CARDIOPULMONARY EFFECTS OF PROLONGED MORPHINE-CHLORALOSE ANESTHESIA IN DOGS

A THESIS

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We hereby recommend that the thesis prepared under our supervision by Cheri Kay Buchanan entitled Cardiopulmonary Effects of Prolonged Morphine-Chloralose Anesthesia in Dogs.

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CHAPTER I

INTRODUCTION

The use of anesthesia in the experimental animal allows a humane in vivo approach for pharmacological and physiological investigations. Unfortunately, the anesthetic depth often varies, impinging on the metabolic state causing fluctuations in the physiological status of the animal. Experimental results are often reported without attention to the physiological stresses that accompany the trauma of surgery and anesthesia. In addition, drugs that cause central nervous system depression to the point of general anesthesia are often associated with profound alterations in the normal homeostatic reflex mechanisms.

Alpha-chloralose is frequently employed when assessing cardiopulmonary parameters and is felt to be superior to some other general anesthetics in cardiovascular studies because it does not depress the autonomic regulatory reflexes and has only minor effects on the cardiovascular and respiratory systems. In neurophysiological research it is a valuable tool as an electroencephalographic activator.

Although alpha-chloralose has been used for several decades, much of its popularity is based on early

observations concerning its pharmacological effects. As later investigations concerning the actions of this drug were reported, many preconceived ideas were challenged, but not substantially enough to supersede them. Hence, in the current literature, references to "beta-isomer contamination" or "enhanced adrenalin release" continue to surface, although no specific quantifiable data is available.

Although it is well recognized that the study of unanesthetized animals offers a more physiological model, this is not always feasible within the framework of the experimental design or with the facilities available. Furthermore, long-term cardiovascular studies are being undertaken as the sophistication of monitoring and surgical technique advances. The dose-dependent and time-duration effects of the anesthetics employed for these investigations are dimensions that are often overlooked but that can have significant effects.

With the rapid increase in the complexity and duration of experimental procedures for evaluating cardiovascular performance more information regarding the long-term effects of anesthetic agents is required. Maintenance of an "even anesthetic level" throughout the experiment has become a consideration to the investigator. Although there is

little data available concerning prolonged cardiopulmonary effects of chloralose, many investigators empirically supplement the anesthetic in an effort to obtain a stable model. Holding the level of anesthesia constant will provide a more stable model during the experiment and will facilitate replication of the conditions. Similarly, establishing dose-dependent effects of this agent on cardiovascular and pulmonary parameters will offer a stable framework for the interpretation of data collected in the chloralose-anesthetized dog.

In this two-phase study, the cardiopulmonary effects of prolonged morphine-chloralose anesthesia were investigated. Cardiac contractility was assessed invasively by the maximum rate of rise of left ventricular pressure (max dP/dt) and by the velocity of contractile element shortening at zero load (Vmax) and at forty (40) millimeters of mercury pressure (V_{40}). Aortic systolic and diastolic blood pressures, pulse pressure, left ventricular filling pressure and heart rate analysis allowed more complete cardiovascular evaluation throughout the twelve (12) hour anesthetic maintenance period. In addition, arterial blood gases were monitored hourly in order to evaluate the effect of chloralose on respiratory parameters.

Phase I of this study provided a comparison between two groups of dogs which were treated in the same manner but maintained with different dosages of alpha-chloralose during the twelve hour experimental period. The marked acidemia and severe hypoxemia that occurred with both dosage regimes of Phase I stimulated further investigation, denoted as Phase II of this study. Phase II provided a comparison between spontaneously breathing and mechanically ventilated dogs. The dogs in the two groups of Phase II, all received the same dosage protocol during the maintenance phase. In addition, the Phase II animals received the supplemental anesthetic as a constant infusion, from induction throughout the twelve hours, in contradistinction from the Phase I dogs which received hourly bolus injections of alpha-chloralose.

Despite the widespread acceptance of alpha-chloralose as an anesthetic agent for many types of cardiovascular experiments, little is known about the prolonged effects of chloralose on cardiopulmonary performance. The purpose of this study was to provide quantitative information on the long-term, dose-related cardiopulmonary effects of morphine-chloralose anesthesia in dogs.

This study was funded by the American Heart Association, Texas Affiliate.

CHAPTER II

REVIEW OF LITERATURE

History

Alpha-chloralose has enjoyed lasting popularity in experimental research since its introduction in the 1890's. However, although the drug was an anesthetic "par excellence" (Greisheimer, 1965) the reason for this limited sphere of influence can be traced in part to its chronological appearance in the history of anesthesia and to some degree, to the "convulsive" component of its biological activity.

