedures, subjects did not experience significant hemodynamic fluctuations or other adverse reactions to morphine.

Oxygen Demand-Induced VO_2I Responses Among Subgroups

Important individual or subgroup differences can be masked by group means, especially when large standard deviations exist (Huck & Cormier, 1996). The lack of significant attenuation of the metabolic response following lateral positioning when subjects received morphine before the turn may be explained by subgroup responses that

were equal and opposite and, therefore, distorted the overall group results. Additional analyses were performed to evaluate the large variances observed in meanVO_2I change scores. Other researchers have described significant differences between subgroups of critically ill patients according to baseline cardiorespiratory characteristics and have correlated the subgroup profiles to distinct physiological response patterns and patient outcomes (Bland et al., 1985; Rouby et al., 1981). Rouby and colleagues (1981) found significant differences in the magnitude of morphine-induced VO_2 responses among subgroups of critically ill patients who were grouped according to baseline VO_2 measurements. Oxygen consumption decreased by 21% in 10 patients who had elevated oxygen consumption immediately prior to receiving morphine. Patients who had normal oxygen consumption at baseline however, experienced only a 9% decrease in oxygen consumption after receiving morphine. The researchers concluded that morphine effects were significant and prolonged in the subgroup with elevated VO_2 at baseline and transient and moderate in the subgroup with normal VO_2. In addition, Weissman and colleagues (1994) described distinct oxygen demand-induced VO_2 responses among subjects and correlated the response patterns to subgroups with different baseline hemodynamic profiles. According to the researchers, critically ill patients who had high DO_2 and low O_2ER (< .20) at baseline demonstrated an increase in O_2ER when oxygen demands increased, while patients with lower DO_2 and high O_2ER (> .30) experienced an increase in cardiac output when oxygen demands increased.

During the study procedures, distinct oxygen demand-induced VO_2I response patterns emerged following lateral positioning that were not discoverable by planned analyses. These clinical observations were not anticipated and the original research hypotheses were not designed to test particular physiological response patterns between groups. Additional analyses were performed on VO_2I measurements to (a) explain the large variances and standard deviations in mean VO_2I, (b) describe important differences in physiological adaptation patterns between subgroups of critically ill patients with low DO_2I, and (c) determine if the effects of morphine are different among subgroups based on mean VO_2I change scores following lateral positioning without morphine. Three distinct VO_2I response patterns to positioning emerged within the sample data during the first phase of the study and included (a) high (> 10%) increase, (b) moderate (0 – 10%) increase, and (c) decrease (< 0%). Results of the exploratory factorial analyses revealed significant differences among the three subgroups in (a) VO_2 recovery patterns following lateral positioning and (b) the effect of morphine on VO_2 response following lateral positioning. Results of the empirical findings are presented in Appendix I.

In conclusion, for cardiovascular surgical patients with low DO_2I, routine lateral positioning was associated with approximately a 17% increase in VO_2I from baseline that occurred within 4 to 5 minutes after the turn. Ten minutes following the turn, VO_2I approximated baseline values. Compensatory mechanisms to an acute increase in VO_2I, included a small and gradual increase in DO_2I that continued throughout the minute 10 measurement period following the turn and was associated with an increase in SVI and

cardiac index. In comparison, when patients received morphine prior to turning, lateral positioning was associated with a 15.5% increase in VO_2I from baseline that was associated with a small increase in O_2ER from baseline that remained elevated throughout the 10-minute measurement period following the turn. Additional observations included a gradual decline in CI, SVI and DO_2I that also continued throughout the 10-minute period following lateral positioning. These changes were attributed to morphine's attenuation of cardiovascular compensatory mechanisms to an acute increase in oxygen demand.

Hypothesis 3

Results of the analyses indicated that mean SvO_2 was significantly higher following lateral positioning when subjects received morphine before turning. Furthermore, the decrease in SvO_2 from baseline to minute 1 following lateral positioning was significantly less when morphine was received prior to the turn. During both phases of the study, the greatest reductions in SvO_2 from baseline were observed between minutes 1 and 2 following lateral positioning. In critically ill patients with low DO_2I, the physiological variation in SvO_2 associated with lateral positioning was similar to the physiological variation that is normally associated with resting conditions. Initial impressions of the findings suggested that morphine administered 20 minutes prior to lateral positioning effectively attenuated the metabolic responses associated with an acute increase in oxygen demand and, therefore, decreases in mean SvO_2 were minimized.

When cardiorespiratory variables were examined in relation to the SvO_2 changes associated with lateral positioning, with and without morphine, interpretations of the findings led to a different conclusion. Three explanations are offered for the SvO_2 responses demonstrated in the analyses of Hypothesis 3 including (a) limited cardiorespiratory reserves and oxygen supply dependency, (b) morphine-induced attenuation of cardiovascular responses, and (c) effects of body position (i.e., position-effect) masked by group means.

Although the sample's cardiorespiratory profile was indicative of a combination low flow-hypermetabolic state (i.e., high VO_2 in relation to low DO_2) supported by increased O_2ER, SvO_2 remained within limits that have traditionally been defined as "normal" and indicative of oxygen supply and demand balance. Similar to the diminutive oxygen demand-induced VO_2 responses observed in the analyses of Hypotheses 2, it is possible that decreased cardiorespiratory reserves secondary to myocardial depression and low CaO_2 also limited SvO_2 responses. According to Noll et al. (1992), SvO_2 normally fluctuates within ± 6% of baseline in critically ill patients during rest. Based on Noll's criteria, the average increase in SvO_2 from baseline observed at minute 1 following lateral positioning in the first phase of the current study closely approximated the upper limits of normal resting SvO_2 fluctuation. When morphine was received before the turn, the average increase in SvO_2 from baseline following lateral positioning fell within the normal parameters of resting SvO_2 fluctuation.

SvO_2 responses observed in the current study did not concur with the findings of other investigators who have consistently demonstrated that lateral positioning is associated with an immediate decrease in SvO_2 by 8% to 12% (Gawlinski & Dracup, 1998; Shively, 1988; Winslow et al., 1990). Results of the current study suggest that critically ill patients with low DO_2I experience *less* reduction in SvO_2 following lateral positioning than previously reported in the research literature. However, large standard deviations associated with the changes in SvO_2 suggest that significant individual differences were masked by the group mean. On further examination, one subject who had a 21% *increase* in SvO_2 from baseline to minutes 1 and 2 following lateral positioning was identified as an extreme outlier and excluded from the subanalysis (n = 29) of Hypothesis 3. Thus, 11 (38%) of the remaining 29 subjects in the current study demonstrated a > 10% *decrease* (i.e., clinically significant) in SvO_2 between baseline and minutes 1 and 2 following lateral positioning. These findings concur with those of Gawlinski and Dracup (1998) who found clinically significant (i.e., $\geq$ 10% change) decreases in SvO_2 following positioning in 38% to 48% of subjects with low LVEF.

For the 11 subjects who had a clinically significant reduction in SvO_2 following lateral positioning, the average decrease from baseline to minute 1 was 13.8% (SD = 3.3, CI 95%, 11.4 - 16.1). In comparison, for the 18 (62%; n = 29) subjects who did not experience a clinically significant reduction in SvO_2, the average decrease in SvO_2 from baseline to minute 1 following lateral positioning was 4.8% (SD = 2.7, CI 95%, 3.5 – 6.1). Interestingly, subjects who had a > 10% decrease in SvO_2 from baseline following

lateral positioning had a slightly *higher* mean SvO_2 at baseline ($M_{\leq 10\%} = 63$, $SD = 8.4$ vs. $M_{> 10\%} = 66$, $SD = 8.3$) though the results were not clinically impressive. More importantly, subjects who had a > 10% *decrease* in SvO_2 from baseline following lateral positioning had *lower* VO_2I ($M_{> 10\%}$ 133, $SD = 17.3$ vs. $M_{\leq 10\%} = 142$, $SD = 25.5$) and O_2ER ($M_{> 10\%}$ .38, $SD = .08$ vs. $M_{\leq 10\%} = .42$, $SD = .13$) than subjects who had a < 10% change following lateral positioning. Mean DO_2I and CI were not clinically different between subjects who had a significant decrease and those who had a "normal" decrease in SvO_2 following lateral positioning. Mean SvO_2 at minute 1 following lateral positioning was not clinically different between subjects who had a > 10% decrease in SvO_2 from baseline and those who had ≤ 10% decrease ($M_{\leq 10\%} = 60$, $SD = 8.6$ vs. $M_{> 10\%} = 58$, $SD = 7.5$).

During the second phase of the study, *baseline* trends following morphine administration included a reduction in VO_2I and O_2ER, and an increase in DO_2I that was not was associated with changes in CI. Following lateral positioning, only 5 (16.6%) subjects demonstrated a > 10% decrease in SvO_2 from baseline to minute 1 following lateral positioning when morphine was received before turning ($M = 13.3$, $SD = 2.9$, *CI* 95%, 10.0 – 17.0). In comparison, for the 25 subjects who did not experience a clinically significant reduction in SvO_2, the average decrease in SvO_2 from baseline to minute 1 following lateral positioning was 2.7% ($SD = 3.9$, *CI* 95%, 1.1 – 4.2). Due to the small number of subjects who experienced a clinically significant decrease in SvO_2, profile distinctions between subgroups were not evaluated. When morphine was received before

turning, mean SvO_2 was higher and the decrease in SvO_2 from baseline was less following lateral positioning. However, the changes in SvO_2 were associated with a reduction in VO_2I, CI, and DO_2I and a small increase in O_2ER that suggested that the effects of morphine were primarily related to a blunting of cardiovascular responses rather than a reduction in metabolic demands. Despite further reductions of oxyhemoglobin, significant reductions in SvO_2 were not observed because VO_2I decreased in accordance with DO_2I.

Oxygen Supply Dependency Theory

Similar to the explanations provided in discussion of Hypothesis 2, it is possible that SvO_2 response following lateral positioning was attenuated due to low DO_2I and high VO_2I, that was maintained by persistently elevated O_2ER. According to the theory of pathological *supply dependency*, when DO_2 decreases below a critically low level, the altered relationship between DO_2 and VO_2 prevents further disparities between oxygen delivery and consumption; thus, SvO_2 may be maintained despite tissue oxygen deprivation (Leach & Treacher, 1994; Vincent, 1990). Under these conditions, VO_2 is completely regulated by DO_2 such that a decrease in DO_2 will result in an immediate decrease in VO_2. The hallmark of pathologic supply dependency is the inability to increase oxygen extraction in response to a primary reduction in DO_2 whereby, O_2ER becomes "*fixed*" even in the presence of increased demand (Dantzker, 1991). Because oxygen extraction compensatory mechanisms are impaired, continuous SvO_2 monitoring as an indicator of DO_2 - VO_2 balance may have limited utility in patients demonstrating

oxygen supply dependency (Enger & Holm, 1990; Vincent, 1990). Van der Hoeven and colleagues (1999) demonstrated that in the presence of anemia, oxygen unloading to the tissues is impaired. Consequently, when DO_2 decreases below a critically low level, anemia may result in a less significant increase in O_2ER and therefore a smaller decrease in SvO_2 that does not adequately reflect the degree of tissue hypoxia or critical reduction in VO_2. Investigators have recommended that SvO_2 monitoring should be used in conjunction with serial measurements of DO_2 and VO_2 to evaluate perfusion abnormalities (Ahrens & Rutherford, 1993; Shoemaker, 1992, 1993).

Fundamental to the concept of SvO_2 as an accurate indicator of oxygen supply and demand balance are the inherent assumptions that normal vasoregulation of blood flow is unimpaired and that VO_2 is equivalent to oxygen demand (Enger & Holm, 1990). Variations in the distribution of blood flow and the metabolic activity of individual tissues are not reflected by SvO_2 values. Consequently, controversy has centered around the reliability of SvO_2 monitoring and the complexity of data interpretation in the presence of decreased VO_2 (i.e., *supply dependency*), hyperoxia, or compensatory cardiovascular reflexes (e.g., arteriovenous shunt) (Cernaianu & Nelson, 1993). In these situations, SvO_2 may remain stable despite inadequacies of regional and global tissue perfusion (Ahrens & Rutherford, 1993). As a preferable approach to patient management, SvO_2 monitoring should be used in conjunction with serial measurements of DO_2 and VO_2 to evaluate perfusion abnormalities and treatment efficacy (Ahrens & Rutherford, 1993; Shoemaker, 1992, 1993).

Effect of Body Position

Several researchers have concluded that the left lateral position is associated with greater reductions in SvO_2 and lower mean SvO_2 than the right lateral position (Gawlinski & Dracup, 1998; Lewis et al., 1997; Shively, 1988). Similar trends were observed in the current study. Further exploration of the empirical findings revealed a statistically significant interaction between body position (left vs. right) and morphine ($F_{1, 28} = 10.49$, $\rho = .003$) that was associated with an observed power of .80 ($\alpha = .025$, two-tailed). Additional analyses were performed to describe the conditional effects of the treatment intervention. Results of the simple effects revealed that in the left lateral position ($n = 15$), mean SvO_2 was significantly higher during the 10-minute period following lateral positioning when morphine was received before the turn ($M = 60.3$, $SD = 8.9$ vs. $M_{MS} = 64.9$, $SD = 7.1$; $F_{1, 14} = 20.49$, $\rho = .000$; observed power = .97). In comparison, when subjects were turned to the right lateral position ($n = 15$), mean SvO_2 was not significantly different when morphine was received before the turn ($M = 62.6$, $SD = 6.6$ vs. $M_{MS} = 63.5$, $SD = 6.3$; $F_{1, 14} = 3.14$, $\rho = .098$; observed power = .27). Although group differences between baseline cardiorespiratory variables did not exceed 10%, results suggested that subjects randomized to the right lateral position were more anemic and compensated by increasing heart rate and O_2ER to maintain tissue oxygenation. Further discussion of the empirical analyses and findings related to the effects of lateral position are presented in Appendix J. Based on these findings, it is possible that the diminished SvO_2 responses following lateral positioning may be partially related to the

differences between the left and right lateral position and that the larger fluctuations associated with the left lateral position may have been masked by the diminished responses associated with the right lateral position.

Hypothesis 4

Results of the analyses indicated that there was not a significant difference in the proportion of variance in SvO_2 accounted for by VO_2I when cardiovascular surgical patients with low DO_2I receive morphine before turning. At minute 3 following lateral positioning without morphine, the variance accounted for in SvO_2 by VO_2I was less than 1%. When morphine was received before the turn, the variance accounted for in SvO_2 by VO_2I was slightly higher (10%). Although the analyses were likely distorted due to the large number of outliers, the most valid explanation for the findings is related to the curvilinear relationship that existed between SvO_2 and VO_2 at minute 3 following lateral positioning. Throughout the 10-minute observation period following lateral positioning with and without morphine, no significant relationships were identified between mean VO_2I and SvO_2. In comparison, at minute 3 following lateral positioning without morphine, VO_2I had a significant, positive relationship with DO_2I ($r = .44$, $\rho = .016$). However, when morphine was received before turning, a significant inverse relationship existed between VO_2I and O_2ER ($r = .67$, $\rho = .000$) following lateral positioning. As demonstrated in the analyses of Hypotheses 3 and 4, minimal changes in mean SvO_2 were observed following lateral positioning, with and without morphine. Diminished SvO_2 responses following lateral positioning have been attributed to limited

cardiorespiratory reserves that were compounded by morphine-induced attenuation of cardiovascular responses. Results of the current study are consistent with Schmidt and colleagues (1984) who demonstrated weak, insignificant, and variable correlations between SvO_2 and VO_2 in serial measurements obtained during the intraoperative and immediate postoperative periods in 20 cardiovascular surgical patients who had impaired ventricular function. However, Schmidt et al.(1984) found that SvO_2 was significantly correlated with O_2ER ($r = -.84$) but was not significantly related to CI or DO_2.

Findings in the current study do not concur with the findings of Gawlinski and Dracup (1998) who determined that at minute 3 following left lateral positioning, the variability in mean SvO_2 was significantly related to DO_2 ($R^2 = .31$, $\rho = .0001$) and VO_2 ($R^2 = .54$, $\rho = .0001$) and that the change in SvO_2 between baseline and minute 3 after turning was significantly related to VO_2 ($R^2 = .46$, $\rho = .0001$) but not to DO_2 ($R^2 = .02$, $\rho = .2254$). The researchers concluded that the greatest proportion of variability in SvO_2 from baseline to minute 3 following lateral positioning is explained by an increase in oxygen consumption. Several explanations are offered for the differences between the findings of the current study and those of Gawlinski and Dracup (1998).

1. Different instrumentation. In the current study, oxygen consumption was measured noninvasively by indirect calorimetry using an open system metabolic monitor that directly and continuously measures the oxygen difference between inspired and expired gases in patients who are mechanically ventilated. In comparison, Gawlinski and Dracup calculated VO_2 using the mathematically derived Fick equation that allows an

approximate measure of VO_2. The researchers reported the correlation coefficient for the measured vs. calculated VO_2 was $r = .87$ ($\rho =< .05$). Several researchers have demonstrated in methods comparison studies, that VO_2 calculated by the Fick equation underestimates VO_2 as measured by indirect calorimetry (Brandi, Bertolini et al., 1999; Epstein et al., 2000).

2. Differences in metabolic demand between the samples. Subjects in the current study had higher mean VO_2 ml/min ($M = 265$, $SD = 61$, CI 95%, 243 – 288) than subjects in the Gawlinski and Dracup study (group I, $M = 227$, $SD = 65$; group II, $M = 222$, $SD = 58$). Although DO_2 ml/min was comparable between the samples in the two studies, Gawlinski and Dracup did not limit enrollment according to baseline DO_2.

3. Differences related to low hemoglobin. Subjects in the current study had significantly lower mean hemoglobin ($M = 10.38$, $SD = 1.22$, CI 95%, 9.9 – 10.83) that also resulted in low CaO_2 ($M = 13.89$, $SD = 1.53$, CI 95%, 13.26 – 14.52). In comparison, subjects in the Gawlinski and Dracup study had significantly higher mean hemoglobin (group I, $M = 12.96$, $SD = 1.96$; group II, $M = 12.52$, $SD = 1.41$).

In comparison to the subjects in the Gawlinski and Dracup study, subjects in the current study had comparably low DO_2I; however, their metabolic demands were higher despite substantially lower oxygen carrying capacity secondary to acute blood loss. Using the formula $O_2ER = VO_2/DO_2$, subjects in the Gawlinski and Dracup study had lower O_2ER (.26 - .28) than subjects in the current study ($M = .41$, $SD = .11$, CI 95%, .36 - .45). Based on these comparisons, subjects in the current study appeared to have a more

clinically profound degree of tissue oxygen debt and severely limited cardiorespiratory reserves than subjects in the Gawlinski and Dracup study who demonstrated physiological adaptation to an acute increase in oxygen demand. Therefore, it is likely that differences in SvO_2 and VO_2 response patterns to an acute increase in oxygen demand would exist among the samples due to different compensatory mechanisms.

Hypothesis 5

During the first phase of the study, SvO_2 returned to baseline within 10 minutes following lateral positioning in only 50% of the sample. However, when morphine was received before turning, 73% of the sample achieved SvO_2 recovery within 10 minutes following lateral positioning. Results indicated that when morphine was received before turning, 46% more subjects achieved SvO_2 recovery within the 10-minute period following lateral positioning. Furthermore, for subjects who achieved SvO_2 recovery, the mean time to recovery (i.e., return to baseline) was 22% less ($M = 1.76$ minutes) when morphine was received before the turn. Mean SvO_2 recovery time following lateral positioning with morphine was approximately 6 minutes compared to 8 minutes without morphine. Results were clinically and statistically significant. Because morphine was associated with a lesser amount of reduction in SvO_2 from baseline during the 10-minute observation following lateral positioning, it is postulated that SvO_2 recovery times were decreased during the second phase of the study because the distance between baseline and nadir was reduced.

Findings in the current study do not concur with the findings of other investigators who have consistently demonstrated that following lateral positioning, SvO_2 returns to baseline within 4 to 5 minutes in critically ill patients (Gawlinski & Dracup, 1998; Shively, 1988; Tidwell et al., 1990; Winslow et al., 1990). Explanations offered for the differences in SvO_2 recovery patterns demonstrated in the current study include (a) limited cardiorespiratory reserves and oxygen supply dependency, and (b) morphine-induced attenuation of cardiovascular responses, as presented in the discussions of the analyses of Hypothesis 2 through 4.

Conclusions and Implications

Turning regimens are an essential component of routine management of critically ill patients. Regular position changes have been demonstrated to reduce atelectasis, improve oxygenation, and prevent skin breakdown (Ibanez et al., 1981; Stotts, 1998; Zack et al., 1974). Previous studies have documented that lateral positioning is associated with a 20% to 50% increase in mean VO_2 and an immediate decrease in SvO_2 from baseline by 8% to 12%. Physiological responses to lateral positioning are attributed to both a stress-like (i.e., metabolic) and an exercise-like response (i.e., cardiovascular) related to increased skeletal muscle activity, pain and anxiety (Bein et al., 1996; Horiuchi et al., 1997; Puntillo et al., 2001). Critically ill patients who have limited cardiorespiratory reserves may demonstrate important tissue oxygenation and hemodynamic derangements associated with lateral positioning. Current thinking is that the patient with limited cardiorespiratory reserve is more likely to be harmed than to

benefit from a prolonged, exaggerated neuroendocrine response (Epstein & Breslow, 1999). Hence, treatment goals are targeted to correct pathophysiologic alterations of disease processes and reduce neuroendocrine activation. In select instances, therapeutic strategies designed to blunt these stress-related physiologic responses may improve outcome.

The present study examined cardiovascular and metabolic consequences of lateral positioning in profoundly ill cardiovascular surgical patients with low DO_2I. This study was designed to evaluate how critically ill patients with severely compromised cardiorespiratory reserves respond to an acute increase in oxygen demand resulting from a routine nursing procedure (i.e., lateral positioning). A secondary aim of this clinical trial was to determine the clinical efficacy of a preprocedural morphine intervention to attenuate metabolic demands associated with routine care procedures in order to facilitate patient adaptation. This is the only study that has (a) evaluated a nurse-administered preprocedural intervention designed to attenuate oxygen demands associated with lateral positioning and (b) focused on patients who have limited cardiorespiratory reserves defined exclusively by sustained low DO_2I. Furthermore, it is one of few studies that has evaluated the temporal relationships between tissue oxygenation variables using independent physiological instruments to measure DO_2 and VO_2, thus avoiding measurement error associated with mathematical coupling and potential threats to internal validity. Determining the effects of nursing interventions is one of the top five current research priorities for the nursing profession (Hinshaw, 2000). Through systematic and

progressive testing, results of pilot research and clinical trial have contributed to the *early* nursing science regarding the clinical efficacy of a nursing intervention to modulate oxygen consumption.

The findings of this study pertain to severely ill patients with decreased cardiorespiratory reserves defined by (a) persistent reductions in DO_2I and CaO_2 and (b) sustained elevation of O_2ER. The major conclusions of the clinical trial include:

1. In low dosages, concomitant administration of morphine (0.10 mg/kg/ibw iv) and propofol (24 μg/kg/min iv) do *not* result in greater attenuation of the metabolic and cardiovascular responses associated with an acute increase in oxygen demand than morphine alone. Further research is needed to validate these findings.

2. In critically ill patients with low DO_2I, lateral positioning is typically associated with a 17.3% increase from baseline VO_2I that occurs between minutes 4 and 5 following lateral positioning. The increase in VO_2I is associated with a small (< 5%) increase in DO_2I that is related to an increase in CI and SVI. Heart rate and O_2ER do not appear to be significantly affected by lateral positioning.

3. Preprocedural morphine in low-dosages (0.10 mg/kg/ibw iv) may *not* produce a significant attenuation of the metabolic response to an acute increase in oxygen demand. Early findings do not support the clinical efficacy of the intervention; however, the investigation was underpowered due to a small sample size. The primary mechanism of morphine's action is associated with a *blunting effect* of the cardiovascular responses resulting in *undesirable* reductions in DO_2I and CI and an increase in O_2ER. Although

the intervention did not enhance tissue oxygenation, no overt *early* clinical complications were apparent and the financial costs associated with the intervention were minimal. Nevertheless, at this time, the *routine* use of preprocedural morphine for the *sole* purpose of attenuating the metabolic response related to routine care procedures is *not* recommended in patients with limited cardiorespiratory reserves who are dependent upon augmented oxygen extraction to maintain metabolic requirements. Rather, a comprehensive cardiorespiratory assessment is recommended prior to routine care procedures to support decisions about activity management including the need to postpone or group activities to facilitate patient adaptation and enhance tissue oxygenation. Furthermore, a comprehensive cardiorespiratory assessment is recommended prior to treatments that attenuate metabolic or cardiovascular responses. Further research is needed to validate the oxygen demand-induced responses of severely ill patients with persistently low DO_2I and hypermetabolism at rest.

4. Preliminary findings suggest that subgroups of critically ill patients with low DO_2I and high O_2ER may demonstrate different VO_2 response patterns to an acute increase in oxygen demand and may respond differently (e.g., favorably or adversely) to interventions that are intended to conserve tissue oxygen requirements. Further research is needed to validate these findings.

5. Critically ill patients characterized by concomitant low-flow and hypermetabolic states, may demonstrate less reduction (i.e., decreases from baseline) in SvO_2 than other critically ill patients following lateral positioning despite significant

tissue oxygen deprivation. In these types of patients, continuous SvO_2 monitoring as an indicator of DO_2 - VO_2 balance may have limitations. Therefore, serial measurements of the components that comprise DO_2 and VO_2 should be evaluated frequently, particularly prior to, during and following changes in oxygen demands.

Although frequent turning is an important nursing intervention, critical care nurses are challenged to promote vital organ functions by maintaining adequate tissue oxygenation in patients who have oxygen demands that exceed oxygen availability. Knowledge of the effects of routine nursing interventions on VO_2 in patients with low oxygen delivery can assist critical care nurses in determining when it is safe to proceed with care activities and when activities should be postponed to avoid stressing the patient. Presently, there are no practical methods of directly measuring tissue oxygenation in the critical care setting. This represents a challenge for clinicians and researchers attempting to measure physiological responses, particularly if the responses are related to oxygenation. Assessment parameters obtained from indirect assessment methods may not accurately reflect the patient's true adaptation level. In most critically ill patients, SvO_2 is a reliable indicator of *global* tissue oxygen balance and is not intended to reflect the oxygenation status of specific organs nor replace the assessment of individual components that comprise DO_2 and VO_2 (Cernaianu & Nelson, 1993). An alteration in SvO_2 signals a nonspecific disruption in oxygen supply and demand balance that warrants additional investigation of the individual components of DO_2 and VO_2. While there is general agreement among researchers that a change in SvO_2 that exceeds 10% for more

than 10 minutes or a sustained SvO_2 value of < 60% may be an early indicator of physiological instability and cardiorespiratory failure (Gawlinski & Dracup, 1998; Noll & Fountain, 1990a; Pena, 1989; Winslow et al., 1990), a few researchers have challenged this position (Lewis et al., 1997; Schlichtig et al., 1986; van der Hoeven et al., 1997, 1999). Findings of this study support the reevaluation of traditionally defined normal SvO_2 parameters and critical indicators in critically ill patients with low DO_2 defined by hypermetabolic states. Therefore, SvO_2 monitoring should be used in conjunction with serial measurements of DO_2 and VO_2 to evaluate perfusion abnormalities and treatment efficacy.

Theoretical Propositions of the Roy Adaptation Model

According to Roy, people demonstrate less ability to adapt physiologically to changes within the environment during illness (Andrews & Roy, 1986). Immediately following lateral rotation, cardiovascular patients with low DO_2I on average experienced an increase in oxygen consumption of approximately 17%. This clinical phenomenon is also observed in healthy subjects and other critically ill patients although to a more pronounced degree. Clinically important differences were observed among subgroups during the study and revealed distinct response patterns to lateral positioning that were masked by the mean group response. Despite impaired gas transport and tissue oxygen deprivation, critically ill patients with low DO_2I demonstrated diminished but "normal" physiological adaptation patterns to the stress of lateral positioning, including small but gradual increases in DO_2I, without further reductions in oxyhemoglobin. Physiological

integrity was maintained as evidenced by VO_2I recovery to baseline within 10 minutes following the turn and hemodynamic demise was not associated with the focal stimulus. Physiological response patterns are similar for healthy subjects who experience an increase in VO_2 following lateral positioning and a return to baseline within 10 to 15 minutes (Verderber & Gallagher, 1994). Findings of the study challenge Roy's theory to predict human responses to nursing interventions during illness. Inconsistencies of human responses and adaptation patterns may exist among subgroups of critically ill patients. Roy's Adaptation Model requires further clarification of tissue oxygenation disturbances within subpopulations of critically ill patients with low DO_2I. Opportunities exist for researchers to extend the theory and determine specific illness states or conditions that do not support adaptation.

According to Roy's theory, adaptation may be facilitated by enhancing an individual's coping mechanisms through interventions aimed at eliminating, reducing, or neutralizing the stimulus responsible for disrupting the environment. Thus, *effective* nursing interventions aimed at managing the stimulus that is responsible for disrupting tissue oxygenation will restore physiological integrity and promote adaptation (Roy & Andrews, 1991). Findings of this study did not support the *routine* use of preprocedural morphine as an effective nursing intervention for promoting physiological adaptation by decreasing oxygen demands in patients with low oxygen delivery. Physiological adaptation as measured by VO_2I and SvO_2 was indicative of achievement of physiological integrity. However, further examination of the tissue oxygenation patterns

revealed that the effects of morphine impaired DO_2I and O_2ER. Thus, all nursing interventions do not facilitate adaptation. Furthermore, adaptation must be determined by a comprehensive assessment of the temporal relationships between cardiorespiratory variables rather than evaluating one or two individual variables. Some nursing interventions may be harmful to patients and may interfere with or prevent adaptation. Clinical research is necessary to identify nursing interventions that are effective in promoting adaptation by attenuating oxygen demands in critically ill patients compromised by cardiorespiratory disease states.

In summary, findings of the study challenge Roy's assumption that during illness human adaptation is impaired during illness. Evidence was presented describing diverse physiological response patterns and adaptation mechanisms demonstrated among subpopulations of critically ill patients and suggested that humans may possess the ability to adapt to situational stressors despite illness states. Further empirical testing is necessary to determine specific illnesses or disease states that prohibit physiological adaptation and do not support physiological integrity. Further development and refinement of the theory is needed to address the following issues:

1. Can clinicians actually determine *when* physiological needs are met?
2. Can health and illness be simplified or reduced to two ends of a continuum?
3. Do people exist in an either an adaptive or maladaptive state?

These concepts are difficult to measure because human existence is complex and dynamic and physiological assessment may be limited by the availability of accurate clinical instrumentation. Depending on the disease or involved organ system(s), physiological integrity may be difficult to quantify. Certain physiologic phenomena are not well understood and instruments to measure or quantify the absence, presence, or degree of significance are limited. Furthermore, it is difficult to measure or predict adaptation without a thorough knowledge of the phenomenon. Nevertheless, the Roy Adaptation Model lends itself to the study of biophysiological phenomena and environmental stressors that may result in alterations or disruptions of the regulatory processes that support or maintain physiological adaptation. In attempting to explain the pathophysiological phenomenon of tissue oxygen deprivation, the theory provides a comprehensive conceptual framework with tight linkages between relevant concepts such as human responses to situational stressors and nursing strategies to promote physiological adaptation.

The preliminary trends that surfaced during the study suggested that severely ill patients with limited cardiorespiratory reserves may manifest dissimilar and inconsistent physiologic responses than other groups of critically ill patients; thus, implying different degrees or *depth* of illness states. Results of this study validated the opinions of Whittemore and Gray (2002) that the science of nursing interventions is complicated by the complexity of human responses to health and illness and the relational elements in many nursing interventions. Further exploration and clarification of subgroup differences

may extend Roy's theory regarding physiological adaptation and the function of regulatory mechanisms during illness states. Implications for nursing practice include a greater understanding of the effects of routine nursing procedures on critically ill patients with limited cardiorespiratory reserves and increased knowledge of adaptation patterns associated with critically illness. Furthermore, results of the study reinforce the critical need for on-going research to identify evidence based therapies and *effective* nursing interventions that support coping mechanisms to facilitate patient adaptation to situational stressors that increase oxygen requirements.

Recommendations for Further Study

The following are suggestions for future research to (a) determine the clinical effectiveness of oxygen consumption modulation therapy in critically ill patients with low DO_2I and (b) refine the systematic and scientific development of the intervention protocol:

1. To avoid the confounding effects of treatment and control, the study should be repeated using a between-subjects design and randomizing the treatment and control phases of the study. Preprocedural treatment interventions should be tested at time intervals following procedures associated with the maximal increases in VO_2. Immediate effects, delayed effects, and decaying effects of the intervention on patient responses should also be studied. Describe the cardiorespiratory adaptation responses of critically ill patients with low DO_2, high O_2ER, and myocardial depression as defined by

low LVEF and/or low CO to acute increases in oxygen demands, with and without oxygen consumption modulation therapies.

2. Conduct a clinical efficacy trial to determine the effects of preprocedural morphine to attenuate oxygen demand-induced VO2 response in critically ill patients with normal DO_2I.

3. Prospectively enroll subjects according to oxygen demand-induced VO_2 response pattern and compare responses to acute increases in oxygen demands associated with routine care produces and effects of oxygen consumption modulation therapies.

4. Compare oxygen consumption modulation effects of pharmaceutical interventions based on ideal body weight with dosages based on adjusted body weight.