From antiquity, live animal experimentation has been instrumental in advancing anatomic and physiologic knowledge. From the time of Galen (129-199 A.D.) to the mid 1800's, these investigations proceeded brutally without the humanity of general anesthesia (U.S. Dept. of HEW, PHS: National Library of Medicine, 1965). The modern authors of anesthesia history wrote isolated, unheeded chapters from Black, Priestley and Davy in the mid-to-late 1700's and early 1800's, until Morton's ether demonstration at the Massachusetts General Hospital in 1846 . . . "Before Whom, in All Time, Surgery was Agony; By Whom, Pain in

Surgery was Averted and Annulled; Since Whom, Science has Control of Pain" (Lee and Atkinson, 1973). John C. Dalton, after witnessing the infamous "Ether demonstration" recognized that teaching physiology by demonstration, using anesthetized live animals, would be an invaluable, as well as a humanitarian step forward. In 1882, he was challenged by "anti-vivisectionists" who protested this use of animals, probably without an appreciation of the origins and history of this mode of investigation and instruction. In rebuttal, Dalton published a vigorous defense of "The Experimental Method in Medical Science" (Leake, 1947).

Alpha-chloralose exerts its anesthetic effect when administered intravenously. The history of this mode of drug administration contributed to the limited use of this agent outside the laboratory. Intravenous narcosis with crude opium extracts, had been documented using dogs, as early as 1656 by Sir Christopher Wren (Smithcors, 1971) and extended to at least one human by the German physician, Dr. Elsholz in 1665 (Smithcors, 1971). However, investigative energies incorporated only the methodology, squelching the discovery of anesthesia for another century and a half. Even Elsholz, who had deliberately narcotized a human, grasped only the significance of the intravenous

route and experiments in blood transfusion began and flourished for a short time.

The history of intravenous anesthesia was dormant for almost two hundred years. Although opium extracts had been used, the societal and religious taboos associated with drug addiction stifled investigation of this class of drugs for medical use until the twentieth century. In 1832, von Liebig discovered chloral, a precursor of chloralose, which was clinically introduced by Libreich in 1889 (Leake, 1947) as an oral hypnotic whose potency was attributed to the slow formation of chloroform in the body (Leake, 1947, citing, Comp. Rend. Acad. Sci. 69:486, 1869); and perhaps that was the stimulus for again attempting a more rapid means of inducing narcosis. In addition, with the contribution of the hypodermic syringe and needle by Pravaz and Wood in 1853, as well as the theory of asepsis in the late 1860s, the time was right for the re-introduction of intravenous technique.

Pierre-Cyprien Ore of Bordeaux, France, initially tested the efficacy of an intravenous solution of chloral in 1872; by 1874-5 he had progressed from his experiments on animals to humans (Dripps, Eckenhoff, and Vandem, 1972; Smithcors, 1971) and reported his success to the medical fraternity in Paris (Davidson, 1965). For almost fifty

years, however, anesthesia by inhalation (ether, nitrous oxide and chloroform) had gained a stronghold in human medicine. Because of the narrow margin of safety of intravenous chloral, as well as its prolonged duration of action, chloral never succeeded as a clinical anesthetic.

Similarly the use of intravenous chloral hydrate twenty years later, suffered almost the same fate in veterinary circles. It was utilized briefly by veterinarians and although Liautard in 1892 praised the intravenous route saying, "it has been shown to be the best of all modes of obtaining anesthesia, but unfortunately it is a method of introducing it into the system which will scarcely ever become sufficiently practicable to be available outside of the laboratory" (Smithcors, 1971). Fortunately the intravenous technique was sufficiently revived to maintain a place in the progressive march of anesthesia history. Although the intravenous mode didn't suit chloral hydrate, oral preparations of this sedative have retained a secure place in human therapeutics and in veterinary medicine.

In 1892, the French investigators Hanroit and Richet synthesized alpha-chloralose from a mixture of glucose and chloral. Previous experimentation by Ore laid the groundwork for the inclusion of intravenous administration of

the new drug. The intravenous (IV) anesthetic effects were profound and even though the onset of action was slow by today's standard, the ten-to-twenty minutes required to reach surgical planes compared favorably with the popular available inhalation agents.

Chloralose was described by early investigators as a "convulsive anesthetic" because of the observed motor hyperexcitability and occasional sporadic myoclonic movements which on rare occasion progressed to generalized convulsions (Balis and Monroe, 1964). Many of these "strychnine-like" effects were attributed to contamination by beta-chloralose but this was largely disproven by Monroe, Balis and Ebersberger in 1963 when they compared equipotent dosages of alpha- and beta-chloralose in rats.

The mechanism responsible for chloralose hyperexcitability or chloralose jerks has attracted much research. The phenomena is most pronounced during the early phases of the anesthetic course (Stenhouse, 1970; Alvord and Fuortes, 1954). Crawford (1970) suggests that chloralose may provide a specific antagonism to the cortical transmitters. Krnjevic (1971) reports that chloralose probably depresses the inhibitory synapses acting on motorneurons. Balis and Monroe (1964) hypothesize that

under chloralose, the subcortical structures are not depressed, but either released from cortical inhibitory tone or acted on directly.

The use of chloralose as an anesthetic in physiological research largely rests with the fact that chloralose augments the neural reflexes allowing the study of autonomic regulation in vivo. In addition, its long-accepted reputation for cardiopulmonary stability (Duchene-Marullaz, Combre and Boucher, 1975; Hayashi, 1969; Bass and Buckley, 1966; Van Citters et al., 1964; Griffin, Emery and Lockwood, 1941; Vincent and Thompson, 1928) especially of the baroreceptor (Cox, 1972a; Korner et al., 1968; Brown and Hilton, 1956a and 1956b; Koppermann, Brendel and Thauer, 1955) and chemoreceptor activity (Korner et al., 1968; Boniface and Brown, 1953; Dripps and Dumke, 1943; Schmidt, 1940) has reserved a secure place for this drug in cardiovascular and neurophysiological research.

Interestingly, even after its success in the laboratory setting with many species, alpha-chloralose never played a significant role in veterinary anesthesia. This may be in part due to the technical difficulties alluded to in 1892 by Liautard, but more likely was due to the latent incorporation of anesthesia by veterinarians

(Smithcors, 1971). This view was expounded by Merillat in 1906:

> In veterinary surgery, anesthesia has no history. . . It reflects greatly to the credit of the canine specialist, however, that he alone had adopted anesthesia to any considerable extent. . . Anesthesia in veterinary surgery today is a means of restraint and not an expedient to relieve pain. So long as an operation can be performed by forcible restraint. . . the thought of anesthesia does not enter into the proposition. . . (Smithcors, 1971; citing, Merillat, L.A., Principles of Veterinary Surgery, p. 223, Alexander Eger, Chicago, 1906).

More recently, the drug has been revived for use in animals, but outside the usual veterinary applications. In the mid 1960s, alpha-chloralose was used as sedative bait for the capture of wild turkeys (Meleagris gallopavo) Harthoorn, 1971; Williams, 1966). The Game and Fresh Water Fish Commission headquartered in West Palm Beach, Florida, had success with this method and altered the dosage in order to capture sandhill cranes (G. c. takida and G. c. pratensis) with low mortality. Capturing these birds facilitated banding for migration and behavioral studies (Williams and Phillips, 1973). Alpha-chloralose narcotized the birds in twenty to sixty minutes, with recovery in about three hours (Williams and Phillips, 1973) and the technique compared favorably with the other currently used trapping methods.

In the late 1960s in England, alpha-chloralose was used successfully as a rodenticide. It was selected for its humane qualities, because of the objections to the anticoagulant rodenticides. After ingestion, alpha-chloralose exerts its lethal effect primarily by the unreversed narcotization of the vital centers (Lees, 1972; Cornwell, 1969).

A hazard associated with this application of alpha-chloralose is the accidental poisoning of domestic animals, particularly cats and dogs (Stopforth, 1970). The LD_{50} in these species is reported as the same for rats (400-600 mg/kg) by Balis and Monroe (1964). It is apparent that accidental ingestion can cause symptomatology but never has caused a death (Lees, 1972; Shepherd, 1971; Stopforth, 1970; Cornwell, 1969) in domestic animals. If accidental poisoning does occur, the major consensus is to treat the symptoms until the drug is metabolized. This may include artificial ventilation (Lees, 1972).