5. Compare the cardiorespiratory response patterns between patients with acute and chronic anemia to routine care procedures that increase oxygen demands. Prospectively enroll patients according to hemoglobin concentration and compare physiological response patterns of tissue oxygenation variables between subgroups with varying levels of anemia. Determine if patients with acute and chronic anemia respond differently to oxygen modulation therapies. Evaluate the effects of blood (RBC) transfusion therapy in anemic patients on cardiorespiratory response to acute increases in oxygen demand and compare the responses using blood products stored < 24 hours with blood products stored for longer periods.

6. Evaluate differences in basal VO_2 and VO_2 response to acute increases in oxygen demands, with and without oxygen modulation therapies, and determine the effects of age, gender, muscle mass, severity of illness, and oxygen debt.

7. Compare the effects of independent and combination pharmaceutical interventions and non-pharmaceutical interventions on tissue oxygenation variables during routine care produces.

8. Study the effects of oxygen modulation therapies on other types of nursing procedures or activities that are associated with an increase in VO_2 (i.e., endotracheal suctioning, weaning from mechanical ventilation, bathing, drain removal).

9. Evaluate the effects of routine care procedures and oxygen consumption modulation therapies in critically ill patients with low DO_2 using a combination of instruments to simultaneously measure systemic and regional tissue oxygenation/perfusion. Determine the temporal relationships between systemic and regional dependent measurements.

In summary, lateral positioning was associated with an increase in VO_2I by approximately 17%. Without preprocedural morphine, critically ill patients with low DO_2I manifested similar, though diminished, adaptation responses to an oxygen demand-induced VO_2 response, as do critically ill patients without low DO_2I. Clinically significant improvements in VO_2I and O_2ER following lateral rotation were not observed when morphine was administered prior to positioning. Consequently, the effect of morphine as a nursing intervention to promote physiological adaptation by reducing

oxygen consumption following lateral rotation was not apparent. With the exception of SvO_2, ineffective responses were more frequently observed when morphine was administered prior to lateral positioning. These findings of this study are specific to critically ill, mechanically ventilated, adult cardiovascular surgical patients. Extrapolation of these findings to other patient populations should be made with caution. Limitations of the study included (a) lack of randomization of control and treatment phases to avoid the *carry over* effects of morphine, (b) comparisons between left and right lateral position changes were not evaluated, (c) comparisons between the supine to lateral and lateral to supine position changes were not evaluated, and (d) stature, age and gender-related differences in metabolic requirements were not accounted for in the findings.

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Table 1

Formulas and Normal Values for Cardiorespiratory Variables

Variable	Acronym	Formula	Normal
Body Surface Index	BSA	$(W[kg]^{0.425} \times H[cm]^{0.725}) \times 0.007184$	1.4 – 2.1 m^2
Stroke Volume Index	SVI	SV ÷ BSA	40 - 60 $ml \cdot beat^{-1}/m^2$
Cardiac Output	CO	(HR x SV) ÷ 1000	4 -6 L/min
Cardiac Index	CI	CO ÷ BSA	2.8 - 4.2 $L/min/m^2$
Mean Arterial Pressure	MAP	DAP + ([SAP – DAP] ÷ 3	85 – 100 mm Hg
Mean Pulmonary Arterial Pressure	MPAP	DPAP + ([SAP – DAP] ÷ 3	10 – 18 mm Hg
Left Ventricular Stroke Work Index	LVSWI	SVI x (MAP-PAOP) x 0.0136	50 - 62 $g\text{-}m\text{-}m^2 \cdot beat^{-1}/m^2$
Systemic Vascular Resistance	SVR	([MAP-RAP] ÷ CO) x 80	800 - 1500 $dynes\text{-}sec\text{-}cm^{-5}$
Systemic Vascular ResistanceIndex	SVRI	([MAP-RAP] ÷ CI) x 80	1900 - 2400 $dynes\text{-}sec\text{-}cm^{-5}/m^2$
Arterial Oxygen Content	CaO_2	$CaO_2 = (0.0031 \times PaO_2) + (1.34 \times Hb \times [SaO_2 \div 100])$	17 - 20 ml/dl
Venous Oxygen Content	CvO_2	$CvO_2 = (0.0031 \times PvO_2) + (1.34 \times Hb \times [SvO_2 \div 100])$	12 - 15 ml/dl
Arterial Oxygen Saturation	SaO_2	$SaO_2 = HbO_2 \div (Hb + HbO_2) \times 100$	95% - 100%
Oxygen Delivery	DO_2	$DO_2 = CO \times CaO_2 \times 10$	950 - 1150 ml/min
Oxygen Delivery Index	DO_2I	$DO_2I = DO_2 \div BSA$	550 - 600 $ml/min/m^2$
Oxygen Consumption	VO_2	$VO_2 = CO \times (CaO_2 - CvO_2) \times 10$	195 - 285 ml/min
Oxygen Consumption Index	VO_2I	$VO_2I = VO_2 \div BSA$	120 - 140 $ml/min/m^2$

Table 1

Formulas and Normal Values for Cardiorespiratory Variables

Oxygen Extraction Ratio	O_2ER	$O_2ER = VO_2I \div DO_2I \times 10$	0.24 - 0.29
Mixed Venous Oxygen Saturation	SvO_2	$SvO_2 = SaO_2 - (VO_2 \div [CO \times Hb \times 1.34 \times 10])$	60% - 80%
Intrapulmonary Shunt	Qs/Qt	$Qs/Qt = (CcO_2 - CaO_2) \div (CcO_2 - CvO_2)$	2% - 5%

Note. SV = stroke volume; HR = heart rate; CO= cardiac output; SAP = systolic arterial pressure; D = diastolic arterial pressure; DPAP = diastolic pulmonary artery pressure; RAP = right atrial pressure; W=weight; H=height; Hb = deoxyhemoglobin; HbO_2 = oxyhemoglobin; P = partial pressure; a = arterial; v = venous; O_2 = oxygen; CcO_2 = pulmonary-capillary oxygen content. From "SvO_2 Monitoring," by J. Jesurum, 1998, in M. Chulay, A. Gawlinski (Eds.), *Protocols for practice* (p. 5). Copyright 1998 by the American Association of Critical Care Nurses. Adapted with permission.

Table 2

Summary of Research Literature on the Effects of Lateral Positioning on Tissue Oxygenation.

Investigator(s) /Date	*Sample*	*Variables/Methods*	*Procedure*	*Results/Conclusions*
Shively (1988)	$N = 30$ Extubated, hemodynamically stable, adult cardiovascular surgical patients enrolled less than 24 hours following coronary artery bypass graft. Thirteen subjects had unilateral pulmonary disease.	▪ Groups I and II: SvO_2 measured at 0 minutes, 15 minutes, and 1-hour post-turn. ▪ Group II had additional SvO_2 measurement at 2 hours post-turn. ▪ Mean SvO_2 rather than change scores were examined. ▪ TDCO measured at baseline and end of protocol; CO, DO_2, VO_2 not reported in findings. ▪ Repeated measures, experimental design. ▪ Non-random sample. Patients with chronic lung disease were excluded.	▪ Random assignment to group based on frequency of position change. ▪ Turn sequence was not randomized. ▪ Group I ($n = 15$) turned every 1 hour ▪ Group II ($n = 15$) turned every 2 hours ▪ Subjects in both groups were turned in the same sequence and completed 4 position changes: right lateral with 20° backrest elevation; supine with 45° backrest elevation; left lateral with 20° backrest elevation; supine with 20° backrest elevation.	▪ Group II had significantly lower SvO_2 than Group I in supine, 20° backrest elevation; supine, 45° backrest elevation; and, left lateral, 20° backrest elevation. ▪ SvO_2 was significantly lower immediately following each turn (0 minutes) than at 15 minutes or 1 hour after the turn ($\rho < .00$). ▪ SvO_2 was not significantly different between minute 15 and 1-hour post-turn. ▪ Lowest SvO_2 was observed immediately after turning to the *left* lateral position. ▪ On average, SvO_2 decreased 5% to 10% and returned to baseline within 5 minutes. SvO_2 changes were clinically unimportant.

Table 2

Summary of Research Literature on the Effects of Lateral Positioning on Tissue Oxygenation.

Pena (1989)	*N* = 12 Mechanically ventilated, hemodynamically stable cardiovascular surgical patients enrolled within 6 hours following surgery	SvO_2 was measured continuously from baseline, immediately after turning and until the next turn. DO_2 and VO_2 were not measured.	Lateral positioning every 2 hours for a total of 2 turns.	▪ Turning was associated with an immediate decrease in SvO_2 by 8.5% during the first turn and by 12.3% during the second turn. ▪ Differences in SvO_2 changes between the first and second turn were significant ($\rho = .02$). ▪ SvO_2 returned to baseline within 4 minutes following lateral rotation and remained at baseline 20 minutes following the turn. ▪ SvO_2 changes were not clinically significant.
Noll & Fountain (1990)	*N* = 30 Mechanically ventilated, hemodynamically stable cardiovascular surgical patients following CABG with a mean age of 56 years. Men comprised 77% of the sample.	Continuous SvO_2	Randomized to 3 sequences of position changes consisting of supine, 20° and 40° backrest elevation	▪ SvO_2 did not significantly change from baseline after placing subjects in a supine-flat or supine with 20° or 40° backrest elevation. ▪ Mean SvO_2 was not significantly different at 0, 5, 15, and 30 minutes following position changes. ▪ SvO_2 returned to baseline within 5 minutes after the position change.

Table 2

Summary of Research Literature on the Effects of Lateral Positioning on Tissue Oxygenation.

Winslow, Clark, White, and Tyler (1990)	$N = 174$ Critically ill adults, predominantly mechanically ventilated (96%), and s/p cardiovascular surgery (61%).	SvO_2 and heart rate were measured continuously and recorded immediately after the turn and every minute thereafter for 4 minutes. DO_2 and VO_2 were not measured.	Randomized to 60° right and left lateral position according to location of the catheter tip in the pulmonary artery. ▪ 85% of subjects turned to the right; 15% turned to the left.	▪ SvO_2 significantly decreased from baseline by 9% immediately after turning ($M_1 = 67\% \pm 8\%$; range 49% - 89%; $M_2 = 61\% \pm 10\%$; range 38% - 89%; $\rho < .00$). ▪ SvO_2 gradually returned to approximate baseline values within 4 to 5 minutes ($M = 66\% \pm 8\%$; range 45 - 89%; $\rho < .00$). ▪ No significant differences in SvO_2 were noted between left and right lateral positions. ▪ Subjects with low CO had more dramatic SvO_2 changes and complications following rotation. ▪ HR increased immediately after the turn by 3% ($\rho < .00$) and returned to baseline within 4 minutes ($n = 183$). ▪ Transient changes in SvO_2 and HR were not clinically important. ▪ Adverse responses to turning (i.e., agitation, hemodynamic demise) were associated with a decrease in SvO_2 of 26%.

Table 2

Summary of Research Literature on the Effects of Lateral Positioning on Tissue Oxygenation.

Tidwell, Ryan, Osguthorpe, Paull, and Smith (1990)	*N* = 33 Cardiovascular surgical patients (CABG), mechanically ventilated, enrolled within 4 to 8 hours following surgery.	▪ Independent variables included position change and minutes following position change ▪ Dependent variables included continuous SvO_2 monitoring and VO_2 measured continuously via indirect calorimetry. ▪ DO_2 not reported. ▪ Repeated-measures, experimental design.	▪ Subjects were passively turned from the supine position with 30° backrest elevation to the left and right 45° lateral positions. ▪ Sequence of turning was randomly assigned to S/RL/S/LL/S or S/LL/S/RL/S. ▪ Subjects were maintained in each position for 30 minutes.	▪ SvO_2 decreased by 8% to 9% immediately following supine-to-lateral and lateral- to-supine rotation ($\rho < .01$) and returned to baseline within 5 minutes. ▪ SvO_2 changes were similar for right and left lateral positions. ▪ SvO_2 changes were not clinically significant or < 60%. ▪ Mean VO_2 ranged from 0.27 to 0.32 L/min. ▪ Significant changes in VO_2 were not observed following position changes. ▪ No significant correlation between SvO_2 and VO_2 at 1-minute post-turn. ▪ Suspected insignificant VO_2 changes following turning related to influences of analgesia and sedation.
Weissman & Kemper (1991)	*N* = 16 Mechanically ventilated critically ill surgical patients who ranged in age from 49 to 88 years	VO_2 measured by indirect calorimetry	Low level activity (i.e., turning/moving) Chest Physiotherapy	▪ Mean resting CI = 3.3±0.9, VO_2I = 114±18, DO_2I = 431±105, and O_2ER = 0.27±0.05 (*n* = 87). *Low level activity (turning/moving)*: ▪ Significant increase in VO_2 of 31% ± 11% ($\rho < .025$) accompanied by a significant increase in DO_2 19% ± 20% ($\rho < .01$) and an insignificant increase in O_2ER.

Table 2

Summary of Research Literature on the Effects of Lateral Positioning on Tissue Oxygenation.

Weissman & Kemper (1991) *continued*				*Chest Physiotherapy:* ▪ VO_2 increased by 62% ± 29% ($\rho < .00$) from baseline. ▪ Significant increases in DO_2 32%± 20% ($\rho < .02$) and O_2ER 38%±23% ($\rho < .00$).
Atkins, Hapshe, & Riegel (1994)	*N* = 30 Predominantly male, hemodynamically stable, cardiovascular surgical (s/p CABG) patients (*n* = 26) with an average age of 61±8 years	Continuous SvO_2	Two bedbaths consisting of *turning* and *bathing phases* in early (3.6 hour) and late (18.5 hours) postoperative periods	▪ SvO_2 significantly decreased from baseline during *turning phase* of early (9.2%) and late (12.1%) bedbaths ($\rho < .01$). ▪ Largest decreases in SvO_2 were observed from lateral to supine positioning. ▪ On average, SvO_2 returned to baseline within 3 to 4 minutes following lateral positioning. ▪ SvO_2 decreased from baseline during early bathing (1.6%, $\rho < .00$) and late bathing (1.9%, $\rho < .03$). ▪ Decreases in SvO_2 during early and late *turn phases* ($\rho = .06$) and *bath phases* ($\rho = .63$) were not statistically significant. ▪ HR increased less during late vs. early turning (3.2% vs. 1%, $\rho = .01$). ▪ Rest period during bathing did not significantly affect SvO_2 or HR ($\rho > .05$).

Table 2

Summary of Research Literature on the Effects of Lateral Positioning on Tissue Oxygenation.

Atkins, Hapshe, & Riegel (1994) *continued*				▪ Clinically severe, prolonged decreases in SvO_2 (< 53%) more common during the early bedbath and were associated with coughing, shivering, agitation, and pain; treat these conditions before bathing or positioning to avoid clinically significant decreases in SvO_2.
Verderber & Gallagher (1994)	$N = 30$ Healthy men and women		Bedbath Passive range of motion Lateral positioning	▪ VO_2 significantly increased by 20% during unassisted turning. ▪ During the bedbath, VO_2 increased by 11.06% for men and 4.01% for women ($\rho < .01$) and returned to baseline within 15 minutes. ▪ No other activities resulted in significant changes.
Gawlinski and Dracup (1998)	$N = 42$ ▪ Critically ill patients with an ejection fraction $\leq 30\%$ ($M = 19.5\%$). ▪ Primary cardiac diagnoses included dilated (50%) or ischemic (46%) cardiomyopathy.	▪ SvO_2 was collected at baseline, every 1 minute for 5 minutes, and at minutes 15 and 25 following the turn. ▪ TDCO was measured at baseline and at minute 3 after each turn.	▪ Random assignment to one of two position sequences. ▪ Group I - supine, right lateral, left lateral ▪ Group II - supine, left lateral, right lateral. ▪ Subjects were maintained in each position for 25 minutes.	▪ SvO_2 was significantly different among the three positions across time ($\rho < .00$) with the greatest difference occurring within the first 4 minutes and in the *left* lateral position. ▪ At 1-minute after turning, SvO_2 decreased from baseline by 8.5% in the *right* lateral position and by 11.3% in the *left* lateral position.

Table 2

Summary of Research Literature on the Effects of Lateral Positioning on Tissue Oxygenation.

Gawlinski and Dracup (1998) *continued*		• DO_2, VO_2, SaO_2, SV, and HR were also measured at minute 3 following each turn. • Experimental, two-group, repeated measures design. • Correlated indirect calorimetery with calculated Fick VO_2 for first 5 subjects; remaining VO_2 per Fick.		• Clinically significant changes in SvO_2 occurred in 38% of subjects turned to right side and 48% of subjects turned to left side. • VO_2 accounted for a greater proportion of the variance in mean SvO_2 with position changes than did DO_2 (54%, $\rho < .00$ vs. 31%, $\rho < .00$). • SvO_2 change scores following turn were significantly related to VO_2 ($R^2 = .46$) but not DO_2 ($R^2 = .02$).

Note. CABG = coronary artery bypass graft; s/p = status post; SvO_2 = mixed venous oxygen saturation; VO_2 = oxygen consumption; O_2ER = oxygen extraction ratio; DO_2 = oxygen delivery; I = indexed to body surface area; CI = cardiac index; HR = heart rate; CO = cardiac output; TDCO = thermodilution cardiac output; SV = stroke volume; CPT = chest physiotherapy; RL = right lateral; LL = left lateral; S = supine; SaO_2 = arterial oxygen saturation; ± = standard deviation.
Source: Author.

Table 3

Analyses of Variance Design for Testing the Hypotheses*

Two-Way (Morphine x Time) Within-Subjects Repeated Measures Factorial Design

Morphine (*A*)	**Minutes Post-Turn (*B*)**		
	Minute 1 (B_1)		Minute 5 (B_2)
Phase 1: Without Morphine (A_1)	X	⇒	X
Phase 2: With Morphine (A_2)	X	⇒	X

Note. Independent variables = *Morphine* and *Time* following lateral positioning; X = observations of dependent variables (SvO_2, VO_2I); * = cell structure for testing Hypotheses 2 and 3; ** $\rho < .025$

Table 4

Schematic Representation of Treatments and Observation Periods of Study Protocol

Schematic Diagram: Within-Subjects Repeated Measures Factorial Design
Phase I: $0_1a \rightarrow 0_2a \rightarrow 0_3a \rightarrow 0_4a \rightarrow 0_5a,b$ - R - $X_1 \Rightarrow 0_1a \Rightarrow 0_2a \Rightarrow 0_3a,b \Rightarrow 0_4a \Rightarrow 0_5a,b \Rightarrow 0_6a \Rightarrow 0_7a \Rightarrow 0_8a \Rightarrow 0_9a \Rightarrow 0_{10}a,b \Rightarrow X_2 \Rightarrow X_3 \Rightarrow^{20}$
Phase II: $0_1a \rightarrow 0_2a \rightarrow 0_3a \rightarrow 0_4a \rightarrow 0_5a,b$ ------ $X_1 \Rightarrow 0_1a \Rightarrow 0_2a \Rightarrow 0_3a,b \Rightarrow 0_4a \Rightarrow 0_5a,b \Rightarrow 0_6a \Rightarrow 0_7a \Rightarrow 0_8a \Rightarrow 0_9a \Rightarrow 0_{10}a,b$

Note. Phase I = protocol for studying effects of lateral positioning on tissue oxygenation variables without morphine; Phase II = protocol for studying effects of lateral positioning on tissue oxygenation variables with morphine; 0 = observation of dependent variables; a = SvO_2 + VO_2I; b = DO_2I + O_2ER; R = randomization to 45-degree left or right lateral position; X_1 = turn supine to 45-degree lateral; X_2 = turn 45-degree lateral to supine position; X_3 = morphine 0.1 mg/kg/ideal body weight iv administration; $\rightarrow$ = 15 seconds interval; $\Rightarrow$ = one minute interval; $\Rightarrow^{20}$ = 20 minute stabilization period; $0_1a - 0_4a$ recorded for purpose of verifying stable baseline during phase I and II; O_5a,b = baseline measurement.

Table 5

Cardiovascular Diagnoses ($N = 30$)

Cardiovascular Diagnoses	*f*	%
Coronary Artery Disease	26	86.7
Hypertension	20	66.7
Congestive Heart Failure	14	46.7
Atrial Fibrillation	5	16.7
Cardiogenic Shock	4	13.3
Ischemic Cardiomyopathy	1	3.3
Rheumatic Heart Disease	1	3.3
Subacute Bacterial Endocarditis	1	3.3
Idiopathic Hypertrophic Subaortic Stenosis	1	3.3
Aortic Dissection Type I	1	3.3
Cerebrovascular Disease	4	13.3
Peripheral Vascular Disease	2	6.7
Previous Myocardial Infarction	15	50
< 48 hours	6	40
48 hours – 1 week	1	6.3
1 – 5 years	1	6.3
> 5 years	5	33.3
Unknown	2	13.3

Note. Diagnostic categories are not mutually exclusive and subjects may have more than one diagnosis; *f* = frequency.

Table 6

Surgical Interventions and Perioperative Data ($N = 30$)

Intervention	*f*	(%)	Mean ± *SD*
Surgical Procedure			
CABG	13	(43.3)	
Valve Replacement	10	(33.3)	
CABG + Valve Replacement	6	(20)	
Aneurysm Repair	1	(3.3)	
Procedure Classification			
Reoperation	7	(23.3)	
Emergent	12	(40)	
Urgent	8	(26.7)	
Elective	10	(33.3)	
Intraoperative Data			
Extracorporeal Circulation Minutes			151 ± 63.8
Aortic Cross Clamp Minutes			117 ± 54.2
Perioperative Events			
Cardiac Arrest	4	(13.3)	
Intra-aortic Balloon Counterpulsation	9	(30)	
Return to OR – Emergent Mediastinal Exploration	4	(13.3)	
RBC Transfusion	25	(83.3)	

Note. CABG = coronary artery bypass graft; OR = operating room; RBC = red blood cell.

Table 7

Clinical Characteristics of the Sample ($N = 30$)

Parameter	*n*	Mean	*SD*	Minimum	Maximum
Blood Temperature (C)	30	37.54	.58	36.30	38.40
Arterial pH	30	7.42	.05	7.33	7.52
$PaCO_2$ mm Hg	30	35.57	5.30	26.30	49.40
PaO_2 mm Hg	30	126.57	41.49	73.00	237.00
Arterial HCO_3	30	23.22	3.38	15.80	30.30
SpO_2 %	30	.98	.02	.94	1.00
Intrapulmonary Shunt Qs/Qt %	25	11.58	5.53	2.80	22.70
Total Hemoglobin g-/dl	30	10.38	1.22	8.70	12.40
Heart Rate bpm	30	94.07	9.95	75.00	116.00
Cardiac Index L/min/m^2	30	2.57	.41	1.90	3.65
Stroke Volume Index ml/beat/m^2	30	27.51	4.92	20.50	43.00
LVSWI g-m-m^2 * beat/m^2	30	23.44	5.69	14.60	36.10
SVRI dynes-sec-cm-^{5}/m^2	30	2188	601	1374	3369
Right Atrial Pressure mm Hg	30	11.73	4.68	2.00	23.00
PAOP mm Hg	30	15.67	5.25	5.00	27.00
Mean Arterial Pressure mm Hg	29	81	14.73	53	109
SvO_2 %	30	63.95	8.29	49.50	79.00
VO_2I ml/min/m^2	30	139.09	22.47	104.58	186.61
DO_2I ml/min/m^2	30	355.34	71.14	217.08	493.01
O_2ER	30	.41	.11	.23	.86
CaO_2 ml/dl	25	13.90	1.53	11.50	17.40

Note. C = degrees Celsius; P = partial pressure; a = arterial; CO_2 = carbon dioxide; O_2 = oxygen; HCO_3 = bicarbonate; SpO_2 = arterial oxygen saturation by pulse oximetry; LVEF = left ventricular ejection fraction; LVSWI = left ventricular stroke work index; SVRI = systemic vascular resistance index; PAOP = pulmonary artery occlusion pressure; SvO_2 = mixed venous oxygen saturation; VO_2I = oxygen consumption index; DO_2I = oxygen delivery index; O_2ER = oxygen extraction ratio; CaO_2 = arterial oxygen content; $n < 30$ = missing or rejected values.

Table 8

Pharmacological Interventions During the Postoperative Period ($N = 30$)

Medications	*f*	(%)	**Mean ± *SD***	**Range**
Continuous Infusions [a]			2.4 ± 1.1	0 - 4
Norepinephrine	26	(86.7)		
Milrinone	13	(43.3)		
Dopamine	11	(36.6)		
Dobutamine	6	(20)		
Epinephrine	5	(16.7)		
Vasopressin	5	(16.7)		
Phenylephrine	2	(6.7)		
Antiarrhythmic	6	(20)		
Intermittent Dosing [b]				
Diuretic	4	(13.3)		
Digoxin	2	(6.7)		
Beta antagonist	1	(3.3)		
Calcium antagonist	1	(3.3)		
Alpha antagonist	1	(3.3)		

Note. [a] = number of vasoactive infusions per subject; maintained during data collection without titration; [b] = administered within two to six hours prior to data collection; *f* = frequency.

Table 9

Baseline Level of Sedation Scores for the Sample ($N = 30$) and for Subjects With ($n = 15$) and Without Propofol ($n = 15$)

Modified Ramsay Sedation Scale[a]		Sample ($N = 30$)	Propofol Infusion[b]	
			Yes ($n = 15$)	No ($n = 15$)
Score	Description	*f* (%)	*f* (%)	*f* (%)
0	Paralyzed, unable to evaluate	0	0	0
1	Awake	5 (16.7)	0	5 (33.3)
2	Lightly sedated, easily arousable	15 (50)	10 (66.7)	5 (33.3)
3	Moderately sedated, follows simple commands	8 (26.7)	5 (33.3)	3 (20)
4	Deeply sedated, responds to nonpainful stimulus	1 (3.3)	0	1 (3.3)
5	Deeply sedated, responds only to painful stimulus	1 (3.3)	0	1 (3.3)
6	Deeply sedated, unresponsive to painful stimulus	0	0	0

Note. Baseline scores on the Modified Ramsay Sedation Scale do not vary as a function of propofol treatment categories: $\chi 2$ (4, $N = 30$) = 9.17, $\rho = .06$; [a] = From "Mechanisms whereby propofol mediates peripheral vasodilation in humans," by B. Robinson, T. Ebert, T. O'Brien, M. Conlinco, and M. Muzi, 1997, Anesthesiology, 86, pp. 64–72; [b] = propofol infusions initiated prior to study enrollment and maintained during data collection without titration.

Table 10

Baseline Physiological Data and Clinical Characteristics of Propofol Groups (n = 15 per group)

Variable	Propofol Infusion	*n*	Mean	*SD*
Blood Temperature °C	Yes	15	37.7	.66
	No	15	37.4	.46
Arterial Oxygen Tension mm Hg	Yes	15	137	46.21
	No	15	117	34.95
Total Hemoglobin g-/dl	Yes	15	10.4	1.27
	No	15	10.3	1.20
Left Ventricular Ejection Fraction %	Yes	7	49.6	14.64
	No	11	49.9	16.50
Heart Rate bpm	Yes	15	96	10.70
	No	15	93	9.28
Cardiac Index L/min/m^2	Yes	15	2.65	.40
	No	15	2.58	.45
Stroke Volume Index ml/beat/m^2	Yes	15	27	5.59
	No	15	28	4.34
LVSWI g-m-m^2 * beat/m^2	Yes	15	23	6.47
	No	15	24	4.93
SVRI dynes-sec-cm-^{5}/m^2	Yes	15	2097	570
	No	15	2279	637
Right Atrial Pressure mm Hg	Yes	15	12	5.56
	No	15	11	3.70
PAOP mm Hg	Yes	15	16	5.68
	No	15	16	4.99
Mean Arterial Pressure mm Hg	Yes	14	80	15.73
	No	15	83	14.14

Table 10

Baseline Physiological Data and Clinical Characteristics of Propofol Groups (n = 15 per group)

Mixed Venous Oxygen Saturation %	Yes	15	64.5	8.52
	No	15	63.5	8.34
Oxygen Consumption ml/min/m^2 ‡	Yes	15	141	27.79
	No	15	137	16.23
Arterial Oxygen Saturation	Yes	15	.98	.02
	No	15	.98	.02
Oxygen Delivery ml/min/m^2	Yes	15	361	73
	No	15	350	71
Oxygen Extraction Ratio	Yes	15	.41	.14
	No	15	.40	.07
Arterial Oxygen Content	Yes	10	13.8	1.81
	No	15	14.0	1.38
Intrapulmonary Shunt (Qs/Qt) %	Yes	10	9.9	5.31
	No	15	12.7	5.58

Note. Baseline data were obtained during phase I, without morphine; C = Celsius; bpm = beats per minute; LVSWI = left ventricular stroke work index; SVRI = systemic vascular resistance index; PAOP = pulmonary artery occlusion pressure; Fifteen subjects per group; $n < 15$ per group implies missing or rejected data; Group mean comparisons evaluated with Student's Independent t test ($\alpha = .01$, two-tailed); ‡ = assumption of equal variance rejected ($\rho < .05$) and comparison evaluated with unequal variance t test; * *$\rho < .01$.

Table 11

Baseline Physiological Data and Clinical Characteristics of Subjects Turned to the Left (n = 15) and Right (n = 15) 45-Degree Lateral Positions

Variable	**Lateral Position**	***n***	**Mean**	***SD***
Blood Temperature (C)	Left	15	37.36	.58
	Right	15	37.73	.53
Arterial pH	Left	15	7.41	.05
	Right	15	7.43	.06
Arterial Oxygen Tension mm Hg	Left	15	121.40	42.42
	Right	15	131.73	41.35
Arterial Oxygen Saturation	Left	15	.98	.02
	Right	15	.98	.01
Intrapulmonary Shunt (Qs/Qt) %	Left	12	12.15	6.15
	Right	13	11.04	5.08
Arterial Oxygen Content ml/dl ‡	Left	12	14.52	1.75
	Right	13	13.32	1.06
Total Hemoglobin g-/dl	Left	15	10.91	1.31
	Right	15	9.85	.88
LVEF %	Left	10	51.10	14.71
	Right	8	48.13	16.99
Mean Arterial Pressure mm Hg	Left	14	75.57	11.78
	Right	15	86.27	15.69
Heart Rate bpm	Left	15	90.20	9.83
	Right	15	97.93	8.75
Stroke Volume Index ml/beat/m^2	Left	15	27.41	3.81
	Right	15	27.62	5.97
Cardiac Index L/min/m^2	Left	15	2.44	.32
	Right	15	2.70	.45

Table 11

Baseline Physiological Data and Clinical Characteristics of Subjects Turned to the Left (n = 15) and Right (n = 15) 45-Degree Lateral Positions

LVSWI g-m-m^2 * beat/m^2 ‡	Left	15	21.29	3.43
	Right	15	25.58	6.74
SVRI dynes-sec-cm-^{5}/m^2	Left	15	2125	534
	Right	15	2250	674
Right Atrial Pressure mm Hg	Left	15	11.20	4.74
	Right	15	12.27	4.73
PAOP mm Hg	Left	15	16.60	4.65
	Right	15	14.73	5.79
Mixed Venous Oxygen Saturation %	Left	15	63.47	8.80
	Right	15	64.43	8.04
Oxygen Consumption ml/min/m^2	Left	15	132.54	22.45
	Right	15	145.65	21.22
Oxygen Delivery ml/min/m^2	Left	15	358	73.05
	Right	15	353	71.66
Oxygen Extraction Ratio	Left	15	.38	.06
	Right	15	.43	.14
Propofol µg/kg/min iv	Left	15	9.21	10.73
	Right	15	14.35	21.89
Minutes Without Analgesic	Left	12	70.33	23.26
	Right	13	78.23	25.15

Note. C = degree Celsius; bpm = beats per minute; LVEF = left ventricular ejection fraction; LVSWI = left ventricular stroke work index; SVRI = systemic vascular resistance index; PAOP = pulmonary artery occlusion pressure; Fifteen subjects per group; $n < 15$ per group implies missing or rejected data; Group mean comparisons evaluated with Student's Independent t test ($\alpha = .01$, two-tailed); ‡ = assumption of equal variance rejected ($\rho < .05$) and comparison evaluated with unequal variance t test; ** $\rho < .01$

Table 12

Tissue Oxygenation Data By Propofol Group At Baseline and Following Lateral Positioning ($N = 30$)

Variable	Group	Without Morphine‡			With Morphine*		
	($n = 15$)	Baseline 1‡	Minute 1‡	Minute 5‡	Baseline 2*	Minute 1*	Minute 5*
VO_2I ml/min/m^2	Propofol	141 ± 27.8	141 ± 28.2	146 ± 24.9	136 ± 29.1	142 ± 32.1	143 ± 25.8
	No Propofol	137 ± 16.2	139 ± 17.7	145 ± 19.0	129 ± 14.7	134 ± 16.8	140 ±15.3
DO_2I ml/min/m^2	Propofol	361 ± 73.2		371 ± 73.6	368 ± 63.0		363 ± 60.0
	No Propofol	350 ± 71.1		371 ± 71.6	350 ± 50.4		348 ± 55.7
SvO_2%	Propofol	64.4 ± 8.5	59.1 ± 7.7	61.0 ± 6.9	66.1 ± 6.7	63.1 ± 6.4	64.2 ± 5.9
	No Propofol	63.5 ± 8.3	59.4 ± 8.5	62.0 ± 9.0	65.6 ± 7.2	63.0 ± 8.1	64.1 ± 7.7
O_2ER	Propofol	.41 ± .14		.40 ± .08	.38 ± .10		.40 ± .10
	No Propofol	.40 ± .07		.40 ± .06	.38 ± .07		.41 ± .08
SpO_2 %	Propofol	98.2 ± .018		97.5 ± .03	98.6 ± .02		98.0 ± .02
	No Propofol	98.0 ± .015		98.1 ± .02	98.3 ± .02		98.1 ± .02

Note. Means and standard deviations; VO_2I = oxygen consumption index; DO_2I = oxygen delivery index; SvO_2 = mixed venous oxygen saturation; O_2ER = oxygen extraction ratio; SpO_2 = oxygen saturation; group with propofol ($n = 15$); group without propofol ($n = 15$); ‡ = without morphine; * = with morphine.