Poisoning in man has occurred (Manzo, Richelmi and Crema, 1979; Gras, Pellissiar and Fauran, 1975; Williams, 1894; Lang, 1893) with symptomatology dependent on the degree of overdose. Manzo, Richelmi and Crema (1979) recorded a case study report of a 62-year-old known epileptic, who had injested a large, unknown amount of

the rodenticide Murex, whose active ingredient is alpha-chloralose. On admission the patient was deeply comatose, having myoclonic convulsions, had stable cardiovascular signs and adequate spontaneous respiration but had an isoelectric electroencephalogram (EEG). The patient had an episode of respiratory failure requiring ventilatory support. Body temperature was normal and clinical laboratory studies were unremarkable. During the next five days, the patient's neurological status and EEG gradually returned to normal and he was dismissed. Others have documented a prolonged effect of chloralose on the EEG (Crawford, 1970; King, 1956). Detection of the drug in cases of unknown poisoning has been possible through family interviews and accurate history-taking. The detection of trichloroethanol in the blood (Manzo, Richelmi and Crema, 1979) or of chloralose in the urine (Gras, Pellissiar and Fauran, 1975) also offer laboratory confirmation of chloralose intoxication.

The history of chloralose in human therapy has been brief and intermittent. In the 1890s, oral preparations of this sedative were given to hysterics and insomniacs (Flemming, 1894). It was intensely popular with physicians (Williams, 1894), but did cause hyperexcitability and even delirium in some patients (Williams, 1894; Lang, 1893)

and gradually lost favor with the advent of the more predictable barbituates and hypnotics.

In the late 1930s, the drug was re-introduced but for use in agitated patients, and patients with psychotic behavior (Balis and Monroe, 1964) with "spectacular results". This stimulated further neuropsychiatric trials, and the drug was combined with scopolamine, a known CNS stimulant, in an attempt to precipitate EEG confirmation of epilepsy. This synergistic combination (S.A.C.) was used with partial success in identifying epilepsy in patients with normal waking EEGs (Bercel, 1953). Normal individuals did not demonstrate any ill effect from the oral preparation of S.A.C. and no abnormal brain activity could be precipitated in these controls (Monroe et al., 1956; Monroe, Jacobson and Ervin, 1956; Bercel, 1953). Further application of S.A.C. as a pharmacological EEG activator to differentiate severe behavioral disorders (particularly schizophrenia), met with limited success (Monroe et al., 1956; Monroe, Jacobson and Ervin, 1956). Since the 1960s, this use of the drug has been surplanted by more dependable agents.

Chemistry

The anesthetic and sedative properties of alpha-chloralose were first described by Hanroit and Richet in 1892 (Monroe, Balis and Ebersberger, 1963; Williams, 1894). Equal amounts of anhydrous chloral and d-glucose were heated in the presence of sulfuric acid. This method of preparation, as detailed by Heffter in 1889 (Ross and Payne, 1923), yielded a mixture of glucochloraloses, including two monoglucochloraloses which can be further separated by ether extraction (Coles, Goodhue and Hixon, 1929). The final crystalline product thus obtained was the more soluble alpha-gluco-chloralose. Hanroit apparently assigned the alpha- and beta- prefixes to differientiate the solubility of these two probable isomers (Butler, 1940). More recently, Hanroits' basic procedure for synthesis has been altered by changing the 1:1 glucose to chloral ratio, to a 1:4.4 (Mikstais, Cirulis and Jakobsons, 1970) or a 1:5 (Barre et al., 1950) ratio, in order to obtain higher yields of alpha-chloralose.

Alpha-chlorolose (alpha-D-glucochloralose; gluco-chloral; anhydroglucochloral; chloralosane; Somino) is a white crystalline powder, relatively insoluble in cold water (one gram in 225 ml water at 15°C), soluble in

alcohol (one gram in 15 ml alcohol at 25°C), and has a melting point of 187°C. It is a non-reducing sugar which rotates the plane of polarized light +19° at 22°C if the concentration is equal to 5 grams in 98% alcohol.

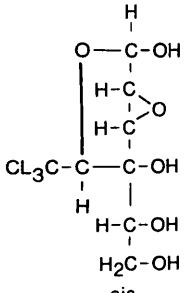
The formula is $C_8H_{11}Cl_3O_6$ and the compound has a molecular weight of 307.96 (Windholz et al., eds., 1978). The generic name is listed as 1,2-O-(2,2,2-trichloro-ethylidene) alpha-D-glucofuranose, and the structural formula (Figure 1c) is illustrated as it appears in the 1976 Merck Index (Windholz et al., eds., 1976).

Since the introduction of alpha-chlorolose, the molecular formula of the glucochloraloses has been debated. One contributing factor to the seventy-year pursuit of this problem, is the alleged difference in pharmacological activity of the two proposed monoglucochloralose isomers (Balis and Monroe, 1964) as well as the paradoxical effects exhibited by alpha-chloralose alone, i.e., sedation and hyperexcitability (Balis and Monroe, 1964; Monroe, Balis and Ebersberger, 1963; Williams, 1894).

Figure 1 (a, b, and c) contains the major chemical structures of chloralose. Originally, Hanroit indicated a cis-, trans- difference in the two isomers with respect to the anomeric carbon. Further, he assumed four hydroxyls, as seen in the glucose structure and a chloral-glucose

(A)

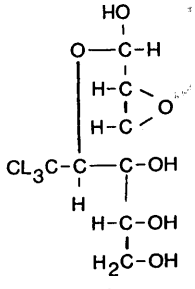
PROPOSED FORMULAE FOR GLUCOCHLORALOSES



cis

α -CHLORALOSE

(ORTHOCHLORALOSE)

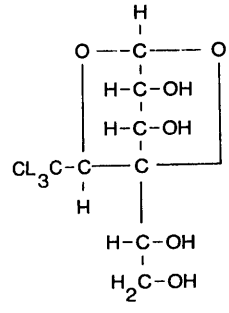


trans

β -CHLORALOSE

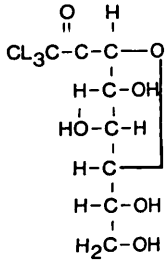
(PARACHLORALOSE)

(HANRIOT, 1892, 1909)

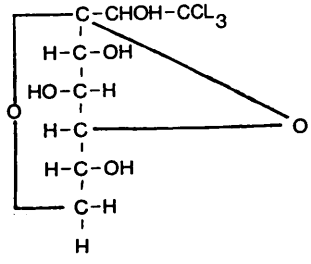


CHLORALOSE

(PETIT AND POLONOVSKI, 1894)

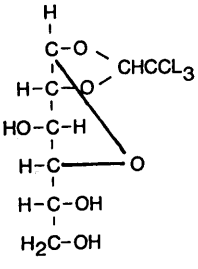


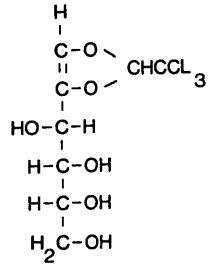
ISOMER β



ISOMER α

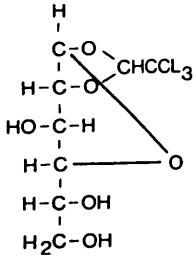
(PICTET AND REICHEL, 1923)



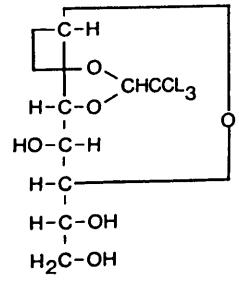


CHLORALOSE

(COLES, GOODHUE, et al., 1929)

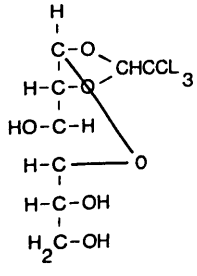


β -CHLORALOSE

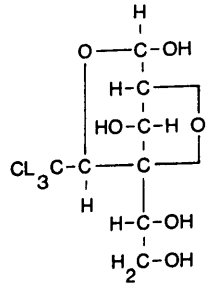


α - CHLORALOSE

(DREFAHL AND MATSCHKE, 1949)



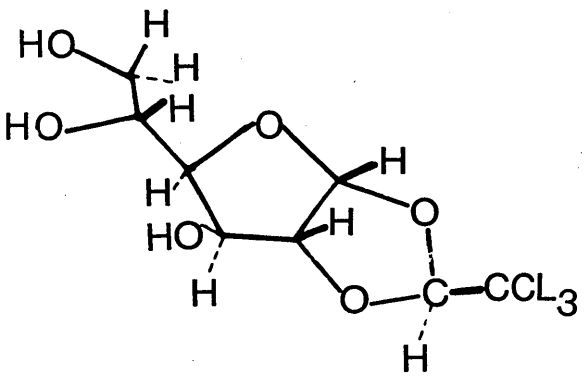
α -CHLORALOSE

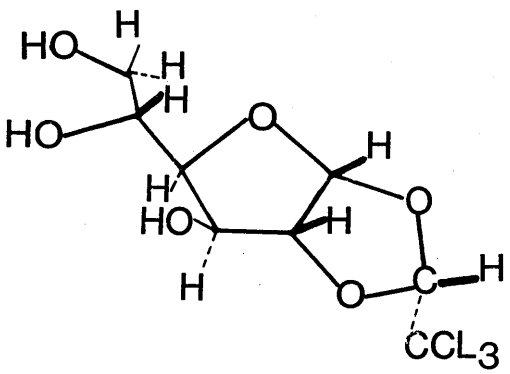


β -CHLORALOSE

FLEURY AND JOLLY, 1950)