Table 13

Hemodynamic Data By Propofol Group at Baseline and Following Lateral Positioning

Variable	Group (n =15)	Without Morphine‡		With Morphine*	
		Baseline 1‡	Minute 5‡	Baseline 2*	Minute 5*
Heart Rate bpm	Propofol	95.5 ± 10.7	94.1 ± 10.6	99.3 ± 16.0	99.8 ± 16.2
	No Propofol	92.6 ± 9.3	92.6 ± 9.2	89.0 ± 8.6	91.8 ± 7.8
MAP mmHg	Propofol	79.6 ± 15.7	83.1 ± 15.4	73.0 ± 13.1	77.7 ± 15.3
	No Propofol	82.5 ± 14.1	85.6 ±15.6	74.8 ± 16.7	79.6 ± 17.2
RAP mmHg	Propofol	12.3 ± 5.6	14.7 ± 5.9	12.0 ± 5.3	14.5 ± 5.0
	No Propofol	11.1 ± 3.7	13.6 ± 4.4	9.8 ± 3.4	12.8 ± 4.2
PAOP mmHg	Propofol	15.5 ± 5.6		16.6 ± 5.7	
	No Propofol	15.8 ± 4.9		14.1 ± 4.1	
PAD mmHg	Propofol	18.8 ± 4.8	22.4 ± 5.4	19.8 ± 6.2	22.3 ± 6.1
	No Propofol	19.4 ± 3.2	21.9 ± 4.4	17.4 ± 2.8	21.0 ± 3.6
Cardiac Index L/min/m^2	Propofol	2.65 ± .40	2.74 ± .52	2.69 ± .47	2.66 ± .34
	No Propofol	2.58 ± .45	2.73 ± .41	2.58 ± .33	2.57 ± .34
SVI ml/min/m^2	Propofol	27.4 ± 5.6	30.3 ± 5.9	27.4 ± 6.2	27.4 ± 5.7
	No Propofol	27.5 ± 4.3	28.6 ± 3.9	29.8 ± 5.5	28.5 ± 4.1
SVRI dynes.sec.cm-^{5}.m^2	Propofol	2097 ± 570	1951 ± 590	1845 ± 481	1880 ± 536
	No Propofol	2279 ± 636	2221 ± 711	2035 ± 577	2102 ± 566
LVSWI g.m.m^{-2}	Propofol	22.8 ± 6.5	26.7 ± 8.4	20.6 ± 6.5	22.1 ± 6.8
	No Propofol	24.0 ± 4.9	26.8 ± 7.2	23.9 ± 5.5	25.2 ± 6.4

Note. Means and standard deviations; bpm = beats per minute; MAP = mean arterial pressure; RAP = right atrial pressure; PAOP = pulmonary artery occlusion pressure; PAD = pulmonary artery diastolic pressure; SVI = stroke volume index; SVRI = systemic vascular resistance index; LVSWI = left ventricular stroke work index; group with propofol (n = 15); group without propofol (n = 15); ‡ = without morphine; * = with morphine.

Table 14

ANOVA Summary Table (*Propofol x Morphine x Time*) for VO_2I Minute 1 and Minute 5 Following Positioning ($N = 30$)

Source	***SS***	***df***	***MS***	F^a	ρ	η^2
			Between-subjects			
Propofol	490.51	1	490.51	0.37	.54	.01
Error Between	36483.14	28	1302.97			
			Between x Within-subjects Interactions			
Propofol x Morphine	122.75	1	122.75	0.25	.62	.01
Propofol x Time	56.98	1	56.98	0.28	.60	.01
Propofol x Morphine x Time	28.56	1	28.56	0.19	.67	.01
Error Within	4223.55	28	150.84			

Note. VO_2I measured at minutes 1 and 5 following lateral positioning during two conditions of morphine (phase I = without; phase II = with) between groups who had a propofol infusion ($n = 15$) and those who did not have a propofol infusion during study procedures ($n = 15$). Univariate tests included main effect of propofol, all two-way and three-way interactions between propofol and the within-subjects factors. Main effects of time and morphine not tested. ^{a} = Exact statistic * $\rho < .10$.

Table 15

ANOVA Summary Table (*Propofol x Morphine x Time*) for SvO_2 Minute 1 and Minute 5 Following Positioning ($N = 30$)

Source	***SS***	***df***	***MS***	F^a	ρ	η^2
		Between-subjects				
Propofol	1.40	1	1.40	0.01	.94	.00
Error Between	5781.16	28	206.47			
		Between x Within-subjects Interactions				
Propofol x Morphine	6.07	1	6.07	0.37	.55	.01
Propofol x Time	1.87	1	1.87	0.38	.54	.01
Propofol x Morphine x Time	.67	1	.67	0.16	.69	.01
Error Within	117.5	28	4.19			

Note. SvO_2 measured at minutes 1 and 5 following lateral positioning during two conditions of morphine (phase I = without; phase II = with) between groups who had a propofol infusion ($n = 15$) and those who did not have a propofol infusion during study procedures ($n = 15$). Univariate tests included main effect of propofol, all two-way and three-way interactions between propofol and the within-subjects factors. Main effects of time and morphine not tested; ^{a} = Exact statistic; * $\rho < .10$.

Table 16

ANOVA Summary Table (*Propofol x Morphine x Time*) for VO_2I
Baseline – Minute 10 Following Positioning ($N = 30$)

Source	*SS*	*df*	*MS*	F[a]	ρ	η^2
		Between-subjects				
Propofol	4741.60	1	4741.60	0.78	.39	.03
Error Between	170401.68	28	6085.77			
		Between x Within-subjects Interactions				
Propofol x Morphine[b]	2568.23	1	2568.23	0.98	.33	.03
Propofol x Time[b]	607.10	4.08	148.97	0.45	.78	.02
Propofol x Morphine x Time[b]	652.92	3.07	212.89	0.53	.66	.02
Error Within[b]	34255.95	85.87	398.92			

Note. VO_2I measured at baseline and every minute through minute 10 following lateral positioning during two conditions of morphine (phase I = without; phase II = with) between groups who had a propofol infusion ($n = 15$) and those who did not have a propofol infusion during study procedures ($n = 15$). Univariate tests included the main effect of propofol and all two-way and three-way interactions between propofol and the within-subjects factors. Main effects of time and morphine were not tested. [a] = Exact statistic; [b] = *F* statistic adjustment with Greenhouse-Geisser epsilon; * $\rho < .10$.

Table 17

ANOVA Summary Table (*Propofol x Morphine x Time*) for SvO_2 Baseline – Minute 10 Following Positioning ($N = 30$)

Source	*SS*	*df*	*MS*	F[a]	ρ	η^2
		Between-subjects				
Propofol	0.00495	1	0.00495	0.00	.99	.00
Error Between	2813.23	28	100.47			
		Between x Within-subjects Interactions				
Propofol x Morphine[b]	3.34	1	3.34	0.45	.83	.00
Propofol x Time[b]	20.98	3.82	5.48	0.47	.74	.02
Propofol x Morphine x Time[b]	20.87	3.88	5.38	0.56	.66	.02
Error Within[b]	981.86	108.60	9.04			

Note. SvO_2 measured at baseline and every minute through minute 10 following lateral positioning during two conditions of morphine (phase I = without; phase II = with) between groups who had a propofol infusion ($n = 15$) and those who did not have a propofol infusion during study procedures ($n = 15$). Univariate tests included the main effect of propofol and all two-way and three-way interactions between propofol and the within-subjects factors. Main effects of time and morphine were not tested; [a] = Exact statistic; [b] = F statistic adjustment with Greenhouse-Geisser epsilon; * $\rho < .10$.

Table 18

ANOVA Summary Table for Planned Simple Effects *(Morphine Within Time)* for VO_2I ($N = 30$)

Source	*SS*	*df*	*MS*	*F*	*ρ*	η^2	Power[c]
		Within-subjects					
A Within B_1							
Morphine at Minute (1)	62.54	1	62.54	0.22	.64	.01	.06
Within + Residual	8166.62	29	281.61				
A Within B_2							
Morphine at Minute (5)	243.64	1	243.64	0.70	.41	.02	.16
Within + Residual	10146.41	29	349.88				

Note. Analyses performed using separate error term for each test; A = morphine; B = minutes following lateral positioning; [c] = observed power; * $\rho < .025$

Table 19

Tissue Oxygenation Data At Baseline and Following Lateral Positioning, With and Without Morphine ($N = 30$)

Variable	Phase	Baseline	Minute 1	Minute 3	Minute 5	Minute 10
VO_2I ml/min/m^2	I: Control	139 ± 22.5	140 ± 23.2	149 ± 19.9	145 ± 21.8	140 ± 24.8
	II: Morphine	133 ± 23.0	138 ± 25.6	142 ± 24.3	141 ± 21.0	136 ± 21.3
DO_2I ml/min/m^2	I: Control	355 ± 71		368 ± 72	371 ± 71	380 ± 94
	II: Morphine	359 ± 57		357 ± 57	356 ± 57	350 ± 53
SvO_2%	I: Control	64 ± 8.3	59 ± 7.9	60 ± 7.4	61 ± 7.9	63 ± 8.2
	II: Morphine	66 ± 6.9	63 ± 7.2	63 ± 6.8	64 ± 6.8	66 ± 6.8
O_2ER	I: Control	.41 ± .11		.42 ± .01	.40 ± .01	.38 ± .01
	II: Morphine	.38 ± .01		.41 ± .01	.41 ± .01	.40 ± .01
SpO_2 %	I: Control	98 ± .02		98 ± .02	98 ± .02	98 ± .02
	II: Morphine	98 ± .02		98 ± .01	98 ± .01	98 ± .02

Note. Means and standard deviations; VO_2I = oxygen consumption index; DO_2I = oxygen delivery index; SvO_2 = mixed venous oxygen saturation; O_2ER = oxygen extraction ratio; SpO_2 = oxygen saturation; phase I = no morphine; phase II = morphine 0.10 mg/kg/ ideal body weight iv.

Table 20

Hemodynamic Data At Baseline and Following Lateral Positioning, With and Without Morphine ($N = 30$)

Variable	Phase	Baseline	Minute 3	Minute 5	Minute 10
Heart Rate bpm	I: Control	94 ± 9.9	94 ± 9.9	93 ± 9.8	93 ± 9.9
	II: Morphine	94 ± 13.7	96 ± 13.0	96 ± 13.1	96 ± 12.8
MAP mm Hg	I: Control	81 ± 14.7	85 ± 15.6	84 ± 15.3	84 ± 15.3
	II: Morphine	74 ± 14.8	79 ±15.6	77 ± 16.1	77 ± 14.7
RAP mm Hg	I: Control	11.7 ± 4.7	14.4 ± 5.3	14.2 ± 5.2	14.0 ± 5.1
	II: Morphine	11.0 ± 4.5	14.0 ± 4.4	13.6 ± 4.6	13.1 ± 4.5
PAOP mm Hg	I: Control	15.7 ± 5.3			
	II: Morphine	15.3 ± 5.1			
PAD mm Hg	I: Control	19.2 ± 4.0	22.4 ± 4.8	22.2 ± 4.9	21.7 ± 4.2
	II: Morphine	18.6 ± 4.9	22.0 ± 5.0	21.7 ± 4.9	21.0 ± 5.1
Cardiac Index $L/min/m^2$	I: Control	2.61 ± .49	2.71 ± .46	2.73 ± .46	2.78 ± .57
	II: Morphine	2.63 ± .40	2.63 ± .36	2.61 ± .34	2.57 ± .32
SVI $ml/min/m^2$	I: Control	27.5 ± 4.9	29.0 ± 5.0	29.4 ± 5.0	29.8 ± 8.6
	II: Morphine	28.6 ± 5.9	28.0 ± 4.4	28.0 ± 4.9	27.6 ± 5.2
SVRI $dynes.sec.cm^{-5}.m^2$	I: Control	2188 ± 601	2075 ± 768	2086 ± 657	2137 ± 685
	II: Morphine	1940 ± 531	1963 ± 528	1991 ± 553	1998 ± 526
LVSWI $g.m.m^{-2}$	I: Control	23.4 ± 5.7	26.5 ± 7.4	26.8 ± 7.2	27.1 ± 9.3
	II: Morphine	22.2 ± 6.2	23.7 ± 6.6	23.7 ± 6.7	22.7 ± 6.1

Note. Means and standard deviations; bpm = beats per minute; MAP = mean arterial pressure; RAP = right atrial pressure; PAOP = pulmonary artery occlusion pressure; PAD = pulmonary artery diastolic pressure; SVI = stroke volume index; SVRI = systemic vascular resistance index; LVSWI = left ventricular stroke work index; ± = standard deviation; phase I = no morphine; phase II = morphine 0.10 mg/kg/ideal body weight iv.

Table 21

Summary Table for *A Within B* Simple Effects (Morphine at Minute 1 and Minute 5 Post-Turn) ANOVA for SvO_2 ($N = 30$)

Source	*SS*	*df*	*MS*	*F*	ρ	η^2
		Within-subjects				
A Within B1						
Morphine at Minute (1)	198.02	1	198.02	16.82	.000*	.37
Within + Residual	341.48	29	11.78			
A Within B2						
Morphine at Minute (5)	112.07	1	112.07	13.55	.001*	.32
Within + Residual	239.93	29	8.27			

Note. Analyses performed using separate error term for each test; * $\rho < .025$.

Table 22

Simple Regression Analyses of VO_2I on SvO_2 at Minute 3 Following Lateral Positioning, With and Without Morphine

Variable ($N = 30$)	M	SD	R^2	B	B 95% CI		SE	β	*t*	Sig.
SvO_2 †	60.33	7.42								
VO_2I	148.64	19.96	.009	.0035	-.108	.179	.070	.096	.51	.61
SvO_2 ‡	63.27	6.81								
VO_2I	141.73	24.30	.010	-.0028	-.136	.080	.053	-.100	-.53	.59

Note. SE = standard error of the estimate; β = standardized regression coefficient; B = unstandardized regression coefficient † = without morphine; ‡ = with morphine; *ρ < .025.

The Roy Adaptation Model

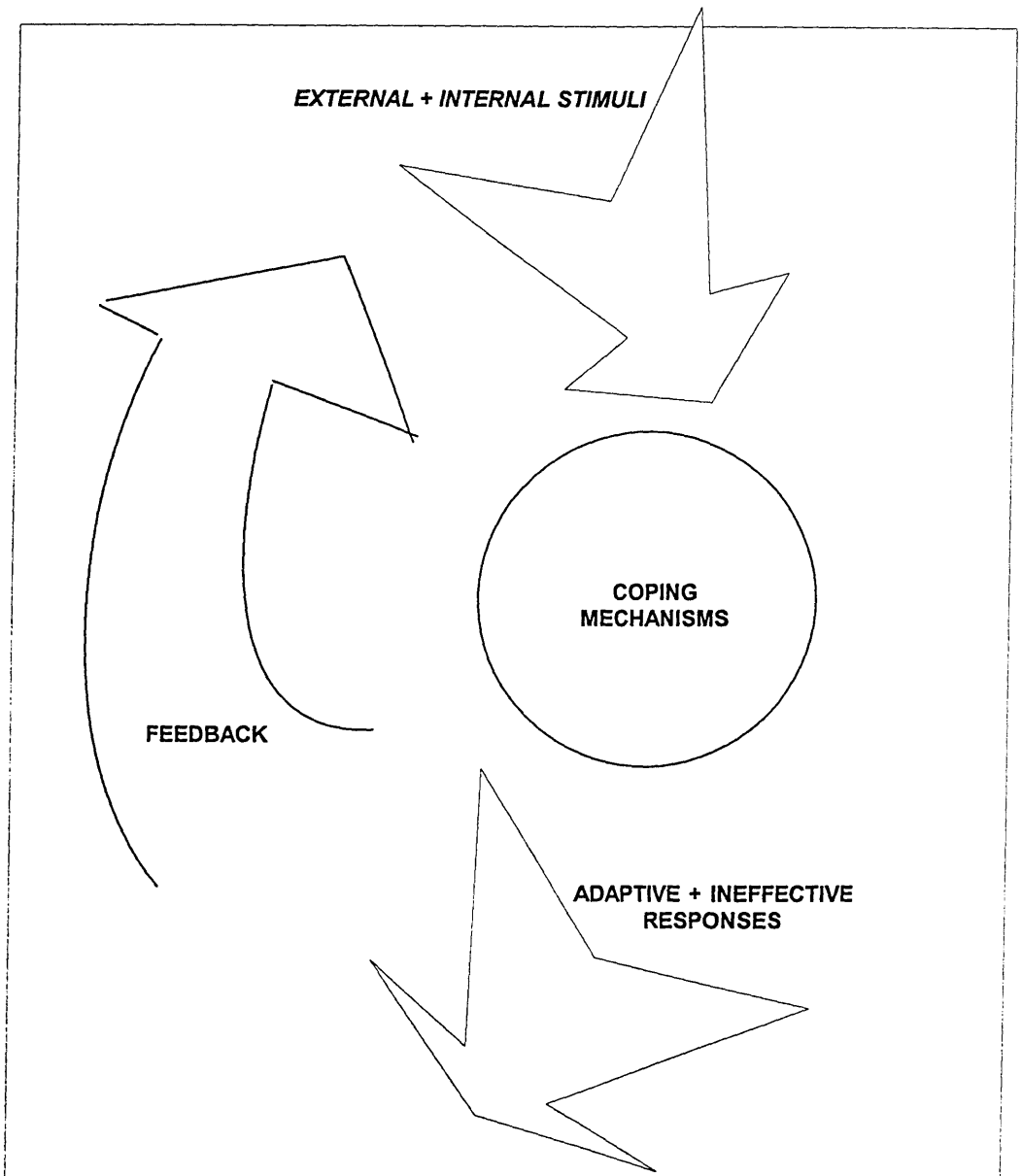

Figure 1. Roy's Adaptation Model - the person as a system. The Roy Adaptation Model incorporates general system theory and the concepts of adaptation level, stimuli, coping mechanisms, responses, and feedback. From *The Roy Adaptation Model: The Definitive Statement* (p. 8), by C. Roy and H. Andrews (Eds.), 1991, East Norwalk: Appleton & Lange. Copyright 1991 by Appleton & Lange. Reproduced with permission.

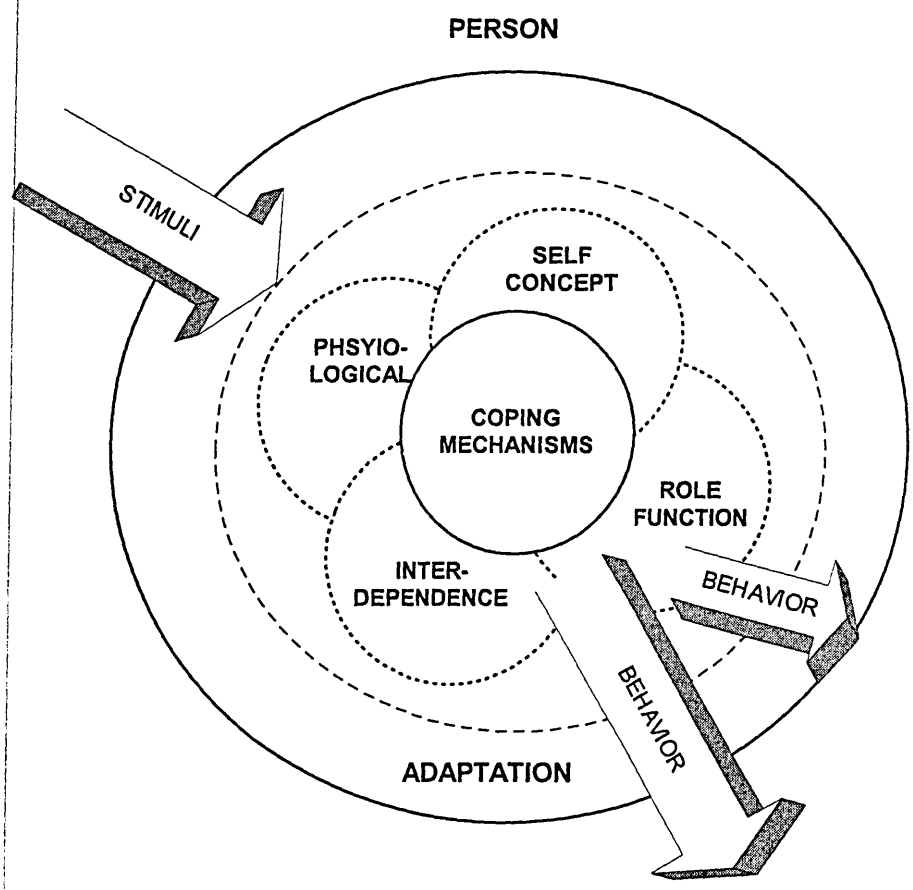

Figure 2. Roy's Adaptation Model - the person as an adaptive system.The interrelationship of the four adaptation modes, coping mechanisms, stimuli, and responses are depicted in the Roy Adaptation Model. Four overlapping circles that represent the holistic nature of humans depict the four adaptation modes including self-concept, physiological, interdependence, and role function. Behavior in one mode may have an effect on or act as a stimulus for one of all of the other modes. Similarly, a stimulus may affect more than one mode. From *The Roy Adaptation Model: The Definitive Statement* (p. 17), by C. Roy and H. Andrews (Eds.), 1991, East Norwalk: Appleton & Lange. Copyright 1991 by Appleton & Lange. Reproduced with permission.

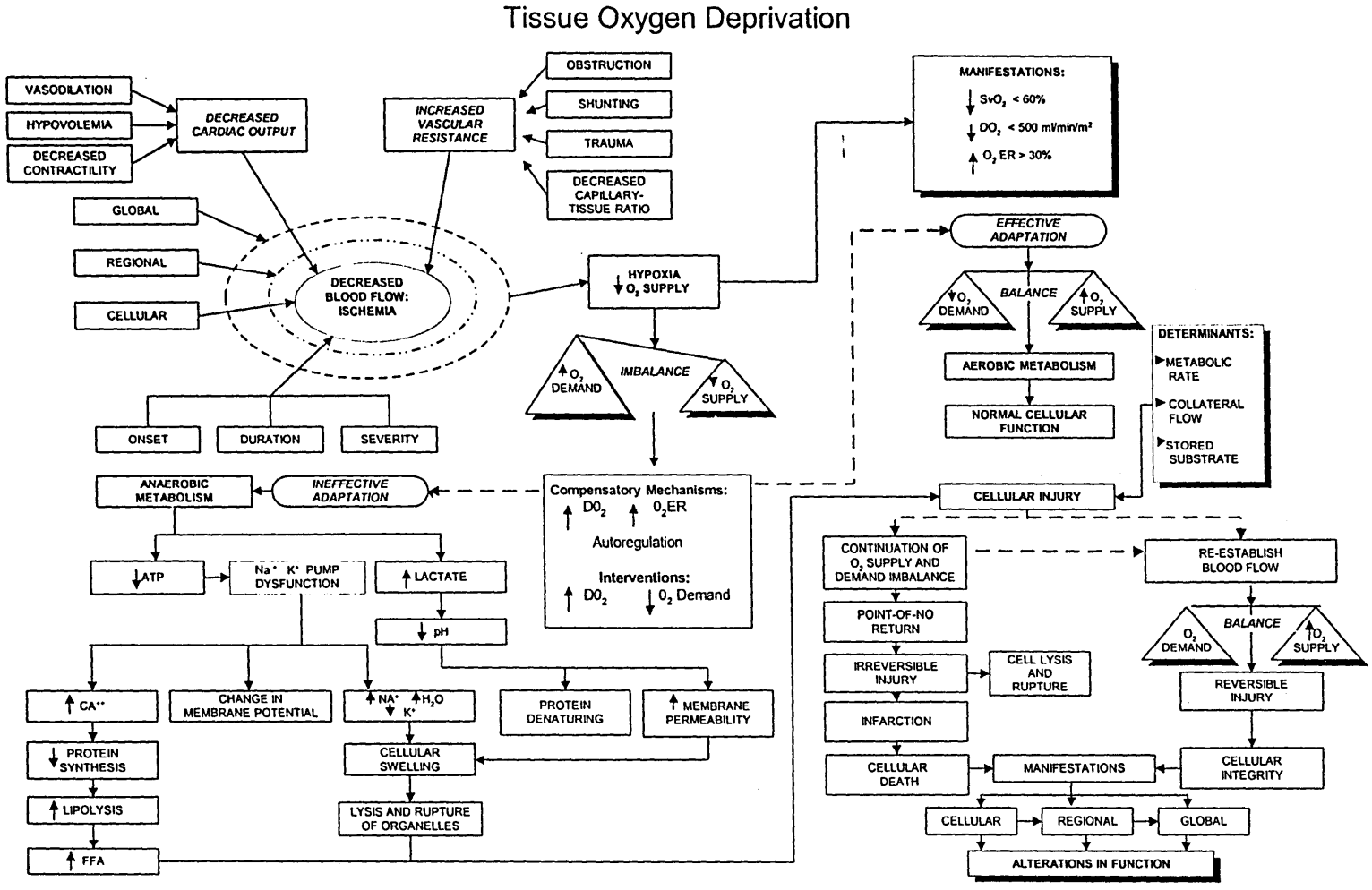

Figure 3. Pathogenesis of tissue oxygen deprivation related to inadequate flow (i.e., perfusion). From "Tissue oxygenation and routine nursing procedures in critically ill patients," by J. Jesurum, 1997, Journal of Cardiovascular Nursing, 11(4), pp.12-30. Adapted with permission.

Figure Caption

Figure 3. Pathogenesis of tissue oxygenation deprivation (i.e., hypoxia) related to inadequate blood flow (i.e., ischemia). SvO_2 = mixed venous oxygen saturation; VO_2 = oxygen consumption; DO_2 = oxygen delivery; O_2ER = oxygen extraction ratio, ATP = adenosine triphosphate; Na^+ = sodium; K^+ = potassium; H_2O = water; Ca^{++} = calcium; FFA = free fatty acid. From "Tissue Oxygenation and Routine Nursing Procedures in Critically Ill Patients," by J. Jesurum, 1997, Journal of Cardiovascular Nursing, *11*(4), p. 15. Copyright 1997 by Aspen Publishers, Inc. Reproduced with permission.

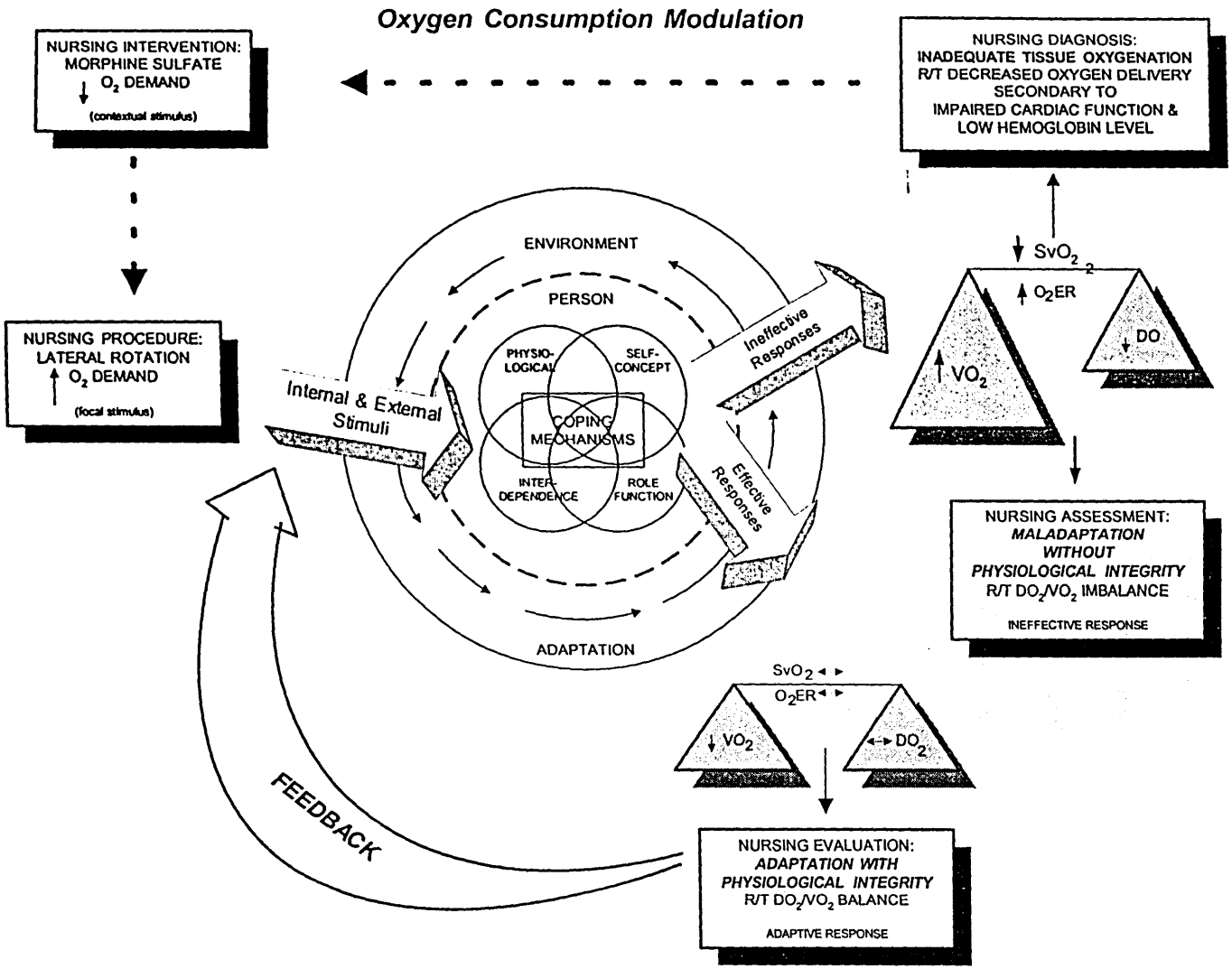

Figure 4. Conceptual model of nursing intervention to promote physiological adaptation in critically ill patients with low oxygen delivery through oxygen consumption modulation. Source: J. Jesurum, 2002.

Figure Caption

Figure 4. Model incorporating the theoretical concepts of the Roy Adaptation Model (Roy & Andrews, 1991) to illustrate the pathophysiological phenomenon of impaired tissue oxygenation related to decreased oxygen delivery. A nursing intervention to optimize tissue oxygenation by modulating tissue oxygen demands and promoting physiological adaptation in critically ill patients during lateral positioning is depicted in the model. SvO_2 = mixed venous oxygen saturation; VO_2 = oxygen consumption; DO_2 = oxygen delivery; O_2ER = oxygen extraction ratio; O_2 = oxygen; R/T = related to; = decrease; = increase; = no change. Source: J. Jesurum, 2002.

Bland Altman Plot: SpO_2 and SaO_2

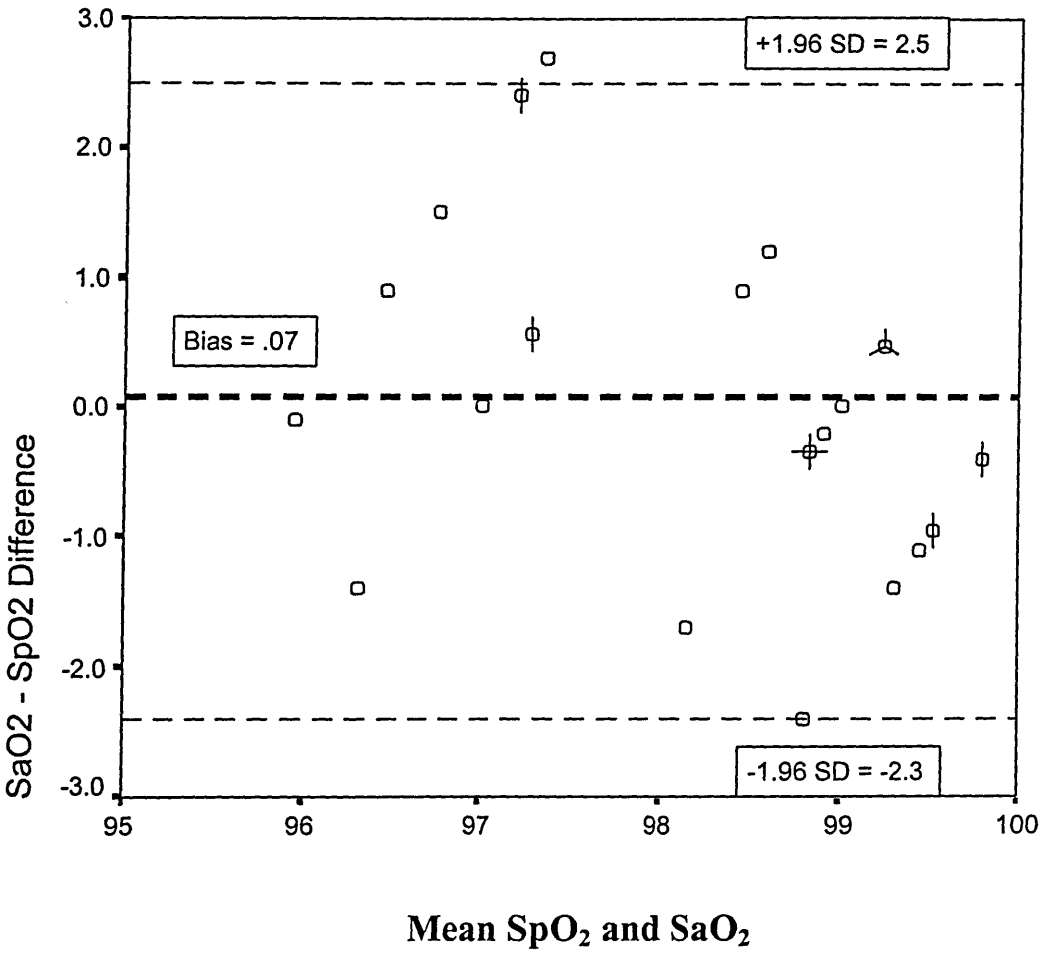

Figure 5. Methods comparison between SpO_2 and criterion SaO_2 ($N = 31$ pairs).