(B)

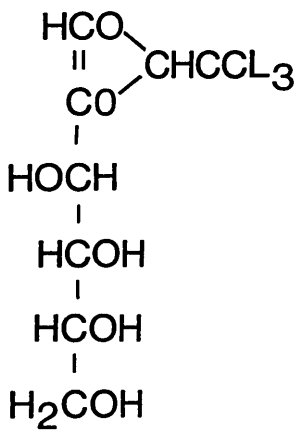




β-CHLORALGLUCOSE **a**-CHLORALGLUCOSE

(FORSEN, et al., 1965)

(C)



(1978 MERCK MANUAL)

linkage of the two major components (Balis and Monroe, 1964). The acetalglucose linkage, an alteration caused by the union of the two compounds, proposed by Coles, Goodhue and Hixon, 1929 has received acceptance, as well as their contention that only three free hydroxyl groups remain in the glucochloraloses after condensation (Balis and Monroe, 1964; Freudenberg and Vajda, 1937; White and Hixon, 1933). These investigators also proposed a keto-enol isomerization which supports a definite relationship between the two hypothesized 'isomeric' forms of chloralose. The beta-chloralose formula of Drefahl and Matschke (1949) corresponds with the 'keto' isomer proposed by Coles et al., in 1929: in 1950, Fleury and Jolly-Collin replicated this same formula but identified it as alpha-chloralose (Balis and Monroe, 1964).

Controversy regarding the structure of chloralose still persists and has undoubtedly hindered complete understanding chloralose pharmacodynamics, such as structure-activity relationships (Fingl and Woodbury, 1975). Even without clear knowledge of the chemical structure of chloralose the pharmacological effects of the drug can be studied to some extent. The following section reviews the pharmacokinetic properties of alpha-chloralose.

Pharmacokinetics

The pharmacokinetics (i.e., absorption, redistribution, metabolism and excretion) of alpha-chloralose has received very little attention. In part, the uncertainty of the molecular structure of this compound has hindered definitive investigation (Monroe, Balis and Ebersberger, 1963). A more plausible explanation though, is that the drug is used in the main by physiologists, not pharmacologists, hence physiological effects have been more intensively studied. In addition, since the drug has little relevance in human medicine (Croft, 1964) or in veterinary medicine, indepth pharmacological research would be largely esoteric.

Chloralose, a monosaccharide chloral derivative, is a non-polar, non-electrolyte which therefore can passively enter cells by diffusion. Further, since lipid solubility is increased by halogenation (Fingl and Woodbury, 1975) rapid equilibration across the blood brain barrier (Jacobs, 1978) is enhanced and general anesthesia can result. The intravenous route of administration allows a rapid effect because of the direct contribution of a high plasma concentration of drug. However, of minor importance is the fact that the uptake of any intravenous

anesthetic is governed partially by the regional hemodynamics of the injection site and the cardiac output of the animal.

A period of latency before drug effects are exhibited following the intravenous introduction of alpha-chloralose has been reported (Monroe, Balis and Ebersberger, 1963; Butler, 1942). Mechanisms responsible may be related to only moderate lipoid solubility, initial dosage, redistribution or perhaps multiple sites of action, different than for other shorter-acting anesthetics, that must be uniformly reached before the clinical effects are seen (Butler, 1942). The duration of action of a single injection was found to vary with the amount of drug given (Fingl and Woodbury, 1975; Butler, 1942) and with redistribution after one arm-brain circulation time (Dundee and Clarke, 1980). Fingl and Woodbury (1975) nonspecifically comment that the time of peak effect is unrelated to dosage while Monroe, Balis and Ebersberger (1963) report that the onset for behavioral effects in rats anesthetized with varying doses alpha-chloralose, shortened from 74 minutes (30 mg/kg) to 10 minutes (300 mg/kg).

Redistribution is the biological removal of a drug from its site of action by binding to plasma proteins or bone or by uptake in other tissues. The vessel-rich

group (VRG) (i.e., brain, heart, liver, splanchnic bed, kidney and endocrine glands) are exposed to the initial high concentrations in the plasma and tissue equilibration proceeds first in these areas (Dripps, Eckenhoff and Vandam, 1972). With the decrease in the plasma concentration after the initial absorption, the concentration gradient reverses and the VRG redistributes to the viscera, muscle, and fat respectively, with varying equilibration times. Without supplementation, by virtue of the redistribution process alone the anesthetic level will lighten. The converse re-anesthetization can occur if the plasma concentration rises to appropriate levels at some point during the redistribution process. This manifestation most likely would occur after consciousness has been regained following an anesthetic course that has required repeated doses.

Repeated administration will result in drug accumulation (as long as complete elimination has not occurred). The elimination half-time is an important determinant of three characteristics: time course accumulation, the extent of accumulation, and the fluctuations between doses (Fingl and Woodbury, 1975). Intermittent administration of a constant dose at specific intervals, or constant intravenous infusion will result in a plateau state in

that the amount excreted will be equal to the amount of drug being introduced. The establishment of this plateau relies on exponential (first-order) kinetics; "that is, a constant fraction of drug present is eliminated per unit time" (Fingl and Woodbury, 1975). In exponential clearance, the amount of drug cleared per unit time is proportional to the amount remaining in the body (Fingl and Woodbury, 1975). Dundee and Clarke (1980) acknowledge this function in relation to injectible anesthetics by recommending lesser doses during the anesthetic course to maintain the anesthetic level. Mathematical calculations predict that the clearance will be nearly complete at four half-times and be altered somewhat for varied absorption, dosage or elimination (Fingl and Woodbury, 1975). No information on plasma drug concentrations is available for intravenous alpha-chloralose, but Fingl and Woodbury (1975) report that the plasma half-life for trichloroethanol is eight (8) hours.

The dimunition of anesthetic effect is also attributed to the biotransformation and the consequent elimination of the drug from the body. All chloral derivatives are converted to the same active intermediate, trichloroethanol (Fingl and Woodbury, 1975) which is reduced to the inactive intermediate, trichloroethanol glucuronide by microsomal

conjugation in the liver (Lees, 1972; Shepherd, 1971; Cornwell, 1969). Chloralose has been utilized when studying liver metabolism in dogs (Schutz et al., 1977) apparently preserving the normal liver function (Reid, 1936a and 1936b). Detoxification can occur in the kidney as well, by the same mechanism. The function of conjugation is to aid renal excretion by making the metabolite more water soluble. The urochloralic acid (the inactive glucuronide) formed is excreted in the urine; the renal tubules active transport system facilitates rapid excretion of glucuronides (Fingl and Woodbury, 1975; Lees, 1972; Cornwell, 1969; Tiffeneau, 1915). An additional hepatic excretory pathway plays a minor role by actively eliminating glucuronides in the bile. This pathway may be cyclic, however, in that some of the end-product is excreted in the feces but most of the glucuronide is reabsorbed in the intestines and returned to the liver for eventual urinary excretion (Fingl and Woodbury, 1975).

Anesthetic Action of Chloralose

When general anesthesia is induced the intricate hemodynamic equilibrium which is autonomically maintained is subjected to profound alterations (Vatner, 1978; Merin, 1975; Clark and Mac Cannell, 1975; Brown, 1969; Etsten and

Li, 1960; Dobkin, 1960; Price, 1960). General anesthetics often exert depressant effects on the reflexes designed to respond to disequilibrium states. Alpha-chloralose is frequently used in cardiovascular research because it is reputed to maintain the integrity of the autonomic reflexes, and even to augment them (Liedtke, Urschel and Kirk, 1973; Seller and Schad, 1973; Cox, 1972a; Strobel and Wollman, 1969; Ginzel, 1968; Greisheimer, 1965; Brown and Hilton, 1956b; Koppermann, Brendel and Thauer, 1955; Vincent and Thompson, 1928). In the following sections, the cardiovascular and hemodynamic effects of alpha-chloralose will be reviewed. An approach to understanding the in vivo hemodynamic effects of this anesthetic would be to examine the recorded effects on commonly utilized hemodynamic parameters such as heart rate, electrocardiogram, blood pressure, total peripheral resistance, cardiac output and index and others.

Hemodynamics

Although values for arterial blood pressure and heart rate have not been standardized for dogs, a survey of "control" data in unanesthetized chronically instrumented resting dogs or trained, awake resting dogs, yields a baseline. Systolic pressure ranged from 118 to 136 mmHg

(Ferranio, Mc Cubbin and Page, 1969; Koppermann, Brendel and Thauer, 1955) while corresponding diastolic pressures were between 91 and 105 mmHg (Koppermann, Brendel and Thauer, 1955) with one reported low of 69 mmHg (Ferranio, Mc Cubbin and Page, 1969). Mean arterial pressure reported from four sources ranged from 87 ± 2 to 105 ± 4 mmHg (Jandhyala and Hamed, 1978; Cox, 1972a and 1972b; Ferranio, Mc Cubbin and Page, 1969).