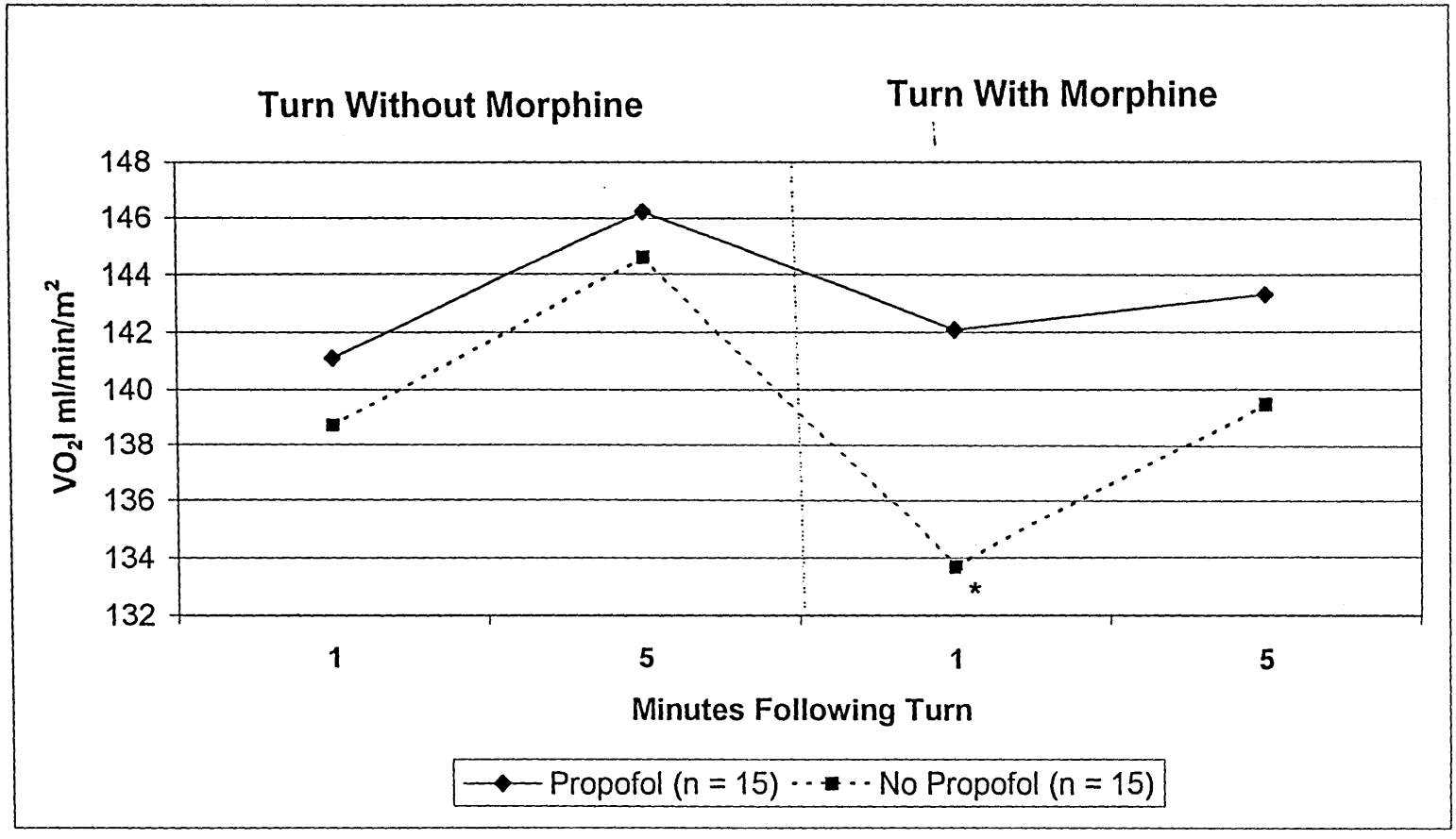

Figure 6. Mean of VO_2I over time by Morphine by Propofol Group (N = 30). Three-Way (2 x 2 x 2) Split Plot ANOVA results indicated there was no significant main effects of propofol $F(1, 28) = 0.37$, $p = .54$, or any signficant two-way or three-way interactions between the three independent variables.
* = unequal variance

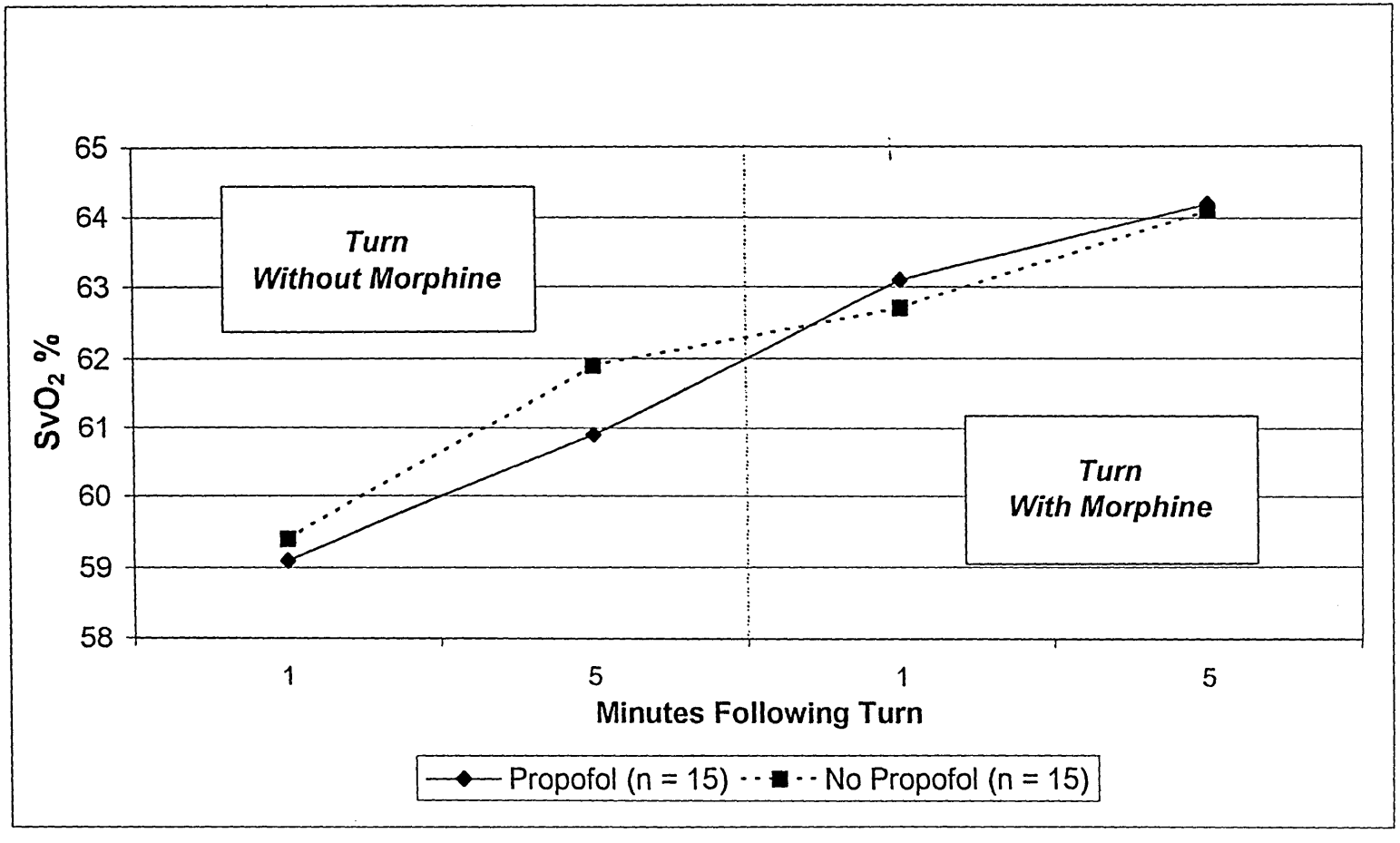

Figure 7. Mean of SvO_2 over time by Morphine by Propofol Group (N = 30). Three-Way (2 x 2 x 2) Split Plot ANOVA results indicated there was no significant main effects of propofol $F(1, 28) = 0.01$, $p = .94$, or any significant two-way or three-way interactions between the three independent variables.

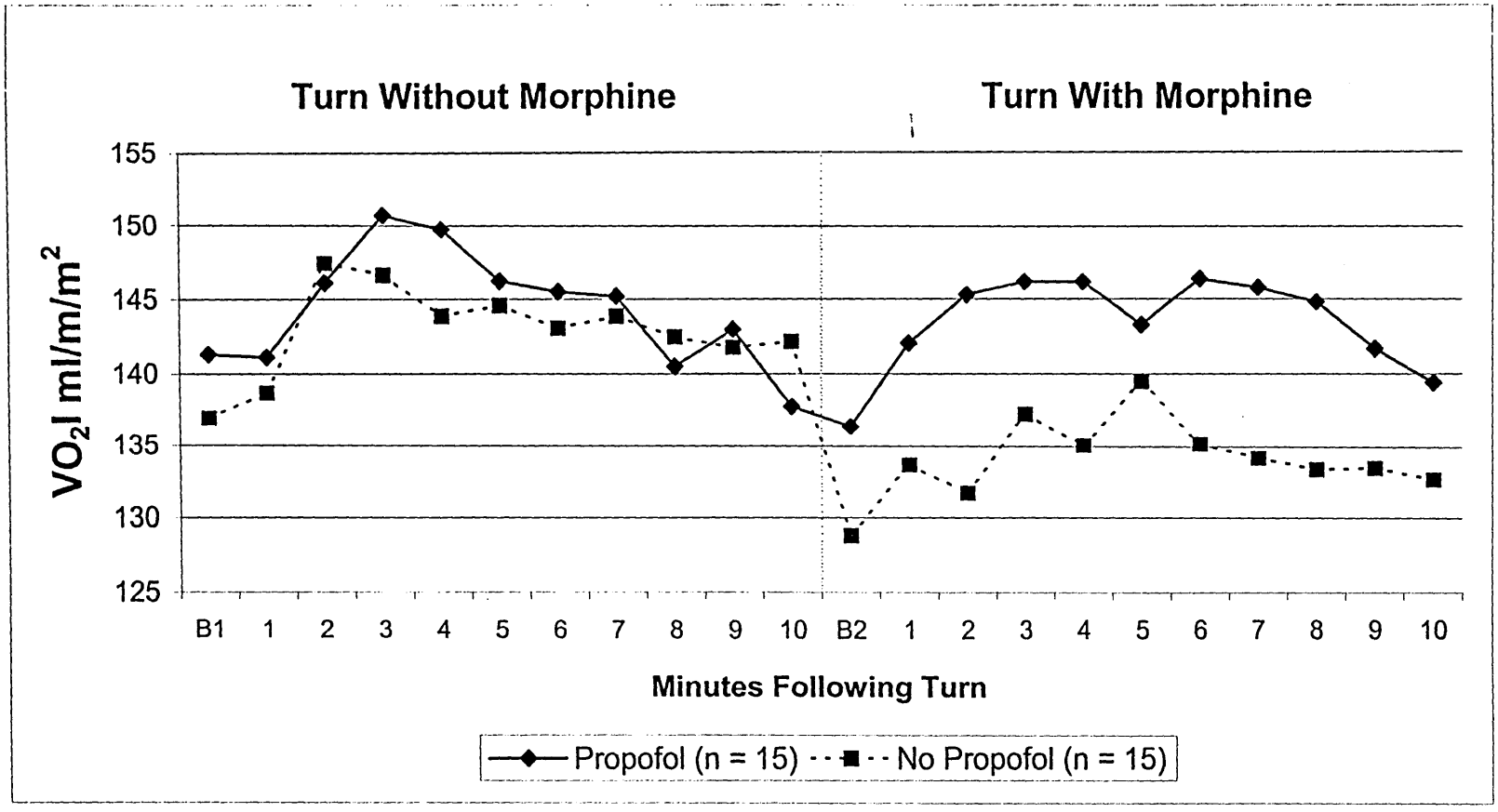

Figure 8. Mean of VO_2I over Time by Morphine by Propofol Group (N = 30). Three-Way (2 x 2 x 11) Split Plot ANOVA results indicated there were no significant main effects of propofol $F(1, 28) = 0.78$, p = .39, or any significant two-way or three-way interactions between the three independent variables; B = baseline.

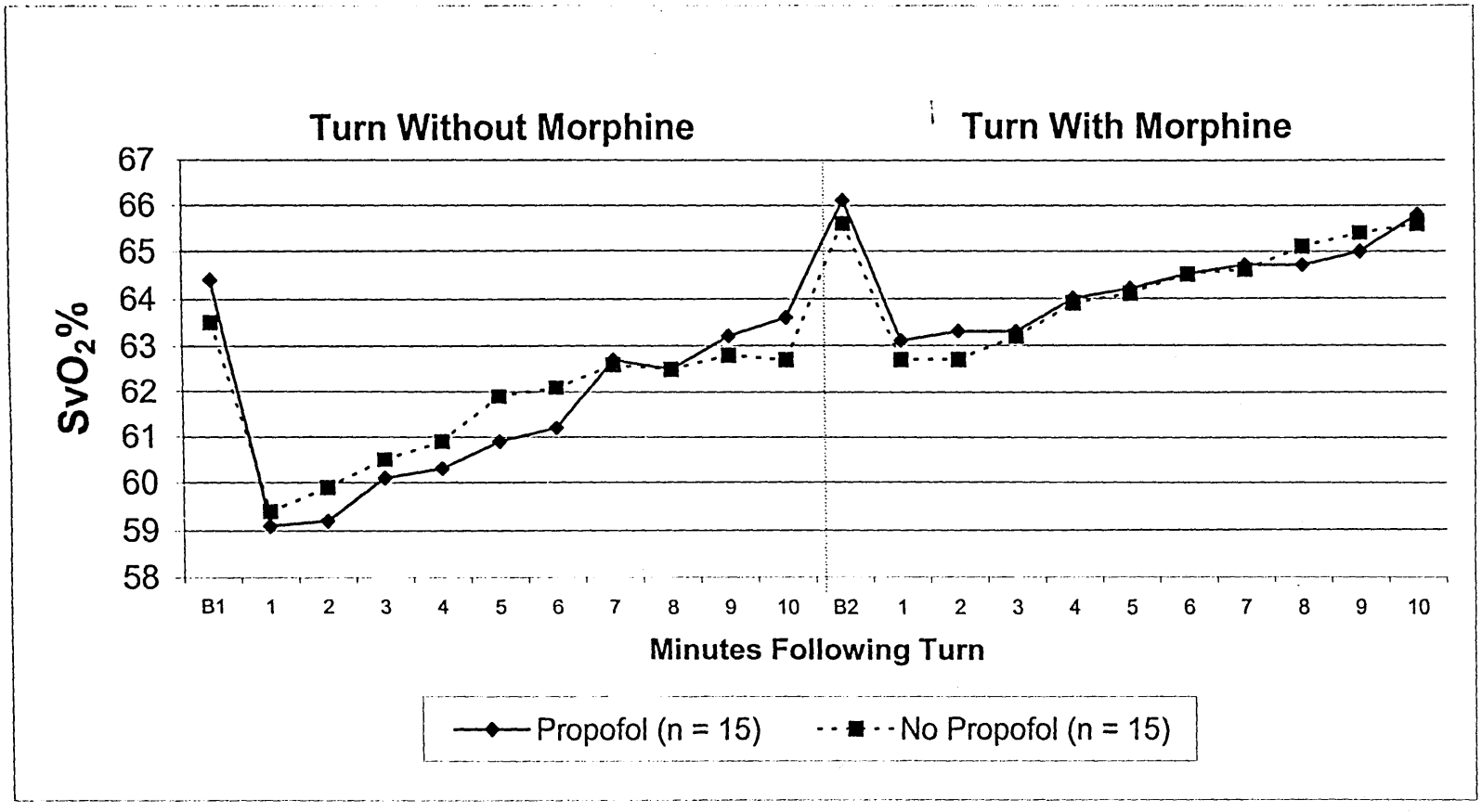

Figure 9. Mean of SvO_2 over Time by Morphine by Propofol Group (N = 30). Three-Way (2 x 2 x 11) Split Plot ANOVA results indicated there was no significant main effects of propofol $F(1, 28) = 0.00$, $p = .99$, or any significant two-way or three-way interactions between the three independent variables; B = baseline.

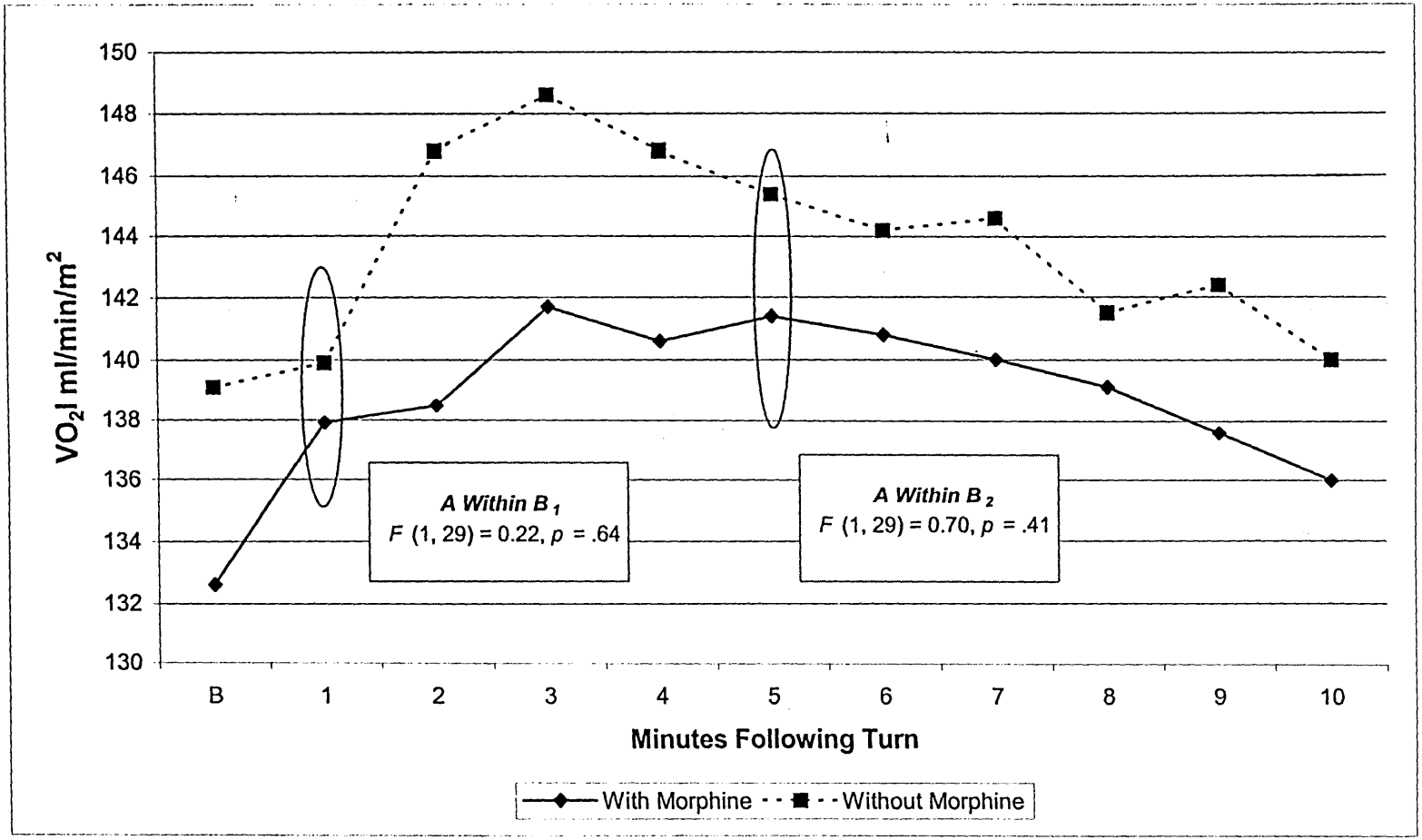

Figure 10. Planned simple effects of morphine at minute 1 following lateral positioning (*A at* B_1) and morphine at minute 5 following lateral positioning (*A at* B_2) on VO_2I. Results indicated that mean VO_2I was not significantly lower at minutes 1 and 5 following lateral positioning when morphine was received prior to turning; Separate error term per contrast; B = baseline; *p < .025.

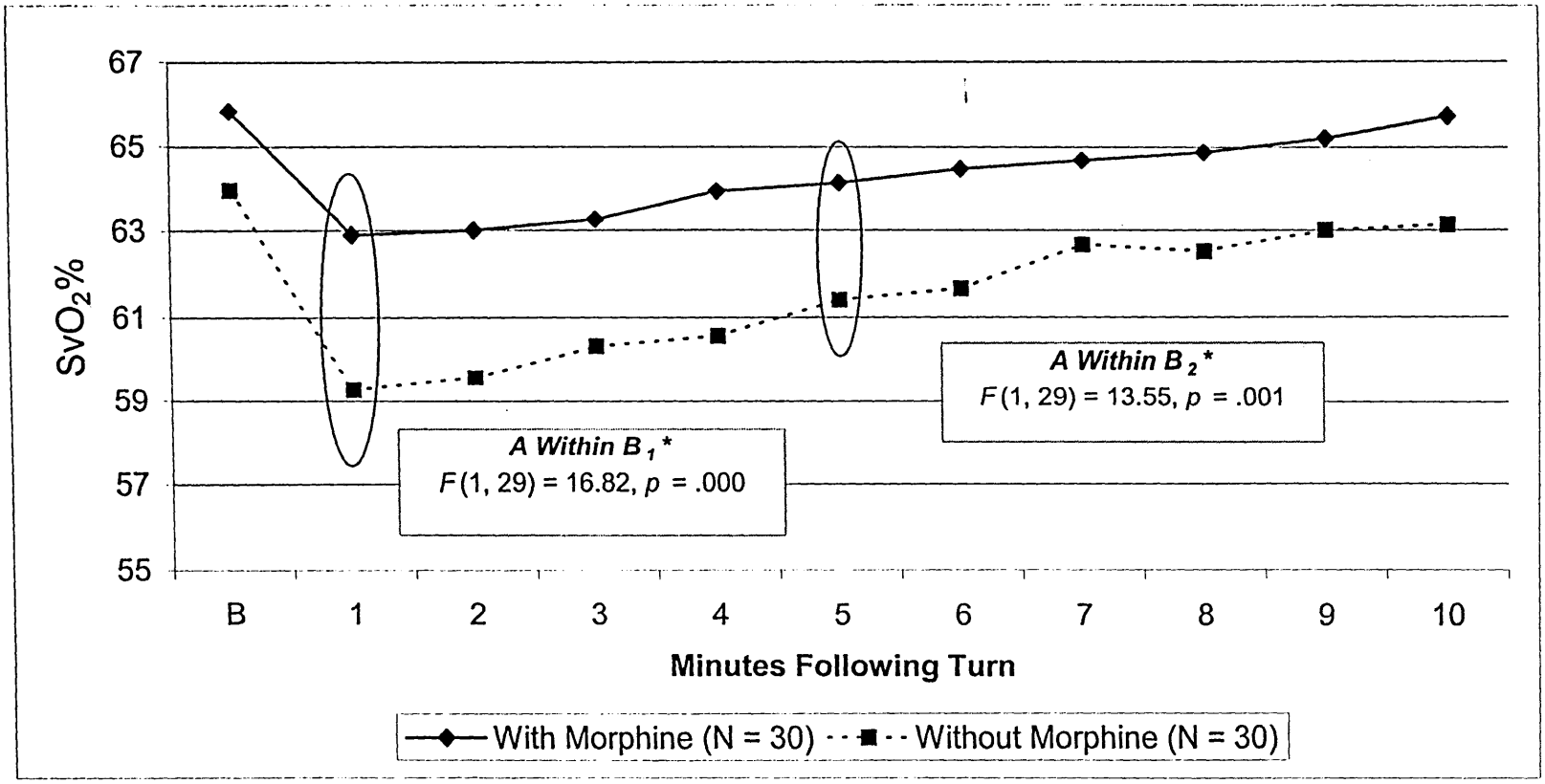

Figure 11. Planned simple effects of morphine at minute 1 following lateral positioning (*A at* B_1) and morphine at minute 5 following lateral positioning (*A at* B_2) on SvO_2. Results indicated that mean SvO_2 was significantly higher at minutes 1 and 5 following lateral positioning when morphine was received prior to turning; Separate error terms per contrast; B = baseline; * $p < .025$.

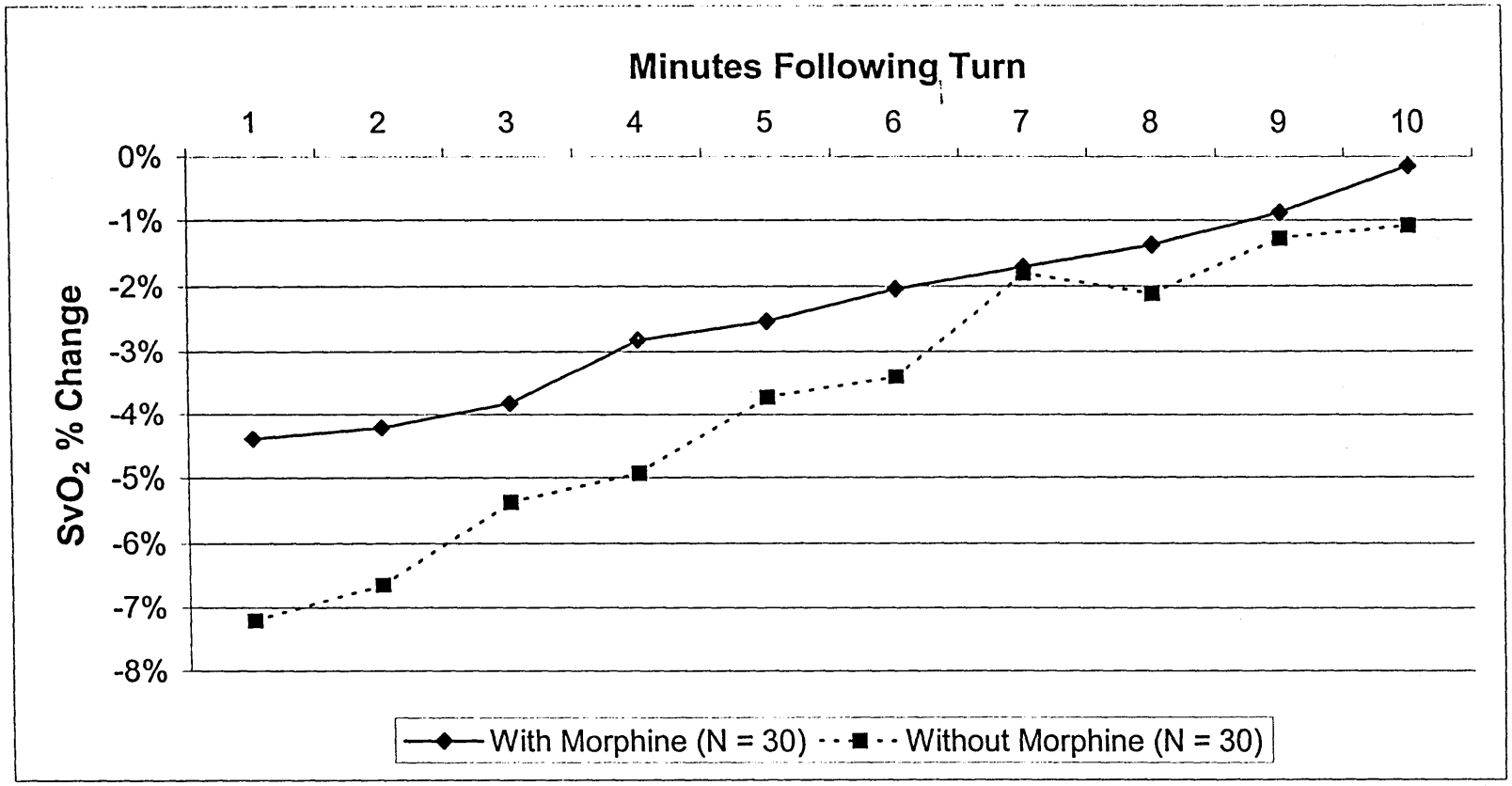

Figure 12. Average SvO_2 change (%) from baseline through minute 10 following lateral positioning, with and without the effects of morphine. When morphine was received prior to turning, the decrease in mean SvO_2 from baseline at minutes 1 and 5 post-turn was substantially less (32% - 38%).

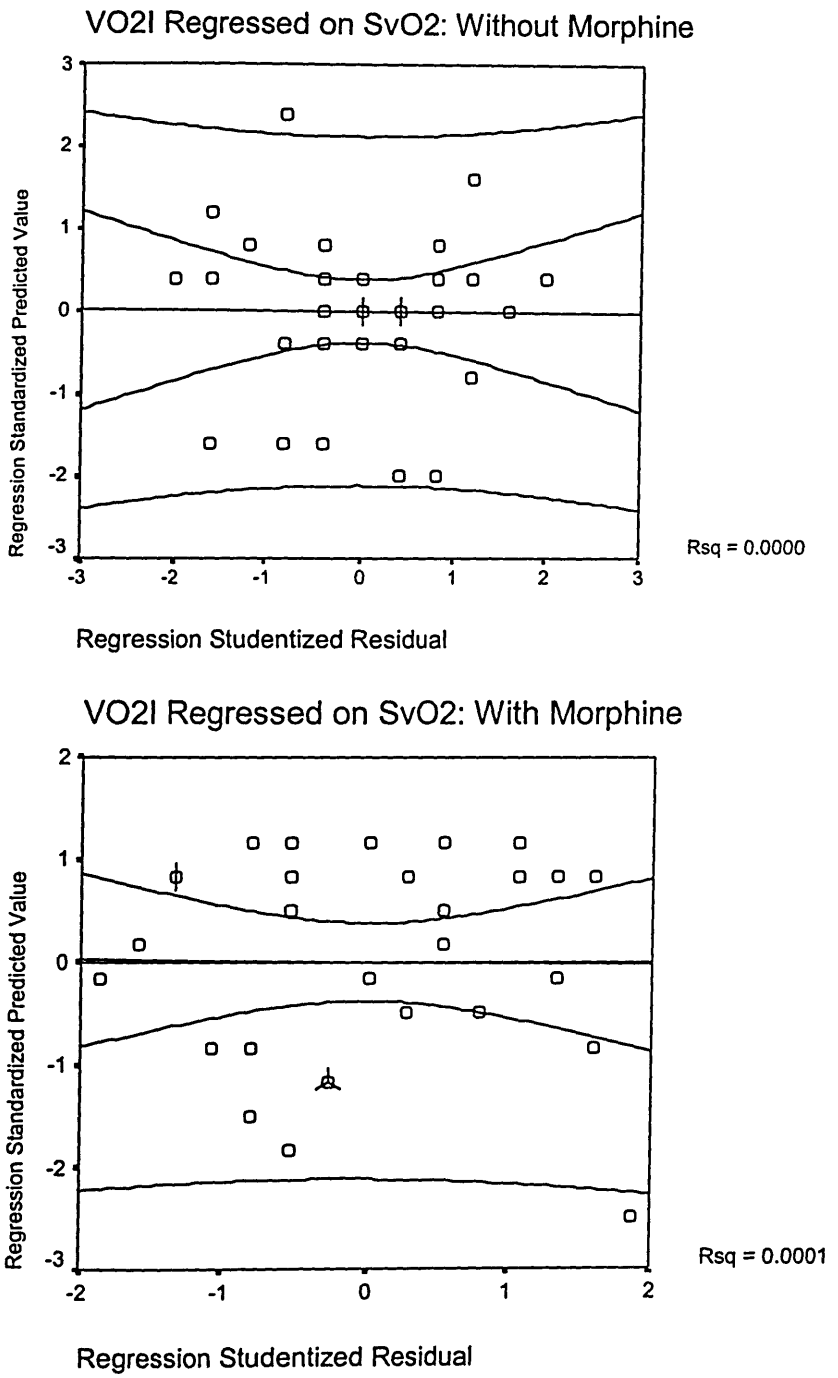

Figure 13. Bivariate scatterplots of the residuals against the predicted and observed SvO_2 scores and the residuals against VO_2I at minute 3 following lateral positioning ($N = 30$).

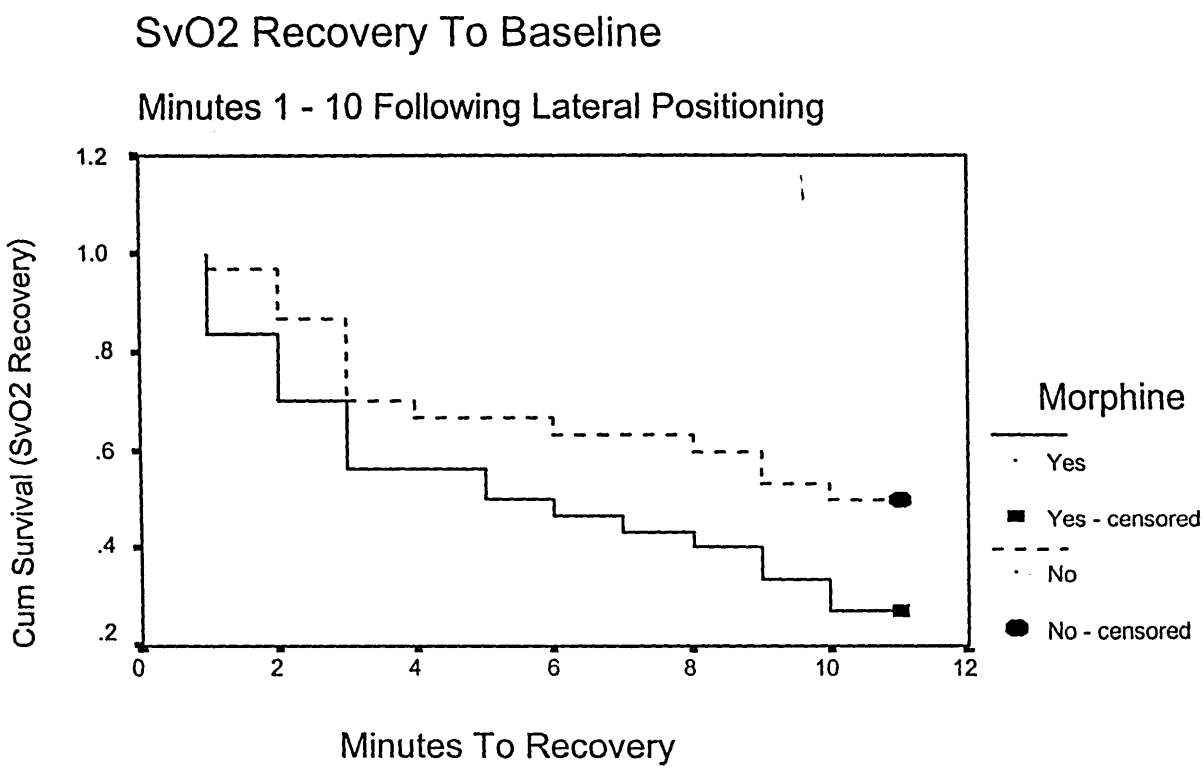

Figure 14. Cumulative survival plot displays actual occurrence of SvO_2 recovery (i.e., return to baseline) that occurred within 10 minutes following lateral positioning during both phases of the study ($N = 30$). Results indicated that when morphine was received before turning, subjects were 46% more likely to experience SvO_2 recovery within 10 minutes after the turn. The slope of the line suggests that SvO_2 recovery occurred in a shorter amount of time when subjects received morphine before the turn. Terminal event = SvO_2 recovery within minutes 1 – 10 following turn; censored = SvO_2 failure to return to baseline by minute 10 following turn; dotted line = phase I - turn without morphine; solid line = phase II - turn with morphine.

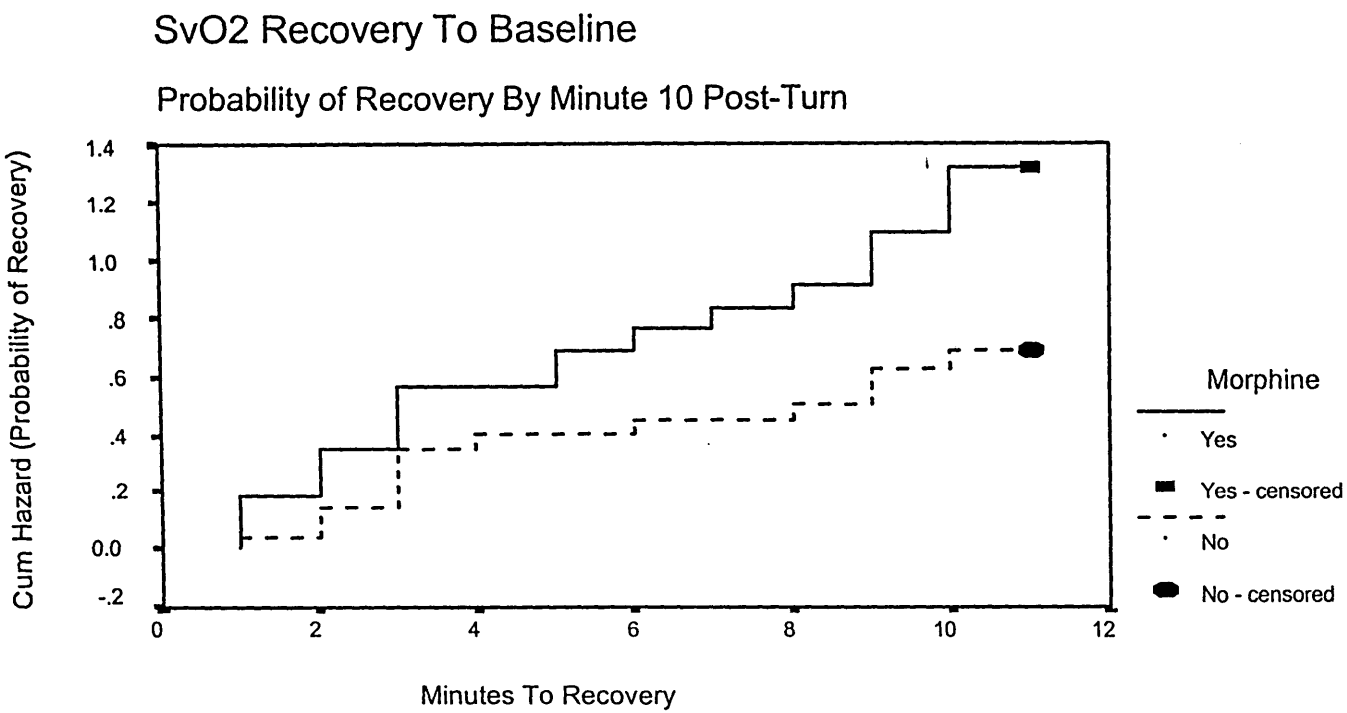

Figure 15. Cumulative hazard plot displays probability of SvO_2 recovery (i.e., return to baseline) *not* occurring within 10 minutes following lateral positioning during both phases of the study ($N = 30$). Results indicated that when subjects received morphine before turning, the estimated probability of SvO_2 *not* returning to baseline within 10 minutes following the turn was .27 vs. .50 without morphine. Terminal event = SvO_2 recovery within minutes 1 – 10 following turn; censored = SvO_2 failure to return to baseline by minute 10 following turn; dotted line = phase I - turn without morphine; solid line = phase II- turn with morphine.

Appendix A

Eligibility Criteria Tool

OXYGEN CONSUMPTION MODULATION:
EFFECTS OF AN OPIOID AGONIST ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY

ELIGIBILITY CRITERIA TOOL

Subject #_____

Date ____/____/____ (mm/dd/yy)

Instructions: Circle the correct response.

Data Collector: 1 = Principal Investigator 2 = Research Assistant

Part A. Inclusion Criteria: All of the items below must be answered **YES** for the patient to be eligible for this study.

1. Patient is $\geq$ 18 years of age.

1= Yes 2=No

2. The patient is able to read and speak English.

1= Yes 2=No

3. The patient is between 6 and 24 hours status post cardiovascular surgery requiring extracorporeal circulation.

1= Yes 2=No

4. Mechanical ventilation with PEEP $\leq$ 10cm H_2O and FiO_2 <0.80.

1=Yes 2=No

5. Functional intra-arterial catheter defined as presence of a blood return.

1= Yes 2=No

6. Functional Abbott OPTI-Q™ SvO_2/CCO pulmonary artery catheter verified to be in the pulmonary artery by radiographic confirmation and waveform analysis.

1= Yes 2=No

7. Sustained low oxygen delivery defined as two or more calculations of $DO_2I<500ml/m^2$ within the hour prior to start of study procedures.

A. Time_____ CCI_____X HGB_____X 1.34 X SpO_2 _____X 10 = DO_2I_____
B. Time_____ CCI_____X HGB_____X 1.34 X SpO_2 _____X 10 = DO_2I_____

1= Yes 2=No

8. Hemodynamic stability defined as a baseline systolic blood pressure ≥90mmHg and a heart rate between 60 to 125 beats/minute.

1= Yes 2=No

9. No documented allergy or intolerance to morphine sulfate.

1= Yes 2=No

10. Written physician or ARNP order to receive intravenous MSO_4.

1= Yes 2=No

11. Hemoglobin ≥ 7.0 g-/dl at time of enrollment

1=Yes 2=No

12. Normothermia as evidenced by pulmonary artery blood temperature < 36.5°C to 38.0°C.

1=Yes 2=No

13. Hemostasis as evidenced by chest drainage < 100 ml/hr during the 2 hour period preceeding the start of study procedures.

1=Yes 2=No

14. No mediastinal or pleural air leak observed in the chest drainage system.

1= Yes 2=No

15. Absence of shivering as evidenced by no repetitive involuntary skeletal muscle contractions.

1= Yes 2=No

16. No contraindications to lateral rotation (i.e., open sternum).

1= Yes 2=No

Part B. Exclusion Criteria: All of the items listed below must be answered **NO** for the patient to be eligible for this study.

1. Written diagnosis of documented infection or sepsis by pulmonologist/intensivist substantiated with CBC analysis, elevated temperature, pulmonary infiltrates, documented pathogen on culture.

1=Yes 2=No

2. Pre-existing documented pulmonary disease requiring treatment with medications including asthma, chronic obstructive pulmonary disease, or restrictive disease.

1=Yes 2=No

3. Diagnosis of unrepaired or previous palliative repair of a congenital cardiac anomaly.

1=Yes 2=No

4. Written diagnosis of respiratory failure/ARDS by pulmonologist/intensivist substantiated by refractory hypoxemia $PaO_2 < 70$ mm Hg despite $FiO_2 \geq .5$/PEEP > 5 cm H_2O; PaO_2:FiO_2 ratio < 200

1=Yes 2=No

TISSUE OXYGENATION RESEARCH STUDY SUBJECT#____
ELIGIBILITY CRITERIA TOOL

Part C. Study Enrollment.

1. Patient meets 100% of inclusion criteria and 0% of exclusion criteria and is therefore eligible to participate in the study.

1=Yes 2=No

2. Patient or family has given oral consent to participate in the study.

1=Yes 2=No

Part D. Conditions: All of the following conditions must exist prior to the start of data collection.

1. At least 1 hour has elapsed since the subject has received intermittent administration of an analgesic, anxiolytic, blood transfusion, autotransfusion, diuretic, or fluid resuscitation.

1=Yes 2=No

2. At least 6 hours have elapsed since the subject has received a paralytic agent (i.e., neuromuscular blockade).

1=Yes 2=No

3. At least 30 minutes have elapsed since titration or adjustment of vasoactive/inotropic infusion or propofol infusion.

1=Yes 2=No

4. At least 30 minutes have elapsed since suctioning, positioning or ventilator changes have occurred.

1=Yes 2=No

Appendix B

Demographic Profile Tool

OXYGEN CONSUMPTIN MODULATION:
EFFECTS OF AN OPIOID AGONIST ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY

DEMOGRAPHIC PROFILE

Subject # _____

Instructions: Circle the correct response and/or fill in the blank.

1. Date of surgery: ___/____/____(mm/dd/yy)

2. Date of admission into CVICU: ___/____/____(mm/dd/yy)

3. Time of admission into CVICU: _____ (military time)

4. Type of CV surgical procedure

   1 = CABG
   2 = Valve procedure
   3 = CABG +valve procedure
   4 = Aneurysm Repair
   5 = Other

5. CV surgical procedure: sequence classification

   1 = Primary
   2 = Re-operation

6. CV surgical procedure: priority status

   1 = Emergent
   2 = Urgent
   3 = Elective

7. Gender

   1 = Male
   2 = Female

8. Date of Birth: ___/___/___(mm/dd/yy)

TISSUE OXYGENATION RESEARCH STUDY
DEMOGRAPHIC PROFILE

SUBJECT#_____

9. Ethnic group

1 = White
2 = Black
3 = Hispanic
4 = Asian
5 = Filipino
6 = Other

10. Preoperative Weight _____ (kgs)

11. Height _____ cm

12. BSA _____ m^2

13. Tobacco history

1 = Current Specify: Packs/day/year _____
2 = Previous Specify: Packs/day/year _____
Stop date: ____/____ (mm/yy)
3 = Never

Preoperative morbidity: Documented in Admitting History and Physical Report.

14. Coronary artery disease

1 = Yes 2 = No 3 = Unknown

15. Hypertension

1 = Yes 2 = No 3 = Unknown

16. Myocardial infarction: Date: _____

1 = Yes 2 = No 3 = Unknown

17. If history of MI, document location:

1 = Anterior
2 = Lateral
3 = Inferior
4 = Septal
5 = Posterior
6 = Unknown
7 = If question #16 is No or Unknown

18. Diabetes mellitus

1 = Yes 2 = No 3 = Unknown

19. If history of diabetes mellitus, document type:

1 = Type I (IDDM) 2 = Type II

20. Cerebrovascular disease

1 = Yes 2 = No 3 = Unknown

21. Renal insufficiency

1 = Yes 2 = No 3 = Unknown

22. Heart failure/ventricular dysfunction

1 = Yes 2 = No 3 = Unknown

23. Peripheral vascular disease

1 = Yes 2 = No 3 = Unknown

24. Left Ventricular Ejection Fraction (%) _____% Unknown

Method_____ Date: ___/____/____

25. Present Diagnoses: (focus on cardiovascular and pulmonary diseases, illnesses)

_____
_____
_____

26. Past Medical Diagnoses: (focus on cardiovascular and pulmonary diseases, illnesses)

_____
_____
_____
_____

27. Surgical History: (focus on cardiovascular and pulmonary)

Procedure	Date
_____	_____
_____	_____
_____	_____

Perioperative Events: Document from Cardiovascular Anesthesia Record.

28. Duration of cardiopulmonary bypass time: _____ minutes

29. Duration of cross-clamp period: _____ minutes

30. Duration of anesthesia: _____ minutes
    Start time _____
    End time _____

31. Return to OR for mediastinal re-exploration.

    1 = Yes Re-admission time _____ date: __/__/__ (mm/dd/yy)
    2 = No

32. Cardiopulmonary resuscitation in the perioperative period (0-24 hours of surgery)

1 = Yes
2 = No

33. IABP/Ventricular assist device inserted in the perioperative period:

1 = Yes Type _____ Date inserted ___/___/___ (mm/dd/yy)
2 = No

34. Received intraoperative or postoperative blood transfusion(s):

1 = Yes Quantity: PRBC_____ FFP ____ Plt ____ Cryoprecipitate _____
2 = No

Appendix C

Cardiorespiratory Parameters

OXYGEN CONSUMPTION MODULATION:
EFFECTS OF AN OPIOID AGONIST ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY

CARDIORESPIRATORY PARAMETERS

Subject #_____

Part I: Instructions: Circle the correct response or fill in the blank.

1. Randomized lateral position:

1 = Left
2 = Right

2. Date ____/____/____ (mm/dd/yy)

3. Blood temperature displayed on Q-Vue CCO Computer System™ ____. ____ C

4. Level of Sedation:

1 = Awake and responding
2 = Sleeping, but responds to normal voice
3 = Sleeping but responds to loud voice or movement
4 = Sedated, unable to respond

5. Work of breathing (subjective assessment):

1 = Nonlabored
2 = Minimal labored
3 = Moderately labored
4 = Very labored

Pharmacologic Interventions

6. List cardiac medications and dosages received within the past 6 hours:

Drug	Dose	Time
_____	_____	_____
_____	_____	_____
_____	_____	_____

7. List sedative medications (i.e. analgesics, anxiolytic) and dosages received within past 2 hours:

Drug	Dose	Time
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

8. List current vasoactive infusions:

Drug: _____ dosage: _____ ug/kg/min or ug/min
Drug: _____ dosage: _____ ug/kg/min or ug/min
Drug: _____ dosage: _____ ug/kg/min or ug/min
Drug: _____ dosage: _____ ug/kg/min or ug/min

8.1 Specify total # of vasoactive infusions _____

9. Ventilator settings:

9.1 FiO_2 _____
9.2 TV _____ cc
9.2 Rate _____ /minute
9.3 PEEP _____ cm H_2O
9.4 PS _____ cm H_2O
9.5 Mode: 1 = SIMV 2 = AC 3 = PC

10. Baseline ABG: Collection time _____ (military hours)

10.1 pH _____
10.2 $PaCO_2$ _____
10.3 PaO_2 _____
10.4 HCO_3 _____
10.5 SaO_2 _____%

11. Dynacare Laboratory IL 482 Co-oximeter: SO_2% _____

12. Dynacare Laboratory IL 482 Co-oximeter: Total Hb _____ g-/dl

13. Calculated VO_2 ____mL/minute (Hewlett Packard Oxygen Calc Procedures)

14. Measured VO_2 _____mL/minute (Puritan-Bennett Metabolic Monitor ™ 7250)

TISSUE OXYGENATION RESEARCH STUDY
CARDIORESPIRATORY PARAMETERS
SUBJECT# ____

Part II

A: Baseline Measurements Without Morphine Sulfate

1. Measurement start time: _____ (military time)

2. Baseline ECG rhythm _____

3. Baseline Hemodynamics

3.1 HR _____ bpm
3.2 CI _____ $L/m/m^2$
3.3 SI _____ mL/beat
3.4 LVSWI _____ gm m/m^2
3.5 SVRI _____ dyne/sec/cm^{-5}/m^2
3.6 RAP _____ mm Hg
3.7 PAS _____ mm Hg
3.8 PAD _____ mm Hg
3.9 PAOP _____ mm Hg

4. Baseline SvO_2 and VO_2: Record every 15 seconds x 4

4.1 SvO_2_____ VO_2 _____
4.2 SvO_2_____ VO_2 _____
4.3 SvO_2_____ VO_2 _____
4.4 SvO_2_____ VO_2 _____

5. VO_2_____ ÷ BSA_____ = VO_2I _____

6. CCI_____ x Hb____ 1.34 x SpO_2 _____ x 10 = DO_2I _____

7. O_2ER_____ = VO_2I_____ ÷ DO_2I_____

TISSUE OXYGENATION RESEARCH STUDY SUBJECT# ____
CARDIORESPIRATORY PARAMETERS

B: Measurements Following Lateral Positioning Without Morphine Sulfate

8. Minute (1): SvO_2_____% Events _____

9. Minute (1): VO_2_____ ÷ BSA_____= VO_2I _____

10. Minute (2): SvO_2_____% Events _____

11. Minute (2): VO_2_____ ÷ BSA_____= VO_2I_____

12. Minute (3): SvO_2_____% Events _____

13. Minute (3): VO_2_____ ÷ BSA_____= VO_2I_____

14. Minute (3): Hemodynamics

14.1 HR _____ bpm
14.2 CI _____ $L/m/m^2$
14.3 SI _____ mL/beat
14.4 LVSWI _____ gm m/m^2
14.5 SVRI _____ $dyne/sec/cm^{-5}/m^2$
14.6 RAP _____ mm Hg
14.7 PAS _____ mm Hg
14.8 PAD _____ mm Hg
14.9 PAOP _____ mm Hg

15. Minute (3): CCI_____ x HB_____ x 1.34 x SpO_2 _____ x 10 = DO_2I _____

16. Minute (3): O_2ER_____= VO_2I_____ ÷ DO_2I_____

17. Minute (4): SvO_2 _____% Events _____

18. Minute (4): VO_2_____ ÷ BSA_____= VO_2I_____

19. Minute (5): SvO_2 _____% Events _____

20. Minute (5): VO_2_____ ÷ BSA_____= VO_2I_____

TISSUE OXYGENATION RESEARCH STUDY
CARDIORESPIRATORY PARAMETERS

SUBJECT# ____

21. Minute (5): Hemodynamics

21.1 HR _____ bpm
21.2 CI _____ $L/m/m^2$
21.3 SI _____ mL/beat
21.4 LVSWI _____ gm m/m^2
21.5 SVRI _____ dyne/sec/cm^{-5}/m^2
21.6 RAP _____ mm Hg
21.7 PAS _____ mm Hg
21.8 PAD _____ mm Hg
21.9 PAOP _____ mm Hg

22. Minute (5): CCI_____ x HB_____ x 1.34 x SpO_2 _____ x 10 = DO_2I _____

23. Minute (5): O_2ER_____ = VO_2I_____ ÷ DO_2I_____

24. Minute (6): SvO_2_____% Events _____

25. Minute (6): VO_2_____ ÷ BSA_____ = VO_2I_____

26. Minute (7): SvO_2_____% Events _____

27. Minute (7): VO_2_____ ÷ BSA_____ = VO_2I_____

28. Minute (8): SvO_2 _____% Events _____

29. Minute (8): VO_2_____ ÷ BSA_____ = VO_2I_____

30. Minute (9): SvO_2 _____% Events _____

31. Minute (9): VO_2_____ ÷ BSA_____ = VO_2I_____

32. Minute (10): SvO_2 _____% Events _____

33. Minute (10): VO_2_____ ÷ BSA_____ = VO_2I_____

34. Minute (10): Hemodynamics

34.1 HR _____ bpm
34.2 CI _____ $L/m/m^2$
34.3 SI _____ mL/beat
34.4 LVSWI _____ gm m/m^2
34.5 SVRI _____ dyne/sec/cm^{-5}/m^2
34.6 RAP _____ mm Hg
34.7 PAS _____ mm Hg
34.8 PAD _____ mm Hg
34.9 PAOP _____ mm Hg

35. Minute (10): CCI_____ x HB_____ x 1.34 x SpO_2 _____ x 10 = DO_2I _____

36. Minute (10): O_2ER_____ = VO_2I_____ ÷ DO_2I_____

37. Calculate Ideal Body Weight (IBW) _____ kg

38. Calculate MSO_4 dosage based on IBW (0.10 mg/kg) = _____ mg

39. MSO_4 administration time _____ (military time)

Part III

A: Baseline Measurements With Morphine Sulfate

1. Measurement start time: _____ (military time)

2. Baseline ECG rhythm _____

3. Baseline Hemodynamics

3.1 HR _____ bpm
3.2 CI _____ $L/m/m^2$
3.3 SI _____ mL/beat
3.4 LVSWI _____ gm m/m^2
3.5 SVRI _____ dyne/sec/cm^{-5}/m^2
3.6 RAP _____ mm Hg
3.7 PAS _____ mm Hg
3.8 PAD _____ mm Hg
3.9 PAOP _____ mm Hg

4. Baseline SvO_2 and VO_2: Record every 15 seconds x 4

4.1 SvO_2_____ VO_2_____
4.2 SvO_2_____ VO_2_____
4.3 SvO_2_____ VO_2_____
4.4 SvO_2_____ VO_2_____

5. VO_2_____ ÷ BSA_____ = VO_2I _____

6. CCI_____ x Hb_____ x 1.34 x SpO_2 _____ x 10 = DO_2I _____

7. O_2ER_____ = VO_2I_____ ÷ DO_2I_____

B: Measurements Following Lateral Positioning With Morphine Sulfate

8. Minute (1): SvO_2_____% Events _____

9. Minute (1): VO_2_____ ÷ BSA_____ = VO_2I _____

10. Minute (2): SvO_2_____% Events _____

11. Minute (2): VO_2_____ ÷ BSA_____ = VO_2I_____

12. Minute (3): SvO_2_____% Events _____

13. Minute (3): VO_2_____ ÷ BSA_____ = VO_2I_____

14. Minute (3): Hemodynamics

14.1 HR _____ bpm
14.2 CI _____ $L/m/m^2$
14.3 SI _____ mL/beat
14.4 LVSWI _____ $gm\ m/m^2$
14.5 SVRI _____ $dyne/sec/cm^{-5}/m^2$
14.6 RAP _____ mm Hg
14.7 PAS _____ mm Hg
14.8 PAD _____ mm Hg
14.9 PAOP _____ mm Hg

15. Minute (3): CCI_____ x HB_____ x 1.34 x SpO_2 _____ x 10 = DO_2I _____

16. Minute (3): O_2ER_____ = VO_2I_____ ÷ DO_2I_____

17. Minute (4): SvO_2 _____% Events _____

18. Minute (4): VO_2_____ ÷ BSA_____ = VO_2I_____

19. Minute (5): SvO_2 _____% Events _____

20. Minute (5): VO_2_____ ÷ BSA_____ = VO_2I_____

21. Minute (5): Hemodynamics

21.1 HR _____ bpm
21.2 CI _____ $L/m/m^2$
21.3 SI _____ mL/beat
21.4 LVSWI _____ $gm\ m/m^2$
21.5 SVRI _____ $dyne/sec/cm^{-5}/m^2$
21.6 RAP _____ mm Hg
21.7 PAS _____ mm Hg
21.8 PAD _____ mm Hg
21.9 PAOP _____ mm Hg

22. Minute (5): CCI_____ x HB_____ x 1.34 x SpO_2 _____ x 10 = DO_2I _____

23. Minute (5): O_2ER_____ = VO_2I_____ ÷ DO_2I_____

24. Minute (6): SvO_2_____% Events _____

25. Minute (6): VO_2_____ ÷ BSA_____ = VO_2I_____

26. Minute (7): SvO_2_____% Events _____

27. Minute (7): VO_2_____ ÷ BSA_____ = VO_2I_____

28. Minute (8): SvO_2 _____% Events _____

29. Minute (8): VO_2_____ ÷ BSA_____= VO_2I_____

30. Minute (9): SvO_2 _____% Events _____

31. Minute (9): VO_2_____ ÷ BSA_____= VO_2I_____

32. Minute (10): SvO_2 _____% Events _____

33. Minute (10): VO_2_____ ÷ BSA_____= VO_2I_____

34. Minute (10): Hemodynamics

34.1 HR _____ bpm
34.2 CI _____ $L/m/m^2$
34.3 SI _____ mL/beat
34.4 LVSWI _____ gm m/m^2
34.5 SVRI _____ dyne/sec/cm^{-5}/m^2
34.6 RAP _____ mm Hg
34.7 PAS _____ mm Hg
34.8 PAD _____ mm Hg
34.9 PAOP _____ mm Hg

35. Minute (10): CCI____ x HB_____ x 1.34 x SpO_2 _____ x 10 = DO_2I _____

36. Minute (10): O_2ER_____= VO_2I_____ ÷ DO_2I_____

37. Measurement stop time _____ (military time)

38. Total study time_____ (minutes)

39. Disqualifying Criteria: There was a disqualifying event(s) that occurred during study procedures.

1=Yes 2= No

1. If yes, document one of the following disqualifying criteria:

TISSUE OXYGENATION RESEARCH STUDY SUBJECT# ____
CARDIORESPIRATORY PARAMETERS

1. Cardiopulmonary instability defined as:

A. New development of serious cardiac rhythm abnormality, such as bradycardia, third degree atrioventricular block, rapid supraventricular rhythm, ventricular tachycardia or fibrillation.

B. SBP < 90mmHg for > 1 minute.

2. A change in dosage of vasoactive or inotrope drug infusion.

3. Initiation of a blood transfusion.

4. Initiation of fluid resuscitation defined as $\geq$ 200cc to be delivered in $\leq$ 30 minutes.

5. Administration of a diuretic.

6. Adjustment of the ventilator setting (i.e. FiO_2, rate, TV, PS or PEEP)

7. Procedure or treatment that requires subject movement or acknowledgement other than study procedures (i.e. ETT suctioning).

8. Disruption of study protocol by patient care activities/procedures.

9. Administration of an analgesic, anxiolytic, or paralytic.

10. Shivering as evidenced by repetitive involuntary muscular movement.

11. Bleeding as evidenced by chest drainage > 100 ml/hr.

12. Subject requests to withdraw from the study.

13. Other: _____

Codes for events occurring during data collection:

(1)=Coughing
(2)=Agitation
(3)=Obvious discomfort
(4)=Premature atrial contraction
(5)=Premature ventricular contraction

Appendix D

Interrater Reliability Tool

OXYGEN CONSUMPTION MODULATION: EFFECTS OF AN OPIOID AGONIST ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY

INTERRATER RELIABILITY TOOL

Subject # _____

Date __/__/__ (mm/dd/yy)

1. Specify Data Recorder:

1 = Principal Investigator

2 = Research Assistant

Part A. Verification of location of pulmonary artery catheter

Instructions: Obtain a strip recording of the pulmonary artery waveform as the balloon of the catheter is inflated with ≤ 1.5 cc of air. The Principal Investigator and Research Assistant will independently evaluate the same waveform. Evaluate the waveform and respond to the following questions to determine if the catheter is located in the pulmonary artery. Circle yes, no, or unknown for your response.

1. The SvO_2 light intensity indicator displayed in the Hewlett Packard Monitor SvO_2 calibration task window is positioned inside the middle and upper sections of the bars and covers at least two small divisions between dots in the bar.

   1 = Yes 2 = No

2. Four or five bars are displayed in the "Quality Signal Indicator" of the Q-Vue CCO Monitoring System™.

   1 = Yes 2 = No

3. Right ventricular (RV) waveform is observed when the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter RV/Distal Thermal Positioning Port (DTPP™) is connected to the RAP transducer.

   1 = Yes 2 = No

4. The characteristic change in waveform from the pulsatile pulmonary artery (PA) shape to the pulmonary artery occlusive (PAO) atrial shape is observed following the inflation of the balloon.

   1 = Yes 2 = No 3 = Unknown

5. The loss of the dicrotic notch on the PA tracing is observed following the inflation of the balloon.

   1 = Yes 2 = No 3 = Unknown

6. The mean PA pressure is > the mean PAO pressure.

   1 = Yes 2 = No 3 = Unknown

7. After the balloon is deflated, there is a return of the characteristic waveform from PAO to PA with return of a systolic-diastolic pattern with a dicrotic notch and higher mean pressure.

   1 = Yes 2 = No 3 = Unknown

TISSUE OXYGENATION RESEARCH STUDY SUBJECT#____
INTERRATER RELIABILITY TOOL

Part B. Transcription of Data

Instructions: Record the SvO_2 two-digit numerical percentage as displayed on the Hewlett Packard Monitor every 10 seconds as determined by the second hand of the wall clock beginning at the predetermined start time as indicated by the Principal Investigator.

1.T (1) _____%SvO_2

2.T (2) _____%SvO_2

3.T (3) _____%SvO_2

4.T (4) _____%SvO_2

5.T (5) _____%SvO_2

6.T (6) _____%SvO_2

Appendix E

Criterion Validation Tool

OXYGEN CONSUMPTION MODULATION:
EFFECTS OF AN OPIOID AGONIST ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY

CRITERION VALIDATION TOOL

Subject # _____

Instructions: Fill in the blank and circle the correct response.

PART A: ARTERIAL OXYGEN SATURATION

1. Hewlett Packard SpO_2% at time of ABG collection _____%
2. Cooximeter Model IL 482 SaO_2% _____%
3. Calculate [absolute] difference SpO_2 - SaO_2 = _____
4. Absolute difference between SpO_2 and SaO_2 is greater than ± 3

1 = Yes If "Yes," abort the study

2 = No If "No," proceed with the study

PART B: OXYGEN CONSUMPTION (record simultaneous measurements)

1. Hewlett Packard Oxygen Calc® VO_2 value _____ mL/minute
2. Puritan-Bennett Metabolic Monitor ™ 7250 VO_2 _____ mL/minute

Appendix F

Swedish Medical Center

Institutional Review Board Approval Notice

SWEDISH MEDICAL CENTER
747 Broadway Seattle, WA 98122-4307
(206) 386-6000

Institutional Review Office (IRO)
Clinical Research Center
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November 8, 2001

Jill Jesurum, PhD(C)
Sweidsh Heart Institute
801 Broadway, Suite 300
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IR File 3600
IRB Committee 01

RE: **REVIEW OF EXPEDITED APPLICATION FOR PROTOCOL/ACTIVITY ENTITLED: THE EFFECTS OF AN OPIOID ANALGESIC ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY**

Dear Jill Jesurum, PhD(C):

Thank you for submitting the above-referenced activity for review by the Swedish Medical Center Institutional Review Board (SMC IRB). Review was carried out in light of Federal regulations on human subjects and of SMC requirements. The IRB Chair has determined that your study qualifies for expedited review.

I am pleased to inform you that approval has been granted, effective 11/7/01 through 10/31/02, and approval documents are enclosed for your records. Additionally, alteration of the required elements of consent pursuant to 45 CFR 46.116(d) was approved as requested.

In accordance with institutional procedures, a progress report is required within 11 months, and a reminder notice will be sent to you prior to expiration of approval. Additionally, the SMC IRB must be notified if there are any protocol changes, including protocol termination, and if there are any untoward effects as a result of this activity. Be sure to include the Institutional Review (IR) File Number on all correspondence submitted to this office. If you have any questions, please contact Ariana Valentine, IRB 01 Committee Coordinator, at the phone number above.

Dissertation/Theses signature page is here.

To protect individuals we have covered their signatures.

Appendix G

Written Information for Verbal Consent

WRITTEN INFORMATION FOR VERBAL CONSENT

TITLE OF STUDY

Oxygen Consumption Modulation: Effects of an Opioid Agonist on Tissue Oxygenation Following Lateral Positioning in Cardiovascular Surgical Patients with Low Oxygen Delivery

INVESTIGATOR: Jill Jesurum, ARNP, PhDc, MN, CCRN, ACNP, FNP
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206-215-2800

24-HOUR PHONE: 206 - 933-7490
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RESEARCH ASSISTANT: Susan Reed, RN, BSN, CCRN
ICU Staff Nurse
Department of Critical Care Nursing
Swedish Medical Center
Seattle, WA
206-215-3408

This is a type of research study. Research studies include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. You are being asked to take part in this study because you have been scheduled to have open-heart surgery. Investigators at the Swedish Medical Center are researching methods to prevent low levels of oxygen in the body after open-heart surgery. Jill Jesurum, ARNP, a doctoral student at Texas Woman's University and a Cardiac Surgery Nurse Practitioner at Swedish Medical

Center, is the researcher who designed this particular research in humans. Susan Reed, RN, a master's student at The University of Washington and a Staff Nurse in the Cardiovascular Intensive Care Unit at Swedish Medical Center, is the Research Assistant.

The following is a summary of the information you were given when this study was discussed with you. Please read it and ask any questions you may have.

PURPOSE, POTENTIAL FOR BENEFIT

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to see if morphine, the medicine routinely given after open-heart surgery to decrease pain, improves patient tolerance to turning. It is standard nursing care in the Cardiovascular Intensive Care Unit to turn patients in bed at least every two hours or more frequently to prevent complications such as pneumonia and skin breakdown. However, certain routine care procedures like turning or repositioning patients require the body to have extra oxygen. Sometimes, turning patients causes the level of oxygen in the body to become low. This research is being done because currently, there is no effective way to prevent changes in oxygen levels that may occur while performing necessary nursing procedures like turning or repositioning. Giving pain medicine like morphine before turning may prevent the oxygen levels from dropping too low.

All procedures used in this study are standard nursing care following open-heart surgery. All patients having open-heart surgery routinely receive pain medicine through an intravenous catheter (IV) and are turned on a regular basis while in bed. However, it is not standard nursing practice to give pain medicine before turning to prevent changes in oxygen levels. The "investigational" part of this study is: (a) giving you pain medicine 20 minutes before turning you in bed and (b) measuring the effects of turning, with and without pain medicine, on blood pressure, heart rate, and oxygen levels. "Investigational" means that the medical benefits of this intervention to prevent oxygen changes in the body have not been firmly established. However, the knowledge gained from the study may help in developing future medical treatment.

TISSUE OXYGENATION RESEARCH STUDY
VERBAL CONSENT FORM

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About forty adult patients having open-heart surgery at Swedish Medical Center will take part in this study between November 2001 and April 2002.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, it is unknown if there will be a direct benefit to you. We hope the information learned from this study will benefit other people having open-heart surgery in the future.

TREATMENT / PROCEDURES

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, the following procedures will occur:

If at least 6 hours but not more than 24 hours have passed since your surgery, you are eligible to participate in this study and you have agreed to participate, you will first be turned from your back to your right or left side without receiving pain medicine (morphine). You will stay on your side supported by a pillow for 10 minutes while measurements of your blood pressure, heart rate, and oxygen levels are made. After 10 minutes has passed, you will be turned on your back and will receive the standard dose of morphine given to decrease pain after surgery. The morphine will be administered through the IV that was inserted during your surgery. Twenty minutes after the pain medicine has been given, you will again be turned to the same side position for an additional 10 minutes and the same vital sign measurements will be made again. After this, the study will be over and you will be repositioned for comfort, as you like. The total time for the study will be less than 50 minutes. The measurements of your blood pressure, heart rate, and oxygen levels will be made using monitoring equipment that is routinely used during and after your surgery to monitor your vital signs. No additional monitoring equipment, blood samples, or lab specimens are required for this research study.

➡ **Procedures That are Part of Regular Care and May be Done Even if You Do Not Join the Study:**

- Regular repositioning and turning while in bed
- Giving you pain medications such as morphine but not necessarily before turning
- Frequent measurements of vital signs including blood pressure, heart rate, and oxygen levels

➡ **Standard Procedures Being Done Because You Are in the Study:**

- Giving you pain medicine (morphine) 20 minutes before turning you in bed
- Measuring the effects of turning, with and without pain medicine, on blood pressure, heart rate, and oxygen levels

➡ **Procedures That are Being Tested in the Study:**

- The effects of turning, with and without pain medicine, on blood pressure, heart rate, and oxygen levels

Information from your medical records, bedside charts and bedside monitoring equipment will be recorded for this study. This information includes age, height and weight, diagnoses, operation and other medical history, medications received after surgery, respirator settings and vital sign measurements from the bedside monitors.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for about 50 minutes.

The researcher may decide to take you off the study if any significant changes in your vital signs (heart rate or blood pressure) or clinical stability occur and the study will be stopped. For example, a change in respirator settings or medicines will disqualify you from continuing the study. Once the study is stopped, you will continue to receive standard medical care.

You can stop participating in the study at any time. However, if you decide to stop participating, you need to talk to the researcher, your doctor, or your nurse and inform him/her of your decision. Prior to beginning the study procedures, the researcher will ask you if you want to participate in the research study. At that time, you will be unable to verbally communicate due to the breathing tube. Therefore, you may use written communication or non-verbal gestures (i.e., head nod, hand squeeze, eye blink) to signal that you want to withdraw from the study.

Your decision to participate in this study is voluntary and you may withdraw your consent at any time, for any reason, without notice. You will continue to receive medical care even if you decide to discontinue participation in this study. If you choose not to take part or to stop at any time, your decision will not affect your future relations with Swedish Medical Center or your physicians. It is possible that the study may be stopped at any time without your consent. If you want to stop taking part in this study, all you need to do is tell or signal to your physician or nurse.

If significant new findings develop during the course of your participation in this study, the investigator will provide this information to you.

RISKS

WHAT ARE THE RISKS OF THE STUDY?

The risks for participating in this research study are minimal and represent no more risk than normally encountered after open-heart surgery. The research study procedures represent standard nursing care procedures. If you experience complications during the study procedures, the study will be stopped and you will receive standard medical care.

However, since all procedures performed in this study are standard nursing care, the only additional risk to you by participating in the study is the potential loss of confidentiality. To decrease this risk to you, your name or other identifying information is not recorded on the study forms. Only a study number is recorded on the data collection forms. All information from the study will be presented as grouped results for presentations or publications.

The researcher will answer any questions about the study, its risks and side effects, and other options available to you now or at any time in the future. You will be instructed on how to contact the researcher in the event you should have any questions or problems.

ALTERNATIVES

WHAT OTHER OPTIONS ARE THERE?

You may choose not to participate in this study. Not participating in this study will not affect your medical care.

OTHER INFORMATION

WHAT ABOUT CONFIDENTIALITY?

All efforts will be made to keep your personal information confidential, however, we cannot guarantee absolute confidentiality. No name or other identification that can be associated with you is recorded on the study forms. Only a study number is recorded on the data collection forms. However, your personal information may be disclosed if required by law. The staff of the Swedish Medical Center Institutional Review Office may inspect and/or copy your research records for quality assurance and data analysis. Your research records will be kept until the data has been analyzed and the findings published. Your personal identity will not be revealed in any publication of study results.

WHAT ARE THE COSTS?

Taking part in this study is not expected to lead to added costs to you or your insurance company. There are no additional costs for participating in this study. No payment will be made directly to you for taking part in this study.

In the unlikely event that you become sick while participating in the study, you will receive medical care. The charges for such care will be billed to you and/or your insurance company. You should be aware that your insurance company may or may not pay for such charges. No payment will be made to you or your family for loss of income, pain and suffering or other consequences of any such injury. However, you do not give up your rights, if any, which otherwise may be available to you by law.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary and you may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about study procedures, risks/side effects, and/or study costs, contact Jill Jesurum, ARNP at 206-215-2800 or 206-933-7490.

To report a study-related injury, contact Jill Jesurum, ARNP at 206-215 - 2800 or 206-933-7490.

For questions about financial responsibility for study-related injury, contact the SMC Swedish Research Center Director at (206) 215-3100.

For questions about your rights as a research participant, contact the SMC Institutional Review Office (IRO) Manager. The IRO Manager administers the Institutional Review Board (a group of people who review this research to protect your rights and welfare) and may be contacted at (206) 215-2403.

WHERE CAN I GET MORE INFORMATION?

For additional information, you may contact the researcher, Jill Jesurum, ARNP

Office: 206-215-2800
Home: 206-933-7490
Pager: 206-405-7673
E-mail: jesurum@mindspring.com

You will get a copy of this form.

TISSUE OXYGENATION RESEARCH STUDY
VERBAL CONSENT FORM

PATIENT'S VERBAL AUTHORIZATION

I have read and understand this consent form and verbally agree to take part in this study. By verbally agreeing to participate in this research study, I do not give up my rights, if any, which may be available to me by law.

CERTIFICATE OF PERSON OBTAINING VERBAL CONSENT:

I have provided an explanation of the above research study and have encouraged the patient to ask questions and request additional information regarding the study and possible alternatives. A copy of this consent form has been given to the patient.

_____
NAME OF PERSON OBTAINING CONSENT (print)

_____ _____
SIGNATURE OF PERSON OBTAINING CONSENT DATE

_____ _____
SIGNATURE OF INVESTIGATOR DATE
(If different from person obtaining consent)

206-933-7490
EMERGENCY PHONE NUMBER

Swedish Medical Center
RESEARCH SITE

cc: Participant and Investigator's File

Appendix H

Research Protocol

OXYGEN CONSUMPTION MODULATION: THE EFFECTS OF AN OPIOID AGONIST ON TISSUE OXYGENATION FOLLOWING LATERAL POSITIONING IN CARDIOVASCULAR SURGICAL PATIENTS WITH LOW OXYGEN DELIVERY

STUDY PROTOCOL

1. Consent and Enrollment

A. Pre-Surgical Patient - evaluate for study participation *prior* to surgery

B. During the presurgical evaluation at the Cardiac Surgery Office or hospital, the Cardiac Surgeon, Principal Investigator, Research Assistant, Physician Assistant or designee will determine patient's interest in participating in the study.

i. The Principal Investigator or Research Assistant will meet with patient and family, explain the purpose of the study, describe the study and the study procedures and provide a copy of the written study description and verbal consent form to the patient and family.

ii. If the patient agrees to participate in the study, write the patient's hospital ID # and tentative day of surgery on the "Preoperative Consent List" and check the box marked "Yes" in the column labeled "Consent,"

iii. Each day at approximately1600 hours (hereafter all references to military time), the Principal Investigator or Research Assistant will identify patients in the Cardiovascular Intensive Care Unit who are status post cardiac surgery within the last 12 hours and who are listed on the Preoperative Consent List as having consented to participating in the study.

iv. To determine if the consented patient is eligible to be enrolled into the study, the Principal Investigator or the Research Assistant will complete an Eligibility Criteria Tool for each cardiac surgical patient who is listed on the Preoperative Consent List as having consented to participate in the study.

v. If the patient meets 100% of the inclusion criteria and 0% of the exclusion criteria as listed on the Eligibility Criteria Tool, *enroll* the patient into the study. Transcribe the patient's initials on the Master Research Subject Roster in the sequential order of enrollment.

vi. Inform the subject that he/she has been enrolled into the study and verify continued interest/willingness to participate in the study.

vii. Identify the 3 digit "Subject Number" located to the left of the patient's hospital ID # on the Master Research Subject Roster and write the "Subject Number" on to each page of the Eligibility Criteria Tool.

viii. Proceed to the protocol section titled "Equipment Assembly."

ix. If the patient does **not** meet 100% of the inclusion criteria and 0% of the exclusion criteria as listed on the Eligibility Criteria Tool, do **not** enroll the patient into the study.

x. Inform the patient that he/she is not eligible to participate in the study.

C. Post-Surgical Patient - evaluate for study participation *after* surgery

i. Each day at approximately1600 hours, the Principal Investigator and/or Research Assistant will identify patients in the Cardiovascular Intensive Care Unit (CVICU) who are status post cardiac surgery within the last 6-24 hours and who are **not** listed on the Master Research Subject Roster.

D. Non-consented surgical patients (who have not been approached prior to surgery regarding the study) will be screened for eligibility to participate in the study. The Principal Investigator or the Research Assistant will complete the Eligibility Criteria Tool to determine if the patient meets criteria for participating in the study.

i. If the patient meets 100% of the inclusion criteria and 0% of the exclusion criteria as listed on the Eligibility Criteria Tool, the Principal Investigator or the Research Assistant will approach the patient's family member or legal representative in the Cardiovascular Intensive Care Unit to discuss the purpose of the study and the study procedures.

ii. Give a copy of the written study description and verbal consent form to the patient's family member or legal representative.

iii. Explain the study to the patient's family member or legal representative. The Principal Investigator or the Research Assistant will request verbal consent to enroll the patient into the study.

E. If the family member or legal representative agrees to the patient's participation in the study, enroll the patient into the study. Transcribe the patient's initial's, patient's hospital ID # and date of surgery on the Master Research Subject Roster in the sequential order of enrollment.

F. Identify the 3 digit "Subject Number" located to the left of the patient's hospital ID # on the Master Research Subject Roster and write the "Subject Number" on to each page of the Eligibility Criteria Tool.

i. Proceed to the protocol section titled "Equipment Assembly"

2. Equipment Assembly

A. Obtain the study cart with the following supplies located inside the Principal Investigator's office and bring to subject's bedside:

i. Protractor
ii. Stopwatch with alarm
iii. Wall clock with second hand and hanging device
iv. Foam body wedge
v. Carpenter's Level
vi. Black felt-tip marker
vii. Puritan Bennett Metabolic Monitor Model 7250™ and equipment:

1. Connector cable with plugs to link monitor to the ventilator
2. Naflon tubings (2)
3. Clear tubing
4. Clear plastic elbow inspiratory line adapter
5. Expiratory sample line
6. Expiratory sample reservoir
7. Clear plastic adapter
8. Silicone reservoir
9. Inspiratory Line Filter
10. Expiratory Line Filter

viii. Packet of blank data collection tools containing the following:

1. Criterion Validation Tool (1)
2. Interrater Reliability Tools (2)
3. Cardiorespiratory Parameters Data Collection Tool (1)
4. Demographic Profile Tool (1)

ix. Envelope for completed data collection tools
x. Envelope with "Lateral Position Random Assignments"
xi. Study In Progress" Sign
xii. 10cc syringes (1)
xiii. 3cc pre-heparinized blood gas syringes (2)
xiv. Connector device (2)
xv. Alcohol pads (3)
xvi. 2x2 sterile gauze sponges (2)
xvii. Pillowcase (1)
xviii. 12 cc syringe (1)
xix. 250cc normal saline bag with attached "Clave On a Stick" (1)
xx. Carpuject (1)

B. Obtain one (1) 10mg vial of morphine sulfate from Pyxis.

C. Obtain a cup of ice chips from the CVICU kitchen.

D. Attach (clip) the completed Eligibility Criteria Tool to one packet of blank data collection records containing the Criterion Validation Tool, Interrater Reliability Tools, Cardiorespiratory Parameters Data Collection Tool, and Demographic Profile.

E. Identify the 3 digit "Subject Number" located to the left of the patient's hospital ID # on the Master Research Subject Roster and write the "Subject Number" on to each page of the Criterion Validation Tool, Interrater Reliability Tools, Cardiorespiratory Parameters Data Collection Tool, and Demographic Profile in the space to the right of "Subject #."

3. Subject Preparation

A. Briefly review study procedures with subject's Registered Nurse and arrange a time for data collection.

B. Place sign "Study in Progress" outside subject's room. Remind staff that verbal communications and interruptions must be kept to a minimum during data collection. Limit unnecessary traffic inside patient room. Dim lights in patient room. Close glass doors. Set thermostat in patient room to 65°F to maintain constant/consistent ambient temperature.

C. Review study procedures with the subject.

D. Position subject for study.

i. Instruct subject to **not** assist with turning procedures.

ii. Place subject in a supine position with head of bed flat (0-degree) and place 1 standard foam pillow behind subject's head.

iii. Place a protractor at the bed frame and adjust backrest elevation until the angle between the horizontal stationary frame and the mobile vertical frame is exactly 20-degrees according to the protractor.

iv. With the subject in a supine position and the head of the bed elevated to 20-degrees, identify the subject's phlebostatic axis (4^{th} intercostal space, midanteriorposterior chest) and mark reference location with an "X" using a black felt-tip marker. All cardiorespiratory measurements will be obtained using the supine, phlebostatic axis as the reference point for the air-fluid interface of the monitoring system.

v. Before obtaining blood samples, wait 30 minutes after the subject has been repositioned or suctioned or after ventilator changes have been made.

4. Equipment Preparation and Calibration

A. Verify bedside monitoring equipment is properly assembled and functioning.

i. Verify that the subject is assigned to the Hewlett Packard Central Monitor®.

ii. Verify that the Hewlett Packard VueLink Module® is located in the satellite rack of the Hewlett Packard Monitor® and that the VueLink cable is connected to the Q-Vue Computer System™.

iii. Verify that the SvO_2 module is located in the satellite rack of the Hewlett Packard Monitor® and that the SvO_2 parameter is numerically displayed on the monitor.

iv. Verify that the Hewlett Packard® bedside recorder is located in the satellite rack of the Hewlett Packard Monitor®. Check the paper supply for the Hewlett Packard® bedside recorder and the central printer. Replace paper supply for printing purposes as necessary. Obtain a test print from the bedside recorder and the central printer.

v. Verify the subject's correct height and weight (recorded on the Cardiovascular Anesthesia Record) are entered in the Q-Vue Computer System™ and Hewlett Packard Monitor® to compute BSA.

vi. Verify that the Q-Vue Computer System™ Continuous Cardiac Output Monitor's "Quality Signal Indicator" displays 4 or 5 bars indicating there is an acceptable signal to noise ratio.

vii. Verify that the Q-Vue Computer System™ Continuous Cardiac Output Averaging Mode is set to "Fast Mode".

viii. Using the supine, phlebostatic reference point, level and zero the hemodynamic transducers (arterial, distal PA and proximal PA air-fluid interface) to atmospheric pressure according to hospital protocol.

ix. Perform square wave test on arterial pressure, PAP, and RAP to check frequency response of monitoring system.

x. Verify pulmonary artery catheter position on the most recent radiographic film.

xi. Verify pulmonary artery catheter position with waveform analysis and reposition if necessary. Obtain a graphic recording of the PAP and PAOP.

B. Set-up and calibrate the Puritan Bennett Metabolic Monitor Model 7250™

i. Connect cable, sample lines, and filters of the Puritan Bennett Metabolic Monitor Model 7250™ to the Puritan Bennett Mechanical Ventilator Model 7200ae™ per Swedish Medical Center Procedure "Metabolic Cart Measurement Through the 7250". The Puritan Bennett Mechanical Ventilators (Model 7200ae™) that are capable of accommodating the Puritan Bennett Metabolic Monitor Model 7250™ will be designated with a label. See policy titled "Metabolic Cart Measurement Through the 7250."

ii. Clear previous subject's stored data from the Puritan Bennett Metabolic Monitor Model 7250™.

iii. For monitoring function #1, select Metabolic Monitor Mode to display subject's oxygen consumption (VO_2).

iv. Skip monitoring functions #2 and #3.

v. For monitoring function #4, perform O_2 sensor calibration procedures.

vi. For monitoring function #5, perform line calibration procedures.

vii. For monitoring function #6, select "1 minute" for the averaging interval to calculate subject information.

C. Calibrate the OPTI-Q™/Q-Vue Computer System and Hewlett Packard SvO_2 Module®.

i. Before obtaining blood samples, wait 30 minutes after the subject has been repositioned or suctioned or after ventilator changes have been made.

ii. Obtain laboratory requisition for "O_2 sat and content, venous" and bring to the bedside.

D. Obtain subject identification label for laboratory specimen located inside the subject's room.

i. Perform an in vivo calibration of the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter (Model 52510) with the results obtained from the Dynacare Laboratory Cooximeter (Model IL 482, Instrumentation Laboratory, Lexington, MA). Refer to Swedish Medical Center Critical Care Department Policy and Procedure Manual. Physiological Monitoring Section on In-Vivo Calibration of OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter (Model 52510).

ii. Collect mixed venous blood specimen in pre-heparinized blood gas syringe according to the hospital standard procedure as follows:

1. From the distal port of the pulmonary artery catheter, *slowly* withdraw 5cc of blood over a 2.5-minute period and discard.

2. *Slowly* withdraw 1cc of blood for clinical analysis over a period of 60 seconds as timed by a stopwatch. Label the specimen and place on ice. Deliver the specimen to the Dynacare Laboratory to obtain SO_2 measurement.

iii. Compare the criterion SO_2 value obtained from the Dynacare Laboratory Co-oximeter Model IL 482 to the stored SvO_2 value on the Hewlett Packard Monitor®.

iv. If a difference exists between the two values, use the arrow function keys on the Hewlett Packard Monitor® to change the stored SvO_2 value to the SO_2 value obtained on the Dynacare Laboratory Co-oximeter Model IL 482.

v. Press the "Confirm" function key when the desired SvO_2 value is displayed on the monitor of the Hewlett Packard Monitor®.

5. Criterion Validation

A. Wait 30 minutes before obtaining blood samples if the subject has been repositioned, suctioned or if ventilator changes have been made.

B. All data collection discussed in this section will be recorded on the Criterion Validation Tool.

C. Obtain laboratory requisition for "Arterial Blood Gas" and bring to the bedside.

D. Obtain subject identification label for laboratory specimen located inside the subject's room.

E. Question #1: Record the corresponding SpO_2 as displayed on the Hewlett Packard Monitor® at the time of arterial blood collection.

F. Collect arterial blood specimen in pre-heparinized blood gas syringe according to hospital standard procedure.

G. Label the specimen and place on ice. Deliver the specimen to the Dynacare Laboratory to obtain arterial blood gas and criterion SaO_2 measurement on laboratory co-oximeter.

H. Question #2: Record the SaO_2 measurement obtained from Dynacare Laboratory.

I. Questions #3 - #4: Calculate the absolute difference between the measured SpO_2 and SaO_2 and record the results. If the difference is >3% points, abort the study.

6. Interrater Reliability

A. All data collection discussed in this section will be recorded on the Interrater Reliability Tools.

B. The Principal Investigator and the Research Assistant will each have a separate Interrater Reliability Tool.

C. Verify the "Subject Number" on each page of both Interrater Reliability Tools.

D. Enter today's date by month/day/year using 2 digits.

E. Question #1: Specify Data Collector as Principal Investigator or Research Assistant.

F. Verify the location of the OPTI-Q™ Catheter in the pulmonary artery.

i. Connect OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter RV/Distal Thermal Positioning Port (DTPP™) to RAP transducer via stopcock connection and verify right ventricular (RV) waveform. After RV waveform verified, turn stopcock off to RV and reestablish RAP continuous waveform tracing on monitor.

ii. Press the "Real-time Record" button on Hewlett Packard Monitor®. Select "PA" and then press, "start recording" to initiate a recording of the pulmonary artery waveform.

iii. After observing waveform variations across 2-3 respiratory cycles, slowly insert $\leq$ 1.5cc of air into the balloon port of the pulmonary artery catheter until a characteristic change in waveform from the pulsatile pulmonary artery (PA) shape to the pulmonary artery occlusive (PAO) atrial shape is observed with loss of the dicrotic notch on the pulmonary artery tracing and a reduction in mean pressure. If the waveform does not change after inserting 1.5cc of air, consult with the Cardiac Surgery Nurse Practitioner.

iv. After observing waveform variations across 2-3 respiratory cycles, disconnect the syringe from the balloon port to allow the balloon to deflate passively.

v. Observe the characteristic change in waveform from PAO to PA with return of a systolic-diastolic pattern with a dicrotic notch and a higher mean pressure.

vi. After observing waveform variations across 2-3 respiratory cycles, press, "stop recording" and remove the graphic strip from the bedside recorder.

vii. Provide the Research Assistant with the graphic strip recording.

viii. Instruct the Research Assistant to evaluate the graphic strip recording for the following criteria: (1) change from characteristic pulsatile waveform to atrial waveform after inflating the balloon with $\leq$ 1.5 cc of air; (2) loss of the dicrotic notch on the pulmonary artery waveform after inflating balloon; (3) mean pulmonary artery pressure > mean PAO pressure; and (4) return of characteristic pulmonary artery waveform with systolic-diastolic pattern with dicrotic notch and higher mean pressure after balloon is deflated.

ix. Part A, Question #1: Instruct the Research Assistant to observe the SvO_2 light intensity bar on the Hewlett Packard Monitor® and determine if it is within an acceptable range. The SvO_2 light intensity indicator displayed in the Hewlett Packard® SvO_2 calibration task window is positioned inside the middle and upper sections of the bars and covers at least two small divisions between dots in the bar.

x. Part A, Question #2: Instruct the Research Assistant to observe the Quality Signal Indicator of the Q-Vue CCO Monitoring System™ to determine if 4 or 5 bars are displayed indicating an acceptable signal to noise ratio.

xi. Part A, Question #3: Instruct the Research Assistant to verify RV waveform tracing on HP monitor after connecting the OPTI-Q™ SvO_2/CCO Flow-Directed Thermodilution Fiberoptic Continuous Cardiac Output Pulmonary Artery Catheter RV/Distal Thermal Positioning Port (DTPP™) to RAP transducer.

xii. Part A, Questions #4 - #7: After the Research Assistant has evaluated the strip recording, instruct him/her to independently answer the questions on the Interrater Reliability Tool.

xiii. The Principal Investigator will repeat steps outlined above on the separate Interrater Reliability Tool using the same strip recording.

G. Data Transcription

i. Verify that a wall clock with a second hand is within close view (< 10 feet) of the Hewlett Packard Monitor®.

ii. Part B, Questions #1 - #6: Both the Principal Investigator and Research Assistant will independently and simultaneously record the two digit numerical SvO_2 displayed on the Hewlett Packard Monitor® every 10 seconds for 6 consecutive measurements. The Principal Investigator will announce the start time of data transcription when the second hand of the wall clock strikes the number twelve (12).

iii. When data transcription has been completed, staple the Interrater Reliability Tools together and attach the strip recording to the front of the page.

7. Procedures for Data Collection

A. All data collection discussed in this section will be recorded on the Cardiorespiratory Parameters Data Collection Tool.

B. Verify that "Subject Number" written on the Cardiorespiratory Parameters Data Collection Tool is the same as that recorded on the Eligibility Criteria Tool, Criterion Validation Tool, and Demographic Profile.

C. Reconfirm that all eligibility criteria and conditions have been met as described on the Eligibility Criteria Tool.

D. Review Disqualifying Criteria listed on page 9 of the Cardiorespiratory Parameters Data Collection Tool. Abort the study if any of these events occur during the data collection period.

E. Verify that atmospheric ports of the pressure transducers are level to subject's phlebostatic axis and have been zeroed to atmospheric pressure.

F. Blindly select a paper from the envelope marked "Lateral Position Random Assignments" which is located in the study cart.

G. Part I: Question #1: Record the randomized lateral position on the Cardiorespiratory Parameters Data Collection Tool. Indicate the lateral position assignment by marking the appropriate box with an "X" as determined by the lateral position random assignment paper.

H. Part I: Question #2: Enter today's date by month/day/year using two digits.

I. Part I: Question #3: Record the blood temperature displayed in centigrade on the Q-Vue Computer™ Screen.

J. Part I: Question #4: Record the subject's current behavior or level of sedation. Check appropriate category that best describes level of sedation.

K. Part I: Question #5: Record subject's work of breathing using a subjective scale: 1 = Non-labored; 2 = Minimally labored; 3 = Moderately labored; 4 = Very labored.

L. Part I: Questions #6 - #8: Refer to the Emtek Computer Charting System to review the subject's flowsheet (medication section) and MAR (medication administration record) for information regarding pharmacological support/interventions. Verify with the subject's Registered Nurse that the information recorded on the medication section of the flowsheet and MAR is correct.

M. Part I: Question #9: Record current ventilator settings including FiO_2, TV, rate, PEEP, PS, and mode (AC/SIMV/PC).

N. Part I: Question #10: Record the pH, $PaCO_2$, PaO_2, HCO_3, and SaO_2 from the latest ABG obtained for Criterion Validity.

O. Part I: Question #11: Record the SO_2 value obtained from Dynacare Laboratory Model IL 482 Co-oximeter.

P. Part I: Question #12: Record the total hemoglobin g-/dl (THB %) obtained from the Dynacare Laboratory Model IL 482 Co-oximeter.

Q. Part I: Question #13: Perform Oxygen Calculations on Hewlett Packard® computer and record calculated VO_2 mL/minute.

R. Part I: Question #14. Simultaneously, as performing calculated VO_2, record measured VO_2 mL/minute as displayed on Puritan-Bennett Metabolic Monitor Model 7250™.

S. Baseline Measurements without Morphine

i. Prior to data collection at least 6 hours must have elapsed since the subject received a paralytic agent.

ii. Prior to data collection at least 1 hour must have elapsed since the subject received an intermittent dose of an anxiolytic or analgesic medication, a blood transfusion, or fluid resuscitation.

iii. Prior to data collection, 30 minutes must have elapsed since titration of vasoactive infusions and propofol infusion; suctioning; positioning; or, ventilator changes have occurred.

iv. Part II: Question #1: Enter current military time as start time.

v. Obtain a 6 second ECG strip from the Hewlett Packard Monitor® and identify the cardiac rhythm.

vi. Part II: Question #2: Record the baseline cardiac rhythm.

vii. Part II: Question #3: Perform a "wedge procedure" to obtain PAOP using waveform analysis and identify end-expiration measurement. Press "enter" to confirm PAOP. Perform a hemodynamic profile that includes HR, CI, SI, LVSWI, SVRI, RAP, and PAS/PAD. Print the record from the Hewlett Packard Monitor®.

viii. Part II: Question #4: Observe the SvO_2 value displayed on the Hewlett Packard Monitor® and VO_2 value displayed on the Puritan-Bennett Metabolic Monitor Model 7250™ and record every 15 seconds for 4 measurements for the purpose of establishing a stable baseline.

ix. Part II: Question #5: Observe and record the VO_2I from the Puritan-Bennett Metabolic Monitor Model 7250™.

x. Part II: Questions #6 - #7: Calculate DO_2I and O_2ER and record.

T. Measurements Following Lateral Positioning Without Morphine

i. Clear stored subject data from Q-Vue Computer System™ by pressing the Abbott Logo button.

ii. Re-enter subject height and weight on the Q-Vue Computer System™

iii. Position subject.

1. Instruct the subject that you are going to turn him or her to the side. Instruct subject **not** to assist with turning. The Principal Investigator and Research Assistant will perform the turning procedure.

2. Place the subject in a 45-degree lateral position as determined by randomization methods and documented in Question #1 on page 1 of the Cardiorespiratory Parameters Data Collection Tool.

3. Verify the 45-degree lateral position by measuring the vertical distance from the nondependent shoulder to the bed and the horizontal distance between the acromial processes of the shoulders.

4. Place the foam wedge body aligner behind the subject's back. The side of the aligner marked with "this side to bed mattress" should be in contact with the bed mattress. The side of the aligner marked "this side to subject's back" should be in contact with the subject's back. Position the side of the aligner marked with "this side towards bedrail" towards the bedrail.

5. Place a protractor at the bed frame and adjust head elevation until the angle between the horizontal stationary frame and the mobile vertical frame is exactly 20-degrees according to the protractor.

iv. Start stopwatch.

v. During data collection, monitor the subject's subjective and objective reaction to repositioning. Visually monitor the cardiac rhythm, heart rate, and arterial blood pressure. Evaluate the subject's level of comfort. Record events occurring during data collection including coughing, agitation, discomfort, and dysrhythmias.

vi. If there is a clinically significant change in the physiological parameters as defined in the "Disqualifying Criteria" section on page 9 of the Cardiorespiratory Parameters Data Collection Tool, document the changes in the physiological parameters and abort the study.

vii. If the subject expresses discomfort and signals a desire to return to the previous position, abort the study and reposition the subject. Document subject complaint and that the study was aborted on the Cardiorespiratory Parameters Data Collection Tool.

viii. Part II: Question #8: Exactly 1 minute following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

ix. Part II: Question #9: Simultaneously, at 1 minute following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

x. Part II: Question #10: Exactly 2 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xi. Part II: Question #11: Simultaneously, at 2 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xii. Part II: Question #12: Exactly 3 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xiii. Part II: Question #13: Simultaneously, at 3 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xiv. Part II: Question #14: During minute 3 post-turn, perform a hemodynamic profile that includes HR, CI, SI, LVSWI, SVRI, RAP, PAS/PAD, and PAOP from the Hewlett Packard Monitor®. Print the record.

xv. Part II: Question #15 - #16: During minute 3 post-turn, calculate DO_2I and O_2ER and record.

xvi. Part II: Question #17: Exactly 4 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xvii. Part II: Question #18: simultaneously, at 4 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xviii. Part II: Question #19: Exactly 5 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xix. Part II: Question # 20: Simultaneously, at 5 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xx. Part II: Question #21: During minute 5 post-turn, perform a hemodynamic profile that includes HR, CI, SI, LVSWI, SVRI, RAP, PAS/PAD, and PAOP from the Hewlett Packard Monitor®. Print the record.

xxi. Part II: Question #22 - #23: During minute 5 post-turn, calculate DO_2I and O_2ER and record.

xxii. Part II: Question #24: Exactly 6 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xxiii. Part II: Question #25: Simultaneously, at 6 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxiv. Part II: Question #26: Exactly 7 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xxv. Part II: Question #27: Simultaneously, at 7 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxvi. Part II: Question #28: Exactly 8 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xxvii. Part II: Question #29: Simultaneously, at 8 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxviii. Part II: Question #30: Exactly 9 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xxix. Part II: Question #31: Simultaneously, at 9 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxx. Part II: Question #32: Exactly 10 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor® and record.

xxxi. Part II: Question # 33: Simultaneously, at 10 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxxii. Part II: Question #34: During minute 10 post-turn, perform a hemodynamic profile that includes HR, CI, SI, LVSWI, SVRI, RAP, PAS/PAD, and PAOP from the Hewlett Packard Monitor®. Print the record.

xxxiii. Part II: Question #35 - #36: During minute 10 post-turn, calculate DO_2I and O_2ER and record.

U. Inform the subject that you are going to turn him/her on their back. Instruct the subject not to assist with the turn.

V. Remove body aligner and place subject in a supine position with head of bed elevated 20-degrees and one standard foam pillow behind head.

W. Obtain subject's preoperative weight in kilograms from the Cardiovascular Anesthesia Record. Round weight to the nearest whole number in kilograms (kg).

X. Part II: Question #37: Calculate ideal body weight and record.

Y.

Z. Part II: Question #38: Calculate morphine dosage (0.10 mg/kg) based on ideal body weight and record dosage.

AA. Part II: Question #39: Draw morphine into a 10 cc syringe and dilute with 10 cc of normal saline. Administer morphine into the central introducer catheter via syringe infusion device over a 5-minute period. Following completion of infusion flush catheter line with 10 cc of normal saline. Start stopwatch. Record administration time. Allow 20 minutes to elapse between start of morphine infusion and beginning of data collection period.

BB. Starting from the time that the morphine infusion was completed, wait 20 minutes according to the stopwatch, before beginning to collect physiological measurements.

CC. Demographic Profile

i. During the 20-minute wait period, complete the Demographic Profile. All data collection discussed in this section will be recorded on the Demographic Profile.

ii. Refer to the Cardiovascular Anesthesia Record, preoperative history and physical report, cardiac catheterization report, and medical progress notes to collect the following information.

iii. Verify that the "Subject Number" located in the top left corner of the Demographic Profile is the same as that on the Eligibility Criteria Tool, Criterion Validation Tool, and the Cardiorespiratory Parameters Data Collection Tool.

iv. Question #1: Refer to the Cardiovascular Anesthesia record to obtain the date of surgery (month/day/year).

v. Questions #2 - #3: Obtain the admission time and date into the Cardiovascular Intensive Care Unit from the first entry of vital signs on the flowsheet section of the Emtek Computer Charting System.

vi. Questions #4 - #6: Refer to the operative note to determine type of cardiovascular surgical procedure; primary or re-operation procedure; emergent, urgent or elective procedure.

vii. Question #7: Refer to the addressograph to obtain gender.

viii. Question #8: Refer to the addressograph to obtain the date of birth (month/day/year).

ix. Question #9: Refer to the admission sheet to obtain the ethnic group.

x. Questions #10 - #11: Refer to the Cardiovascular Anesthesia Record to obtain the weight in kilograms (rounded to the nearest whole number) and height in centimeters (rounded to the nearest whole number).

xi. Question #12: Record the calculated BSA in meters^2 as calculated by the Hewlett Packard Monitor® after entering subject's weight and height.

xii. Question #13: Refer to the admission history and physical report and nursing admission database to obtain tobacco history. Record if subject is currently smoking, has previously smoked, or has never smoked. Record pack/day/year and stop date if available.

xiii. Questions #14 - #23: If preoperative morbidity conditions are documented in the history and physical report, circle "Yes" below each disease/illness. If the history and physical report denies a preoperative morbidity, circle "No." If the history and physical report does not confirm or deny existence of preoperative morbidity, circle "Unknown."

xiv. Questions #24: Refer to the cardiac catheterization report to determine the left ventricular ejection fraction. Record EF method and study date.

xv. Questions #25 - #27: Obtain the admitting medical diagnoses (e.g., CAD, valvular insufficiency), past medical diagnoses (e.g., HTN, diabetes mellitus, myocardial infarction), and surgical history from the history and physical report. Focus on cardiovascular and pulmonary diseases or procedures.

xvi. Questions #28 - #30: Refer to the Cardiovascular Anesthesia Record and record the time in minutes of cross-clamp duration, cardiopulmonary bypass duration, and anesthesia duration.

xvii. Questions #31 - #33: Refer to the operative note to determine if the subject returned to the OR for re-exploration, had a cardiorespiratory arrest, and/or placement of an IABP or VAD, circle "Yes" under the corresponding event.

DD. Baseline Measurements With Morphine

i. All data collection discussed in this section will be recorded on the Cardiorespiratory Parameters Data Collection Tool.

ii. Part III: Question #1: Enter current military time.

iii. Obtain a 6 second ECG strip from the Hewlett Packard Monitor® and identify cardiac rhythm.

iv. Part III: Question #2: Record a baseline cardiac rhythm.

v. Part III: Question #3: Perform a "wedge procedure" to obtain PAOP using waveform analysis and identify end-expiration measurement. Press "enter" to confirm PAOP. Perform a hemodynamic profile that includes HR, CI, SI, LVSWI, SVRI, RAP, and PAS/PAD. Print the record from the Hewlett Packard Monitor®.

vi. Verify that the SvO_2 light intensity bar is within an acceptable range. The SvO_2 light intensity indicator displayed in the Hewlett Packard® SvO_2 calibration task window is positioned inside the middle and upper sections of the bars and covers at least two small divisions between dots in the bar.

vii. Part III: Question #4: Exactly 20 minutes following the completion of the morphine infusion, as determined by the stopwatch, observe the SvO_2 value displayed on the Hewlett Packard Monitor® and the VO_2 value displayed on the Puritan-Bennett Metabolic Monitor ™ 7250 and record every 15 seconds for 4 measurements for the purpose of establishing a stable baseline.

viii. Part III: Question #5: Observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

ix. Part III: Questions #6 - #7: Calculate DO_2I and O_2ER and record.

EE. Measurements Following Lateral Rotation With Morphine

i. Clear stored subject data from Q-Vue Computer System™ by pressing the Abbott Logo button.

ii. Re-enter subject height and weight on the Q-Vue Computer System™.

iii. Position subject.

1. Instruct the subject that you are going to turn him or her to the side. Instruct subject **not** to assist with turning. The Principal Investigator and Research Assistant will perform the turning procedure.

2. Place the subject in a 45-degree lateral position as determined by randomization methods and documented in Question #1 on page 1 of the Cardiorespiratory Parameters Data Collection Tool.

3. Verify the 45-degree lateral position by measuring the vertical distance from the nondependent shoulder to the bed and the horizontal distance between the acromial processes of the shoulders.

4. Place the foam wedge body aligner behind the subject's back. The side of the aligner marked with "this side to bed mattress" should be in contact with the bed mattress. The side of the aligner marked "this side to subject's back" should be in contact with the subject's back. Position the side of the aligner marked with "this side towards bedrail" towards the bedrail.

5. Place a protractor at the bed frame and adjust head elevation until the angle between the horizontal stationary frame and the mobile vertical frame is exactly 20-degrees according to the protractor.

iv. Start stopwatch.

v. During data collection, monitor the subject's subjective and objective reaction to the position. Visually monitor the cardiac rhythm, heart rate, and arterial blood pressure. Evaluate the subject's level of comfort. Record events occurring during data collection including coughing, agitation, discomfort, and dysrhythmias.

vi. If there is a clinically significant change in the physiological parameters as defined in the "Disqualifying Criteria" section on page 9 of the Cardiorespiratory Parameters Data Collection Tool, document the changes in the physiological parameters and abort the study.

vii. If the subject expresses discomfort and signals a desire to return to the previous position, abort the study and reposition the subject. Document subject complaint and that the study was aborted on the Cardiorespiratory Parameters Data Collection Tool.

viii. Part III: Question #8: Exactly 1 minute following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

ix. Part III: Question #9: Simultaneously, at 1 minute following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

x. Part III: Question #10: Exactly 2 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xi. Part III: Question #11: Simultaneously, at 2 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xii. Part III: Question #12: Exactly 3 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor® and record.

xiii. Part III: Question #13: Simultaneously, at 3 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xiv. Part III: Question #14: During minute 3 post-turn, perform a hemodynamic profile that includes HR, CI, SI, LVSWI, SVRI, RAP, PAS/PAD, and PAOP from the Hewlett Packard Monitor®. Print the record.

xv. Part III: Question #15 - #16: During minute 3 post-turn, calculate DO_2I and O_2ER and record.

xvi. Part III: Question #17: Exactly 4 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xvii. Part III: Question #18: Simultaneously, at 4 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xviii. Part III: Question #19: Exactly 5 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xix. Part III: Question #20: Simultaneously, at 5 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xx. Part III: Question #21: During minute 5 post-turn, perform a hemodynamic profile that includes HR, CI, SI, LVSWI, SVRI, RAP, PAS/PAD, and PAOP from the Hewlett Packard Monitor®. Print the record.

xxi. Part III: Question #22-#23: During minute 5 post-turn, calculate DO_2I and O_2ER and record.

xxii. Part III: Question #24: Exactly 6 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xxiii. Part III: Question #25: Simultaneously, at 6 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxiv. Part III: Question #26: Exactly 7 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xxv. Part III: Question #27: Simultaneously, at 7 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxvi. Part III: Question #28: Exactly 8 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xxvii. Part III: Question #29: Simultaneously, at 8 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxviii. Part III: Question #30: Exactly 9 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor®.

xxix. Part III: Question #31: Simultaneously, at 9 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxx. Part III: Question #32: Exactly 10 minutes following the turn as determined by the stopwatch, observe and record the SvO_2 value displayed on the Hewlett Packard Monitor® and record.

xxxi. Part III: Question #33: Simultaneously, at 10 minutes following the turn as determined by the stopwatch, observe and record the VO_2I from the Puritan Bennett Metabolic Monitor Model 7250™.

xxxii. Part III: Question #34: During minute 10 post-turn, perform a hemodynamic profile that includes HR, CI, SI, LVSWI, SVRI, RAP, PAS/PAD, and PAOP from the Hewlett Packard Monitor®. Print the record.

xxxiii. Part III: Question #35 - #36: During minute 10 post-turn, calculate DO_2I and O_2ER and record.

FF. Part III: Question #37: Enter current military time as stop time.

GG. Part III: Question #38: Calculate and record duration of study procedures in minutes for questions in Part II and III.

HH. Part III: Question #39: Circle "Yes" if subject disqualified during study procedures. Circle "No" if subject completed study procedures.

II. Part III: Question #39: If "Yes" circled, specify reason that subject was disqualified from study, by circling #1-#10 items, if applicable.

JJ. Instruct the subject that you are going to turn him/her on their back. Instruct the subject <u>not</u> to assist with turning.

KK. Remove body aligner and position subject for comfort or as desired.

LL. Thank subject for participating in study.

MM. Staple the following forms together and place in the envelope marked "Data Collection Records - Completed".

1. PAP and POAP graphic recordings
2. Baseline ECG dual channel recording
3. Hemodynamic profile recordings (6)
4. Eligibility Criteria Tool (1)
5. Criterion Validation Tool (1)
6. Demographic Profile (1)
7. Cardiorespiratory Parameters Data Collection Tool (1)
8. Interrater Reliability Tool (2)

NN. Return study cart and completed data collection records to Principal Investigator's office.

OO. This concludes the study protocol.

Appendix I

Empirical Findings:
VO_2 Response Subgroups

EMPIRICAL FINDINGS

VO_2 RESPONSE SUBGROUPS

During the study procedures, distinct oxygen consumption (VO_2I ml/min/m^2 = indexed to body surface area) patterns emerged in response to lateral positioning that were not discoverable or explained by the analyses of the original hypotheses. These clinical observations were not anticipated and the original research hypotheses were not designed to test particular physiological response patterns among groups. Consequently, important individual or subgroup differences may have been masked by group means. As detailed in the original study protocol (Appendix H), additional measurements of VO_2I were obtained every minute from baseline through minute 10 following lateral positioning, with and without the effects of morphine. Additional post hoc analyses were performed on VO_2I measurements to (a) explain the large variances in mean VO_2I as discussed in the analyses of Hypothesis 2, (b) describe differences in physiological adaptation patterns among subgroups of critically ill patients with low oxygen delivery (DO_2I ml/min/m^2), and (c) determine if the effects of morphine are different among subgroups based on mean VO_2I change scores following lateral positioning without morphine.

VO_2I Response Patterns

On examining individual responses to lateral positioning during the first phase of the study (without morphine), three distinctive VO_2I profile patterns were identified. Most subjects demonstrated VO_2I response patterns that began immediately (minute 1)

after positioning and were sustained until minute 4 following lateral positioning. Thus, minutes 1 through 4 following the turn were termed *VO_2 change phase*. VO_2I recovery typically began around minute 4 post-turn and was evidenced either by a plateau in VO_2I or by a return to baseline. Thus, the *VO_2 recovery phase* occurred between minutes 5 and 10 following the turn. These observations were similar to the mixed venous oxygen saturation (SvO_2) response patterns presented in the analysis of Hypothesis 5. VO_2I response patterns during the *change phase* were categorized by immediate and sustained response to lateral positioning through minute 4 post-turn and included: (a) greater than 10% increase from baseline (Group 1); (b) less than 10% increase from baseline (Group 2); and, (c) decrease from baseline (Group 3). Each subject was assigned to one of the three groups (i.e., VO_2I Response Group) based on their VO_2I response pattern. Group response patterns are graphically represented in Appendix I: Figure 1.

VO_2I Response Group Characteristics

To describe the groups, baseline clinical characteristics were analyzed using descriptive statistics. Means, standard deviations and ranges of baseline physiological measurements for each group are summarized in Appendix I: Table 1. One-way, between-subjects analyses of variance (ANOVA) tests (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983) were performed on baseline physiological measurements to identify group differences ($\alpha = .01$; two-tailed). Homogeneity of variance assumption was evaluated using the Levene Statistic ($\alpha = .05$; two-tailed). Cardiac index ($\rho = .007$) and stroke volume index ($\rho = .008$) demonstrated unequal variance among groups. Because of the

unequal sample size among groups and the small number of subjects per group, comparisons for these measures represent preliminary findings and trends.

Although no statistically significant differences were found between groups, clinically important differences were observed among groups on baseline measures of oxygen extraction ratio (O_2ER) ($F_{2,27} = 4.55$, $\rho = .02$), intrapulmonary shunt (Qs/Qt) ($F_{2,22} = 4.36$, $\rho = .03$), and VO_2I ($F_{2,27} = 3.04$, $\rho = .06$). On average, subjects who experienced a decrease in VO_2I following lateral positioning (Group 3) had higher VO_2I and O_2ER, and lower Qs/Qt at baseline. Additionally, subjects in Group 3 had a lower left ventricular ejection fraction (LVEF) ($n = 5$, M = .44, $SD = .18$) than subjects in Group 1 ($n = 7$, M = .50, $SD = .14$) or Group 2 ($n = 6$, M = .54, $SD = .16$). In comparison, subjects who had greater than a 10% increase in VO_2I following lateral positioning (Group 1) had higher DO_2I, cardiac index (CI), and hemoglobin. On average, all groups demonstrated normal SvO_2 values (> 62%) at rest.

Between group comparisons were performed to evaluate if there was equal distribution of (a) subjects turned to the left and right lateral positions, and (b) subjects who received propofol during the study procedures. Results of the Pearson Chi-square equality of proportions test revealed that there was equal distribution among groups in terms of left and right lateral positioning ($\chi^2 = 1.43$, dfs = 2, $\rho = .49$). Fisher's Exact Tests (SPSS, 1999) for small samples were used for pairwise comparisons between groups to determine if the proportion of subjects who received propofol varied between groups. Results suggested that the proportion of propofol infusion between groups was

not significantly different (Group 1 vs. 2, $\rho = .324$; Group 1 vs. 3, $\rho = .363$; Group 2 vs. 3, $\rho = .157$). For the subjects who received propofol during the study, average dosages were not significantly different between groups ($F_{2,14} = .183$, $\rho = .835$).

Findings

Effects of Group x Morphine x Time. Analyses were performed to determine if the effects of time and morphine worked differently when subjects were grouped according to VO_2I response pattern. To test the main effects and interactions of the time, morphine and group, a three-way (Group x Morphine x Time), repeated measures, split plot ANOVA was performed using the General Linear Model Repeated Measures procedure in the SPSS ™Advanced Models 9.0 statistical program (SPSS, 1999). A full factorial model was specified to test the main effects and interactions of the independent variables. The within-subjects, repeated factor time had 11 levels (baseline through minute 10 post-turn) and the within-subjects, repeated factor morphine had two levels (phase I = without morphine; phase II = with morphine). VO_2I Response Group, the between-subjects factor, had three levels that included Group 1 (>10% Increase, $n = 14$), Group 2 (0 – 10% Increase, $n = 7$), and Group 3 (Decrease, $n = 9$).

Because the risks of violating the assumption of multivariate normality were increased due to the small sample size, analyses of the main effects were performed using the univariate approach. Tests of the interactions involving VO_2I Response Group were analyzed using the Wilk's lambda exact statistic because there were three levels of the between-subjects factor (Maxwell & Delaney, 1990). Variance was calculated using the

Type III technique that adjusts for effects within a nonorthogonal design and provides an unweighted test of the marginal means (Maxwell & Delaney, 1990; SPSS, 1999). Normality was statistically evaluated using Shapiro-Wilk's test. Results indicated the normality assumption was satisfied. Homogeneity was assessed using the Levene's Statistic to test the equal variance assumption of the between-subjects factor, VO_2I Response Group. Only one of the 22 dependent measurements, VO_2I at minute 1 following lateral positioning, did not demonstrate equal variance ($\rho = .001$). To ensure the tests involving the time factor were robust to violations of homogeneity, the *df*s were adjusted with the Greenhouse-Geisser procedure to produce a more conservative *F* statistic (Maxwell & Delaney, 1990). Level of significance for the Omnibus *F* tests for the major effects was set at $\alpha = .05$ (two-tailed).

Omnibus F tests. Results of the analyses indicated that there were no significant differences in mean VO_2I during the study procedures that related to the two-way interaction between Morphine x Time ($F_{3.69, 277} = 0.97$, $\rho = .42$). However, the two-way interactions between VO_2I Response Group x Morphine ($F_{2, 27} = 3.97$, $\rho = .03$) and VO_2I Response Group x Time ($F_{20, 36} = 2.07$, $\rho = .03$) and the three-way interaction between VO_2I Response Group x Morphine x Time were significant ($F_{20, 36} = 2.15$, $\rho = .02$). Details of the statistical analyses for the main effects and interactions of VO_2I Response Group x Morphine x Time are presented in the ANOVA summary table in Appendix I: Table 2.

Rather than testing all possible post-hoc comparisons, specific post-hoc analyses were selected that addressed the fundamental aims of the study. The first aim of the study, to describe the physiological response patterns of tissue oxygenation variables in critically ill patients with low DO_2I following lateral positioning, was addressed by post-hoc comparisons that focused on the VO_2I Response Group x Time interaction without the effects of morphine. The second aim of the study, to test the effects of morphine on reducing oxygen consumption, was explored through post-hoc analyses on the Morphine x Time interaction at each level of VO_2I Response Group. Main effects of group, time, and morphine were not interpreted because the interactions were significant (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983).

Simple effects: VO_2I Response Group (C) within Time (B) without Morphine (A_1). Group mean VO_2I scores from baseline through minute 10 following lateral positioning, without the effects of morphine, are graphically represented in Appendix I: Figure 1. The graphical depiction indicated that the effect of time on VO_2I following lateral positioning depends on VO_2I Response Group. To test the magnitude of the group effect at different levels of time following positioning while controlling for morphine, simple effects comparisons were performed using separate error terms. To capture the maximal effects of lateral positioning on oxygen consumption and the VO_2I recovery time, two time intervals were selected for the analyses including (a) *change response*, the average of minutes 4 and 5 (B_1), and (b) *recovery response*, the average of minutes 9 and 10 (B_2). These time intervals were selected based on the findings presented in the analysis of

Hypothesis 2. To control for a Type I error rate by maintaining the α_{FW} at .05, the observed *F* statistic was compared to the Tukey's HSD adjusted critical value to determine the level of significance (Maxwell & Delaney, 1990). By controlling the family-wise Type I error rate, the Tukey method permits multiple *post hoc* comparisons of the Omnibus F (Glass & Hopkins, 1984). According to the Table of Critical Values (Maxwell & Delaney, 1990), the critical q was 4.34 for $\alpha = .05$, *df*s = 27, and six means.

VO_2 Peak-Change Phase. Results indicated that averaging over minutes 4 and 5 following lateral positioning, without morphine, there was a significant difference in mean VO_2I between groups ($F_{2,27} = 4.73$, $\rho = .02$). According to the eta-squared (η^2) statistic, 26% of the variability in mean VO_2I at minutes 4 through 5 following lateral positioning was related to VO_2I response pattern (Group). Observed power of the *F* statistic to detect a statistically significant difference in mean VO_2I between groups at minutes 4 through 5 following lateral positioning was .63 ($\alpha = .025$, two-tailed). Further analyses of the cell mean comparisons at minutes 4 through 5 were indicated.

VO_2 Recovery Phase. Averaging over minutes 9 and 10 following lateral positioning without morphine, the results inferred that there was not a statistically significant difference in mean VO_2I between groups ($F_{2,27} = 3.21$, $\rho = .05$). Observed power of the *F* statistic to detect a statistically significant difference in mean VO_2I between groups at minutes 9 through 10 following lateral positioning was .44 ($\alpha = .025$, two-tailed).

Power Analysis. To avoid a Type II error related to insufficient sample size, power analysis was calculated using methods described by Maxwell and Delaney (1990) for repeated measures designs. Using the pooled standard deviation ($SD = 23.76$) and observed correlation between groups with the highest and lowest mean scores ($r = .5$, Group 1, $M = 152.43$; Group 3, $M = 129.97$), results of the power analysis revealed a standardized mean difference (d) of 0.95, that according to Cohen (Cohen, 1983) is a large effect size. To test the null hypothesis that the three levels of population means are equal with a power of .80 ($\alpha = .05$, two-tailed), 13 subjects would be required per group (cell). Because the available sample size was insufficient, the test was underpowered for Groups 2 and 3 to detect a significant difference. Further analyses of the cell means comparisons at minutes 9 through 10 were not indicated.

Cell mean comparisons: VO_2I Response Group (C) within Time (B_1) without Morphine (A_1). To isolate group differences in mean VO_2I at minutes 4 through 5 following lateral positioning, cell mean comparisons were performed using a separate error term for each contrast. To control for a Type I error rate by maintaining the α_{FW} at .05, the observed F statistic was compared to the Tukey's HSD adjusted critical value to determine the level of significance. According to the Table of Critical Values (Maxwell & Delaney, 1990), the critical q was 4.34 for $\alpha = .05$, dfs = 27, and six means. For the analyses, mean VO_2I averaged over minutes 4 and 5 were compared between Groups 1 and 2, Groups 1 and 3, and Groups 2 and 3 (Group 1, $M = 157$, $SD = 15.64$; Group 2, $M = 138$, $SD = 18.72$; and, Group 3, $M = 135$, $SD = 22.1$).

Averaging over minutes 4 and 5 following lateral positioning, without morphine, there was a significant difference between mean VO_2I in Groups 1 and 3 ($F_{1,27} = 8.55$, $\rho = .007$). Without the effects of morphine, subjects categorized as having a > 10% increase VO_2I response pattern to positioning (Group 1) had significantly higher mean VO_2I averaged over minutes 4 through 5 following lateral positioning ($M_1 = 157$, $SD = 15.64$) than subjects who were categorized as having a decrease VO_2I response pattern (Group 3) ($M_1 = 135$, $SD = 22.1$). For the second contrast that averaged over minutes 4 and 5, without morphine, there was also a significant difference in mean VO_2I between Group 1 and subjects in Group 2 who were categorized as having a 0 to 10%moderate increase VO_2I response pattern ($F_{1,27} = 6.55$, $\rho = .016$). Without morphine, subjects in Group 1 had significantly higher VO_2I averaged over minutes 4 and 5 following lateral positioning than subjects in Group 2 ($M_1 = 138$, $SD = 18.72$). For the third and final contrast, there were no significant statistical or clinical differences in mean VO_2I averaged over minutes 4 and 5 between Groups 2 and 3 (F 1, 27 = 0.40, $\rho = .54$).

Post-hoc analyses using multiple stepwise regression to explain the changes in VO_2I and the relationships between VO_2I with other tissue oxygenation variables was not possible due to the small sample size of the three groups. Therefore, data was evaluated using the means, standard deviations, and 95% confidence intervals of the physiological measurements over time and correlations between the variables.

Conclusion. Preliminary findings suggest that mean VO_2I following lateral positioning is dependent on the initial VO_2I response pattern observed within minutes 1

through 4 following the turn. Subjects who had > 10% increase in VO_2I following lateral positioning had significantly higher mean VO_2I scores at minutes 4 through 5 post-turn than subjects who experienced < 10% change in VO_2I from baseline (Groups 2 and 3). Although sample size was insufficient to detect a statistical difference, it appeared that the differences in mean VO_2I between groups would also exist at minutes 9 through 10 following the turn. The analyses suggested (a) the ability to predict early and late VO_2I recovery following positioning based on three distinct VO_2I immediate response profiles and (b) subjects who have > 10% increase in VO_2I at minutes 1 through 4 following lateral positioning have significantly higher mean VO_2I during the recovery period than subjects who have < 10% increase in VO_2I at minutes 1 through 4 following lateral positioning. Further research is needed to substantiate these findings.

Simple effects: Morphine (A) within Time (B_1) at each level of VO_2I Response Group (C_{1-3}). Mean values of VO_2I from baseline through minute 10 following lateral positioning, during both phases of the study, are graphically represented for each group in Appendix I: Figures 2 - 4. The graphical depiction indicated that the effect of time on VO_2I following lateral positioning depends on VO_2I Response Group. To test the magnitude of the effect of the morphine intervention on VO_2I following lateral positioning at each level of group, simple effects comparisons were performed using separate error terms. The power of the treatment intervention (morphine) was tested on VO_2I averaged over minutes 4 and 5 (B_1) following lateral positioning. At this interval, oxygen consumption is expected to be highest following lateral positioning according to

the findings presented in the analysis of Hypothesis 2. To control for a Type I family-wise error rate, the observed *F* statistic was compared to the Tukey's HSD adjusted critical value to determine the level of significance. According to the Table of Critical Values (Maxwell & Delaney, 1990), the critical q was 4.69 for $\alpha = .05$, *df*s = 13, and six means.

Morphine (A) within Time (B_1) at Group 1. Averaging over minutes 4 and 5 following lateral positioning, mean VO_2I was significantly lower when subjects in Group 1 received morphine before the turn ($M_1 = 157$, $SD = 15.64$; $M_2 = 140$, $SD = 20.64$; $F_{1, 13} = 6.54$, $\rho = .02$). During the first phase of the study, subjects in Group 1 experienced an average increase of 21% in mean VO_2I from baseline to minutes 4 through 5 following lateral positioning (*CI 95%*, 11.3 – 30.0). However, when morphine was received before the turn, subjects experienced only a 9.6% increase in mean VO_2I during the same interval (*CI 95%*, 1.5 – 17.7). On average, the preprocedural morphine intervention accounted for a 54% relative reduction in the increase in mean VO_2I from baseline to minutes 4 through 5 following lateral positioning for subjects in Group 1. These results are clinically and statistically important. Using the pooled standard deviation (*SD* = 18.14) and observed correlation between the highest and lowest mean scores ($r = .13$, $M_1 = 157.12$, $M_2 = 140.45$), results of the power analysis revealed a standardized mean difference (*d*) of 0.94, that according to Cohen (1983) is a large effect size. Approximately 17 subjects would be required to test the null hypothesis that the population means are equal with a power of .80 ($\alpha = .05$, two-tailed).

Morphine (A) within Time (B_1) at Group 2. Although subjects in Group 2 had lower VO_2I over minutes 4 and 5 following lateral positioning when morphine was received before the turn, the results were not statistically or clinically impressive (M_1 = 138.42, SD = 18.72; M_2 = 132.06, SD = 14.81; $F_{1,6}$ = 0.34, ρ = .58). On average, the morphine effect accounted for a 4.6% relative reduction in the increase in mean VO_2I from baseline to minutes 4 through 5 following lateral positioning for Group 2. To avoid a Type II error related to the small number of subjects in Group 2, power analysis was calculated according the methods described by Maxwell and Delaney (1990) for repeated measures designs. Using the pooled standard deviation (SD = 16.76) and observed correlation between the highest and lowest mean scores (r = -.48, M_1 = 138.42, M_2 = 132.06), results of the power analysis revealed a standardized mean difference (d) of 0.38, that according to Cohen (1983) is between a small and moderate effect size. Approximately 100 subjects would be required to test the null hypothesis that the population means are equal with a power of .80 (α = .05, two-tailed). In comparison to Groups 1 and 3, subjects in Group 2 demonstrated the least amount of change in mean VO_2I following lateral positioning and they experienced earlier VO_2I recovery to baseline, with and without morphine. For these subjects, peak VO_2I following lateral positioning occurred between minutes 2 and 3 (M = 3.32%, SD = 4.51) rather than minutes 4 and 5 (M = 1.78, SD = 2.32). Therefore, for Group 2, the effect of preprocedural morphine on peak VO_2 response following lateral positioning was not evaluated.

Morphine (A) within Time (B_1) at Group3. For subjects in Group 3, mean VO_2I averaged over minutes 4 and 5 following lateral positioning was significantly higher when morphine was received before the turn ($M_1 = 135$, $SD = 22.11$; $M_2 = 148.8$, $SD = 24.25$; $F_{1,8} = 6.85$, $\rho = .03$). During the first phase of the study, subjects in Group 3 experienced a 12% (*CI 95%*, -6.4% to -16.5%) *decrease* in mean VO_2I from baseline to minutes 4 through 5 following lateral positioning. When morphine was received before the turn, subjects experienced a 6.7% *increase* in mean VO_2I (*CI 95%*, -2.8% – 16.2%) from baseline to minutes 4 through 5 following lateral positioning. According to the eta-squared (η^2) statistic, 46% of the variability in VO_2I between minutes 4 and 5 following lateral positioning was related to the morphine intervention. For Group 3, the observed power of the *F* statistic to detect a statistically significant difference in mean VO_2I averaged over minutes 4 and 5, with and without morphine was .63 ($\alpha = .05$, two-tailed). Although unexpected and difficult to explain, these results are clinically and statistically significant.

Conclusion. Preliminary results suggest that the effect of preprocedural morphine on VO_2I following lateral positioning is different for subgroups of critically ill patients. Patients who have > 10% increase in VO_2 within 5 minutes following turning may experience greater attenuation of the response with preprocedural morphine than patients who experience < 10% increase in VO_2 after turning. The empirical findings provided an explanation for the findings in Hypothesis 2 and the large variance observed in mean VO_2I at minutes 1 and 5 following lateral positioning. For subjects in Group 1 (> 10%

increase), mean VO_2I averaging over minutes 4 and 5 following lateral positioning was significantly lower when subjects received morphine before the turn. On average, morphine accounted for a 54% reduction in mean VO_2I following lateral positioning in this group of subjects. However, for subjects in Groups 2 and 3, VO_2I was not significantly lower following lateral positioning when morphine was received before the turn.

Discussion

According to the findings of Hypothesis 2, there were no significant differences in mean VO_2I following lateral positioning when morphine was received before the turn. However, the large variances observed in the mean VO_2I following lateral positioning suggested the need for further investigation. Three distinct VO_2I response patterns to positioning emerged within the sample during the first phase of the study and included (a) > 10% increase, (b) 0 – 10% increase, and (c) decrease. Accordingly, subjects were assigned to one of three subgroups (i.e., VO_2I Response Group) based upon their initial and sustained VO_2I response to lateral positioning during minutes 1 through 4 in the first phase of the study. Results of the factorial analyses revealed that (a) following lateral positioning, VO_2 response over time may be predicted by the VO_2I response observed between baseline and minute 4 after the turn, and (b) the effects of preprocedural morphine on oxygen demand-induced VO_2 response vary within subgroups of critically ill patients. For subjects in Group 1 who demonstrated a > 10% increase in VO_2I following turning, VO_2I was significantly lower at minutes 4 through 5 when morphine

was received before the turn. Subjects in Group 2 (0 – 10% increase) had lower VO_2I at minutes 4 through 5 following lateral positioning when morphine was received before the turn; however, the reductions in VO_2I were not as large as those observed in Group 1. Peak VO_2I following lateral positioning occurred at minutes 2 through 3 for this group of subjects; therefore, the true magnitude of morphine effect may not have been tested. Subjects in Group 3 demonstrated unanticipated VO_2I response patterns during both phases of the study. Without morphine, lateral positioning was associated with a reduction in mean VO_2I. However, at minutes 4 through 5 following lateral positioning, VO_2I was significantly *higher* when morphine was received before the turn. Clinical characteristics that differentiated Group 3 from the other subjects included lower LVEF, higher VO_2I and O_2ER, and lower Qs/Qt at baseline. Additional research is warranted to substantiate these findings using an adequate sample size.

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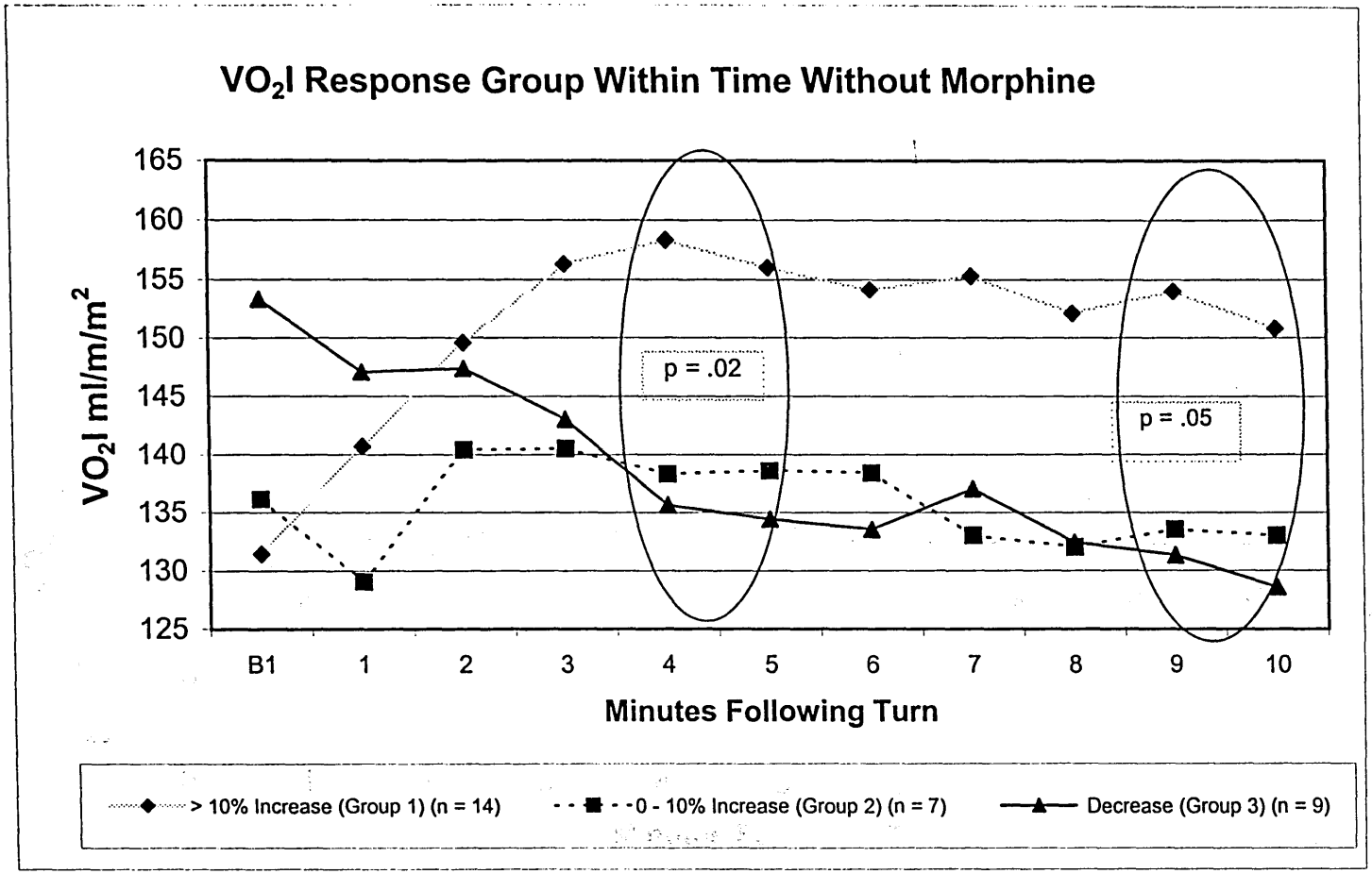
Appendix I: Table 1

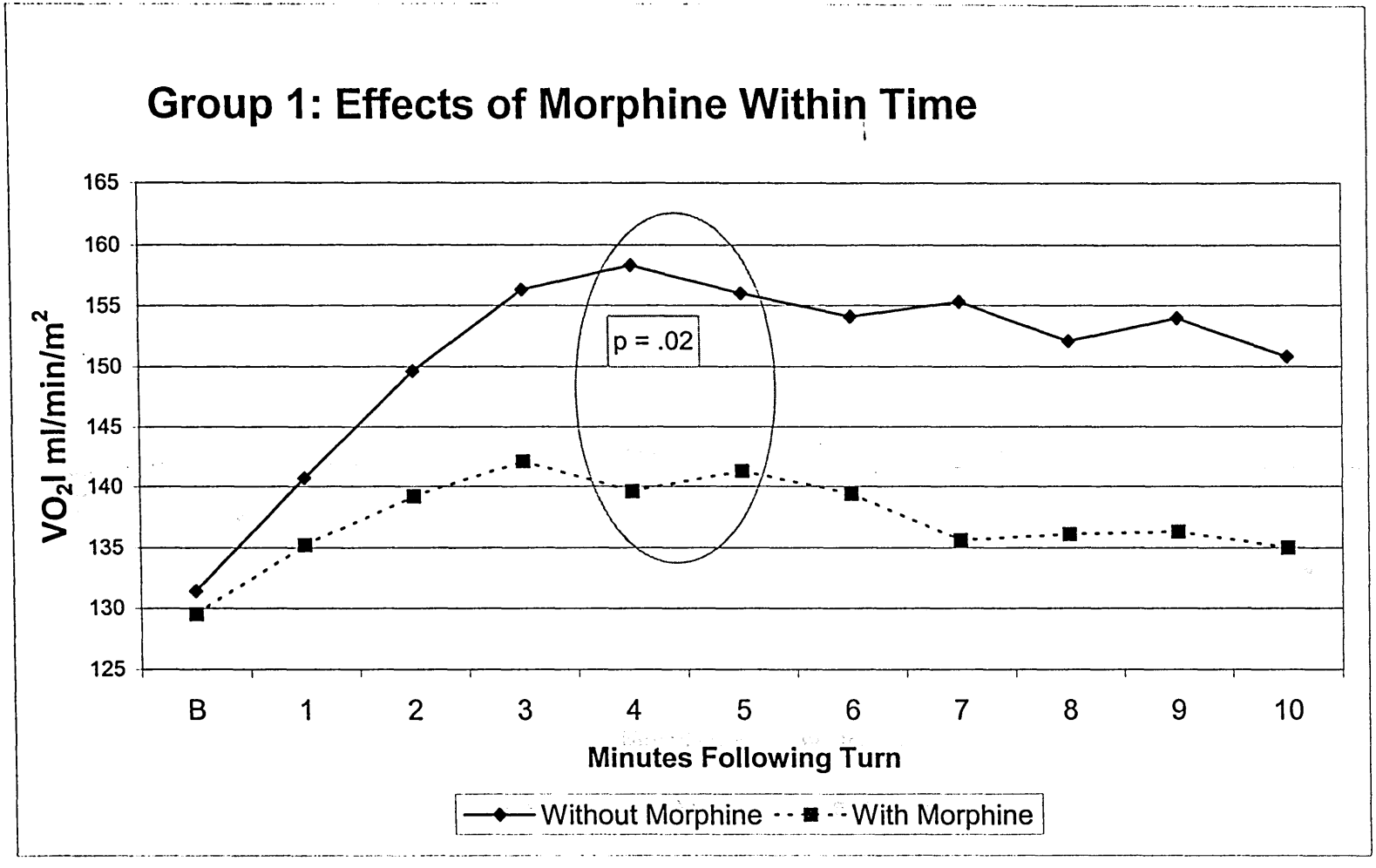
Baseline Clinical Characteristics of VO_2I Response Groups

Parameter	Group 1: > 10% Increase (n = 13)		Group 2: 0 - 10% Increase (n = 7)		Group 3: Decrease (n = 9)	
	Mean	***SD***	**Mean**	***SD***	**Mean**	***SD***
VO_2I ml/min/m^2	131.44	16.10	136.14	19.38	153.29	28.13
DO_2I ml/min/m^2	377.80	69.51	340.31	47.28	332.10	84.45
SvO_2 %	63.82	8.26	66.64	7.80	62.06	9.07
O_2ER	.36*	.06	.40*	.05	.49*	.16
Cardiac Index L/min/m^2	2.64	.54	2.58	.28	2.46	.23
Stroke Volume Index ml/beat/m^2	28.86	6.17	28.33	3.00	24.78	2.65
PAOP mm Hg	15.71	5.51	16.71	5.99	14.78	4.68
RAP mm Hg	11.36	5.57	13.14	3.93	11.22	3.90
MAP mm Hg †	78.85	11.61	79.14	14.92	85.89	18.80
Heart Rate bpm	92.36	9.28	91.14	8.49	99.00	11.18
SpO_2	.98	.02	.98	.01	.99	.01
CaO_2†	14.35	1.82	13.62	1.50	13.39	.92
QS.QT % †	13.08*	5.58	14.58*	5.25	7.45*	3.24
Hemoglobin	10.74	1.30	10.24	1.31	9.93	.94
Blood Temperature C°	37.50	.44	37.60	.87	37.57	.57

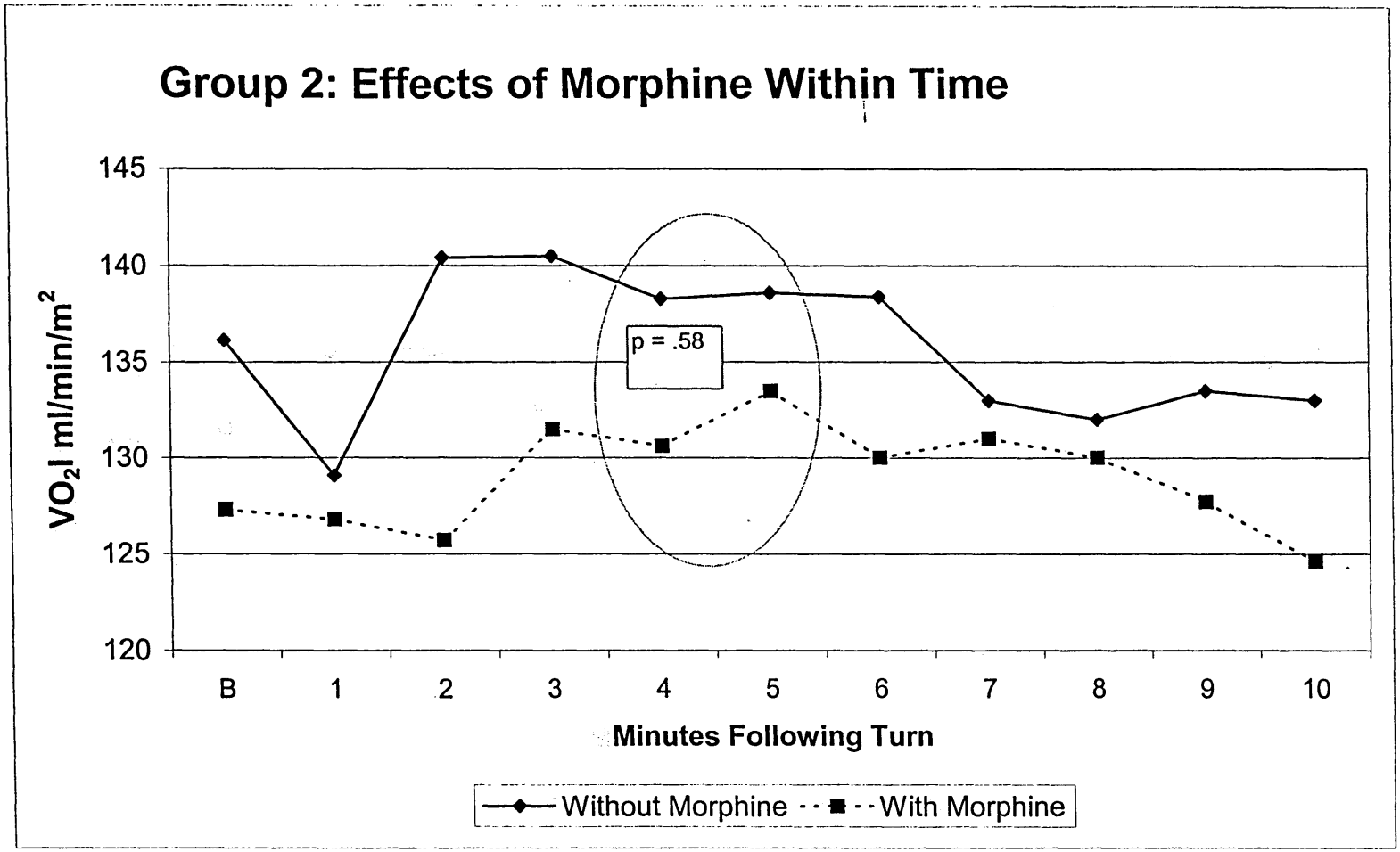
Note. VO_2I = oxygen consumption index; SvO_2 = mixed venous oxygen saturation;; DO_2I = oxygen delivery index; O_2ER = oxygen extraction ratio; PAOP = pulmonary artery occlusion pressure; RAP = right atrial pressure; MAP = mean arterial pressure; SpO_2 = arterial oxygen saturation by pulse oximetry; CaO_2 = arterial oxygen content; QS.QT = intrapulmonary shunt; C = degree Celsius; † = frequency < *n* due to missing data; *SD* = standard deviation; * $\rho < .05$; $\alpha = .01$.



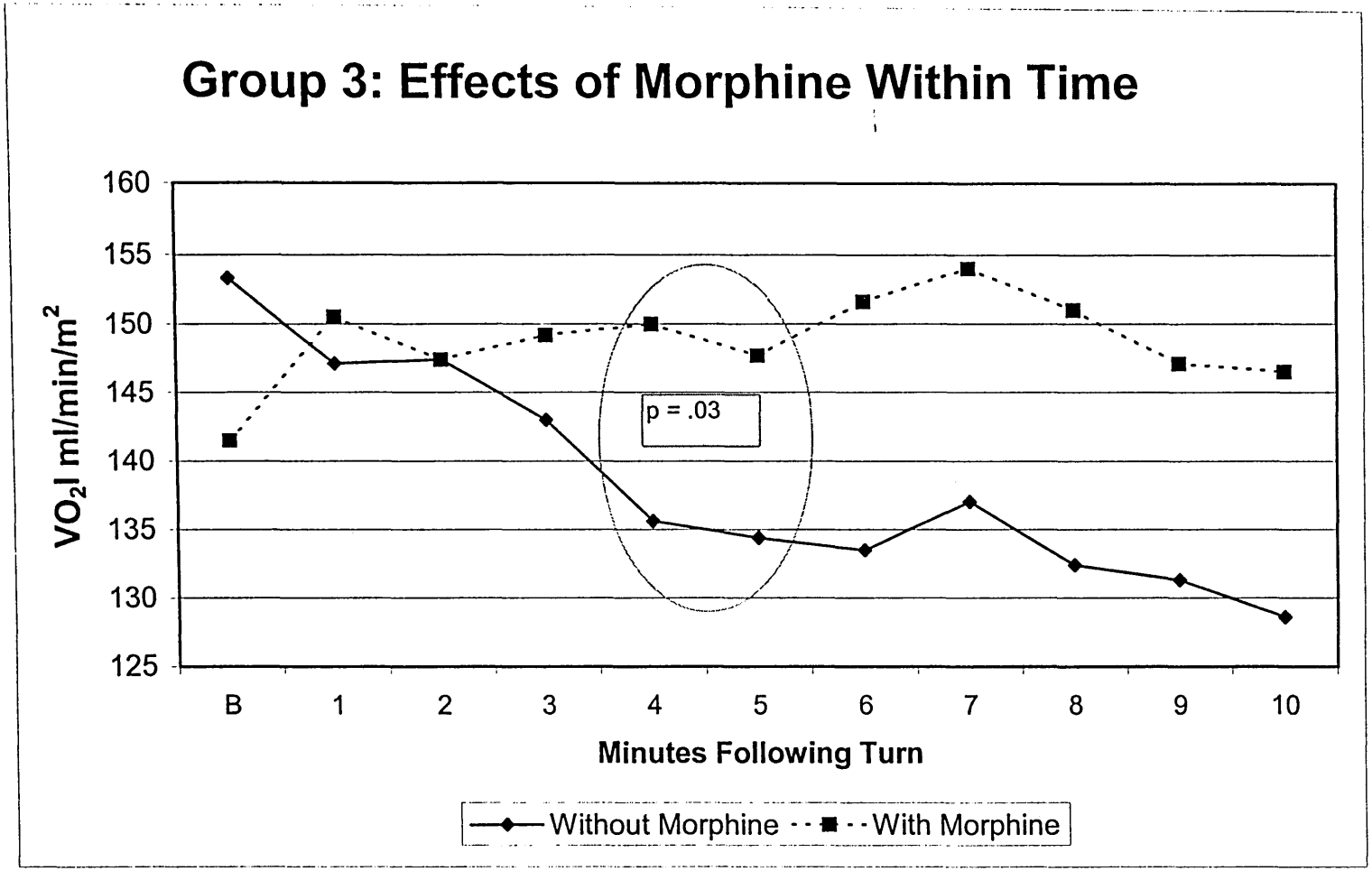
Appendix I: Figure 1. Simple effects of *VO_2I Response Group* within *Time* without the effects of *Morphine*. Analyses included two levels of *Time*: (1) averaged over minutes 4 and 5, and (2) averaged over minutes 9 and 10.



Appendix I: Figure 2. Simple effects of *Morphine* within *Time*, averaged over minutes 4 and 5, with and without the effects of morphine, for *VO_2I Response Group 1* (> 10% increase).



Appendix I: Figure 3. Simple effects of *Morphine* within *Time*, averaged over minutes 4 and 5, with and without the effects of morphine, for *VO_2l Response Group* 2 (0 - 10% increase).



Appendix I: Figure 4. Simple effects of *Morphine* within *Time*, averaged over minutes 4 and 5, with and without the effects of morphine, for *VO_2I Response Group 3* (Decrease).

Appendix J

Empirical Findings:

Lateral Position Effect

EMPIRICAL FINDINGS

LATERAL POSITION EFFECT

As detailed in the original study protocol (Appendix H), additional measurements of SvO_2 were obtained every minute from baseline through minute10 following lateral positioning, during the first and second phase of the study. Several researchers have documented that individual SvO_2 response following lateral positioning varies depending on the direction of the turn (Gawlinski & Dracup, 1998; Lewis et al., 1997; Shively, 1988). In an attempt to explain the differences in mean SvO_2 during both phases of the study, further exploration and analyses were conducted to determine if lateral position (i.e., left vs. right 45-degree position) was a confounding between-subjects factor that was responsible for a portion of the variance. Additional post hoc analyses were performed using a three-way (Morphine x Time x Lateral Position), repeated measures, split plot analyses of variance (ANOVA) to test the main effects (Tabachnick & Fidell, 1983)of lateral position and all two-way and three-way interactions involving lateral position with the other independent variables, morphine and time (H_0: $\mu 1 = \mu 2$; $\alpha = .025$, two-tailed). The within-subjects repeated factor *time* had 10 levels (minutes 1 through 10 post-turn) and the within-subjects repeated factor *morphine* had two levels (phase I = without morphine; phase II = with morphine). *Lateral position*, the between-subjects factor, had two levels that included left lateral position ($n = 15$) and right lateral position ($n = 15$).

Homogeneity of treatment–difference variances was evaluated using Mauchly's Test of Sphericity (Maxwell & Delaney, 1990). As anticipated, the assumption was rejected due to the high correlation between pairs of measures within the repeated factor of *time*. Because the multivariate approach is not robust to violations of homogeneity, analyses involving the repeated within-subjects factor *time* (Morphine x Time x Lateral Position, Time x Lateral Position) were performed using a univariate approach and the *df*s were adjusted with the Greenhouse-Geisser procedure to produce a more conservative *F* statistic (Maxwell & Delaney, 1990). Shapiro-Wilk's test of normality and Levene's Test of equal variance indicated that the assumptions of normality and homogeneity of variance of the between-subjects factor, lateral position, were satisfied. Although lateral position was determined by a randomization procedure, an equal number of subjects were randomized to the left and right positions; thus, the design was balanced and orthogonal. Level of significance for the Omnibus *F* tests for the major effects was set at $\alpha_{FW} = .025$ (two-tailed).

Omnibus F tests. Results of the analyses indicated that there were no significant differences in mean SvO_2 during the study procedures that related to the three-way interaction between Lateral Position x Morphine x Time ($F_{3.17, 88.92} = 0.45$, $\rho = .73$) or the two-way interaction between Lateral Position x Time ($F_{3.08, 86.24} = 0.97$, $\rho = .41$). However, the interaction between Lateral Position x Morphine was significant ($F_{1, 28} = 10.49$, $\rho = .003$). The main effect of lateral position was not interpreted because the interaction between lateral position and morphine was significant (Maxwell & Delaney,

1990). Mean SvO_2 between baseline and minute 10 following lateral positioning, with and without morphine, is graphically represented in Appendix J: Figure 1.

Graph interpretation: Lateral Position x Morphine. To explore the relationship between the independent variables, cell means of SvO_2 were collapsed over the 10-minute period following lateral positioning and graphically depicted as shown in Appendix J: Figure 2. Findings revealed that when the morphine intervention was received before turning, SvO_2 increased an average of 5 points (7.8%) in the group of subjects who were turned to the left lateral position ($M_1 = 60.23$, $SD = 8.9$; $M_2 = 64.91$, $SD = 7.1$). However, in the group of subjects who were turned to the right lateral position, SvO_2 increased by only 1 point (1.5%) when morphine was received before the turn ($M_1 = 62.59$, $SD = 6.6$; $M_2 = 63.52$, $SD = 6.3$). Simple effects analyses of the Lateral Position x Morphine interaction were indicated. Main effects of lateral position and morphine were not interpreted because of the disordinal relationship that was apparent in the graphical depiction of the significant interaction (Maxwell & Delaney, 1990).

Simple effects: Morphine (B) within Lateral Position (A). To test the magnitude of the morphine effect at different levels of lateral position (i.e., B at A_1, B at A_2), simple effects comparisons were performed using separate error terms. To control for a family-wise Type I error rate, the observed F statistic was compared to the Tukey's HSD adjusted critical value ($q_{.05,\, b,\, df_{error}}$)$^2/2$) to determine the level of significance (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983). Results indicated that when morphine was received before the turn, mean SvO_2 was significantly higher in the group of subjects who were positioned in the *left* lateral position ($F_{1,14} = 20.49$, $\rho = .000$). According to the

eta-squared (η^2) statistic, 60% of the variability in mean SvO_2 was attributed to the effects of morphine when subjects were positioned in the left lateral position. Observed power of the *F* test to detect a statistically significant difference in the means of SvO_2, with and without morphine, when subjects were turned to the left lateral position was .97.

In contrast, there was no significant effect of morphine on SvO_2 when subjects were turned to the right lateral position ($F_{1, 14} = 3.14$, $\rho = .098$). Less than 20% (η^2) of the variability in SvO_2 was attributed to the effects of morphine when subjects were positioned in the right lateral position. For purposes of avoiding a Type II error, power analysis was conducted using SamplePower™ (SPSS, 1997) to determine if the available sample size was sufficiently sensitive to detect a statistically significant difference in mean SvO_2 between the conditions of morphine when subjects were turned to the *right* lateral position. Using the common within-group standard deviation of 6.45, results of the power analyses revealed a standardized mean difference (*d*) of 0.14, that according to Cohen (1983), is less than a small effect size. For the given effect size (population means 63.52 vs. 62.59), standard deviations (6.6, 6.3), sample size (15 per group) and $\alpha = .025$ (two-tailed), the test had power of .035 to detect a statistically significant difference. To test the null hypothesis that the two population means are equal with a power of .80 ($\alpha = .025$, two-tailed), 793 subjects would be required in each group. Results of the statistical power analysis supported the findings of the simple effects analyses. Significant findings were not apparent because morphine had minimal effect on SvO_2 in the group of subjects who were turned to the right lateral position. Therefore, the probability of a Type II error was unlikely and the decision to not reject the null hypothesis was retained.

Simple effects: Lateral Position (A) within Morphine (B). To test the magnitude of the lateral position effect at different levels of morphine (i.e., A at B_1, A at B_2), simple effects comparisons were performed using separate error terms. To control for a family-wise Type I error rate, the observed F statistic was compared to the Tukey's HSD adjusted critical value $(q_{.05,\, b,\, df_{error}})^2/2$) to determine the level of significance (Maxwell & Delaney, 1990; Tabachnick & Fidell, 1983). Results of the post hoc comparisons revealed that when morphine was received prior to lateral positioning, there were no significant differences in mean SvO_2 between subjects in the left lateral position (M = 64.91, SD = 7.1) and subjects in the right lateral position (M = 63.52, SD = 6.33; $F_{1,28}$ = 14.42, ρ = .58). Similarly, when subjects were turned without morphine, there were no significant differences in mean SvO_2 between subjects in the left lateral position (M = 60.23, SD = 8.9) and those in the right lateral position (M = 62.59, SD = 6.6; $F_{1,28}$ = 42.01, ρ = .41). According to the eta-squared (η^2) statistic, when patients received morphine before turning, less than 1% of the variability in mean SvO_2 following the turn was attributable to the direction of the turn (lateral position). When patients did not receive morphine before turning, less than 3% of the variability in mean SvO_2 following the turn was related to lateral position.

Conclusion. Additional post hoc analyses of the third hypothesis revealed that the effects of morphine were not generalizable across both left and right lateral positions Findings of the two-way Lateral Position x Morphine interaction revealed that the effect of preprocedural morphine on mean SvO_2 following lateral positioning does depend on the direction of the turn (right vs. left). When stratified by lateral position, subjects who

were turned to the left lateral position demonstrated significantly higher mean SvO_2 when morphine was received before the turn. In comparison, subjects who were turned to the right lateral position did not have significantly higher SvO_2 when morphine was received before the turn. Thus, the effects of morphine on mean SvO_2 are not generalizable across both conditions of lateral position. Although group differences between cardiorespiratory variables did not exceed 10%, results suggested that subjects randomized to the right lateral position were more anemic and compensated by increasing heart rate and O_2ER to maintain tissue oxygenation.

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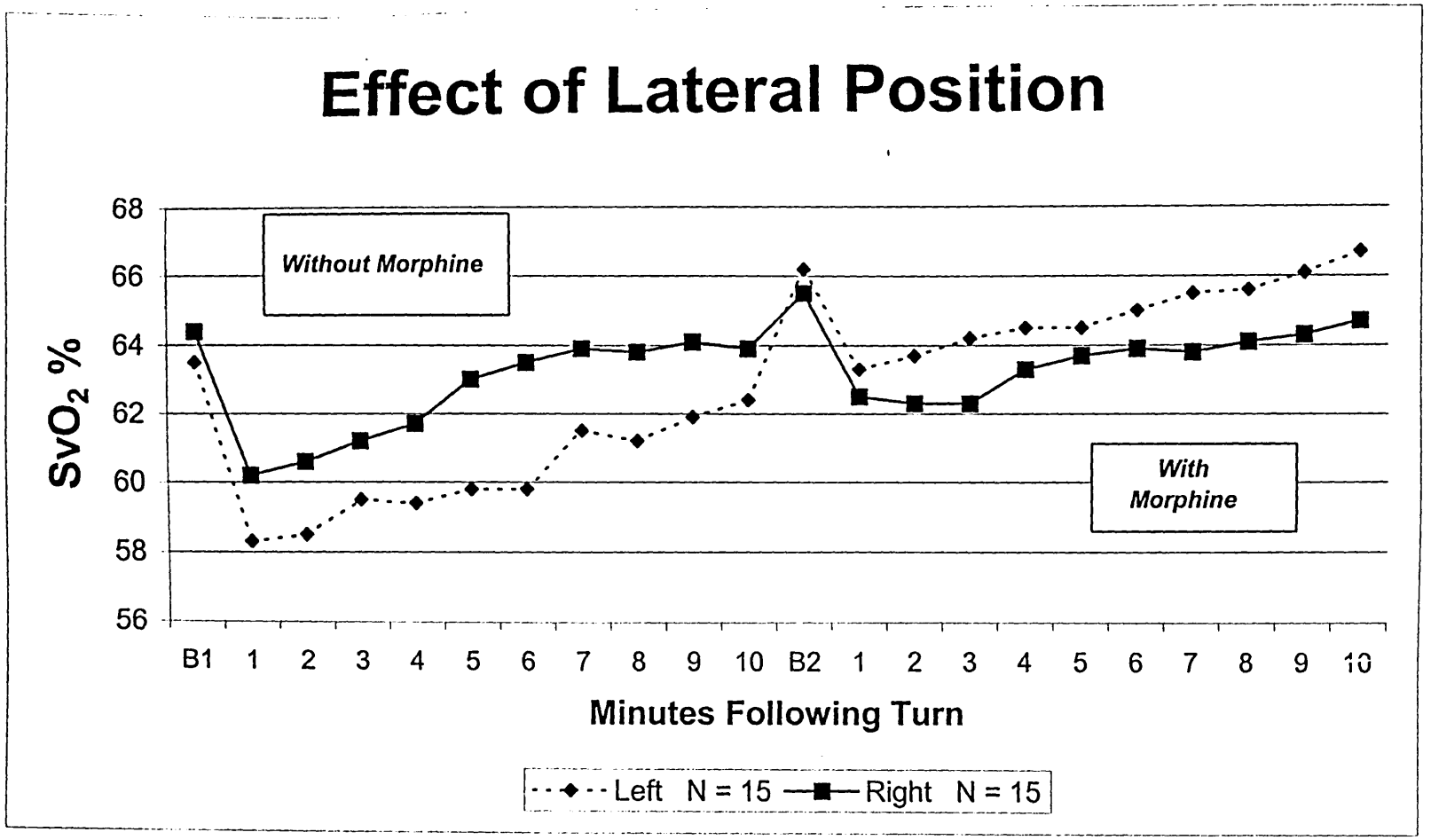
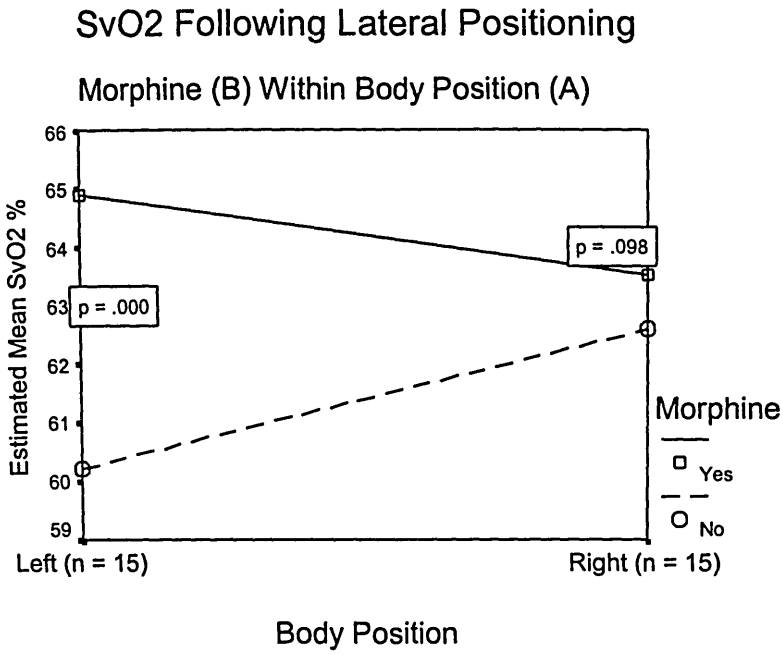
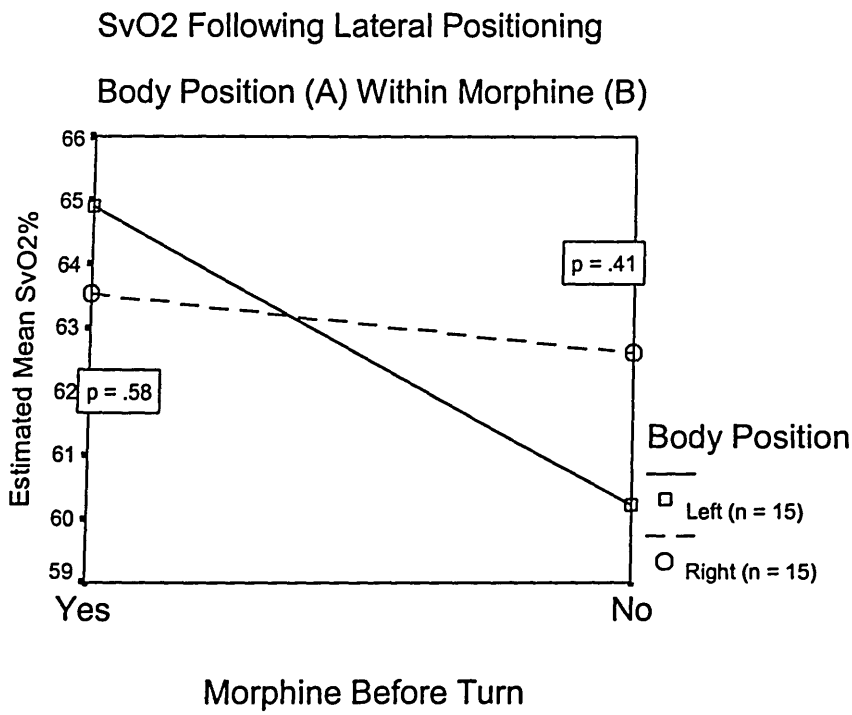


Appendix J: Figure 1. Findings suggested that when preprocedural morphine was received before the turn, mean SvO_2 was significantly higher in the group of subjects who were positioned in the left lateral position ($F_{1,14} = 20.49$, $\rho = .000$) but not in the right lateral lateral position ($F_{1,14} = 3.14$, $\rho = .098$); B = baseline.





Appendix J: Figure 2. Simple effects of *Body Position x Morphine* Interaction on estimated marginal means of SvO_2 following lateral positioning ($N = 30$).