The observation by Kirchheim (1976) that heart rate in the dog varies widely (as much as 80-90 bpm) in relation to the animal's parasympathetic tone seems to support data pooled from several authors. Resting heart rates range from 50 bpm (Kirchheim, 1976) to 100 bpm (Cox and Bagshaw, 1979; Jandhyala and Hamed, 1978; Ferranio, Mc Cubbin and Page, 1969; Van Citters, Franklin and Rushmer, 1964; Koppermann, Brendel and Thauer, 1955) in the dog.

Arterial blood pressure is often used for comparisons of hemodynamic effects and applied to many species. Abberencies such as seasonal variation, senile deterioration (Wiggers, 1944), and even factors such as the level of training (Ledsome, Linden and Norman, 1971; Ferranio, Mc Cubbin and Page, 1969) can contribute to fluctuations in the "normal" blood pressure in dogs. Similar difficulties in ascertaining the "normal" cardiac output

(Shabetai, Fowler and Hurlburt, 1963) and other hemodynamic measurements has plagued investigators and often times leads to unjustified assumptions (Rushmer, Van Citters and Franklin, 1963).

In addition, the magnitude of a pressor response whether experimentally induced or encountered naturally may be influenced by the initial blood pressure level (Davy et al., 1977; Pavlik, 1971; Brown and Hilton, 1956a). Cox and Bagshaw (1979) tested this hypothesis in five halothane-anesthetized dogs. The blood pressures in the anesthetized animals were increased to awake values with phenylephrine then responses to carotid sinus hypotension (by proximal occlusion of the common carotid or brachiocephalic artery) were recorded. They found significantly larger increases in mean arterial pressures in the dogs that initially had high blood pressure when compared to the anesthetized animals that did not receive a blood pressure increase with phenylephrine.

Heart Rate

Chloralose has often been cited as less deleterious than other anesthetics by researchers who have compared the hemodynamic effects of different agents (Sapru and Krieger, 1979; Parker and Adams, 1978; Cox, 1972a and 1972b;

Norman and Atkinson, 1970; Greisheimer, 1965; Shabetai, Fowler and Hurlburt, 1963; Smith et al., 1960; Koppermann, Brendel and Thauer, 1955). In this regard, it is surprising that the reports of the hemodynamic effects of this drug are so diverse. Chloralose has been reported to elicit a sustained tachycardia (Jandhyala and Buckley, 1977; Scher and Young, 1970; Harley, Behar and Mc Intosh, 1968; Shabetai, Fowler and Hurlburt, 1963; Smith et al., 1960; Brendel, Koppermann and Thauer, 1954), but in decerebrate rats treated with chloralose, a negative chronotropic effect was recorded (Sapru and Kreiger, 1979).

Part of the hemodynamic responses seen initially with chloralose have been attributed to a mild adrenergic action exerted directly by this anesthetic (Balis and Monroe, 1964; Vincent and Thompson, 1928). Charney, Bass and Buckley (1970) demonstrated experimentally that in alpha- and beta-receptor blocked dogs, as well as in catecholamine depleted dogs, the rise in blood pressure and heart rate associated with chloralose administration did not occur. These investigators attribute these early hemodynamic changes seen with chloralose to be (partly) mediated by catecholamines. Vincent and Thompsons' (1928) theory that a specific compound is formed from chloralose and endogenous catecholamines has been largely repudiated

(Milosevic, 1956). Although Millar and Morris (1961) have shown that circulating levels of catecholamines can increase in adrenalectomized dogs anesthetized with ether, halothane or cyclopropane, Roizen et al. (1978) found that this is not the case with chloralose. Chloralose, in fact, markedly depressed the usual profound increase in plasma catecholamines associated with decapitation in rats (Roizen et al., 1978).

Chloralose can be given in combination with other anesthetic agents, or given following a premedication, or given alone. Hence, the disagreement about the chronotropic effect of chloralose may reflect differences in methodology, rather than actual drug effect (Balis and Monroe, 1964). In addition, the basal state of the animal undergoing an anesthetic induction is known to alter sympathetic nervous system activity and thereby may camouflage the actual hemodynamic responses to the anesthetic agent. Although it is unclear what effects chloralose anesthesia has on plasma catecholamine concentrations in the dog, it is evident that the heart rates in calm, trained dogs (Cox, 1972a) or in morphinized dogs (Harley, Behar and Mc Intosh, 1968) undergoing a chloralose anesthetic are quite similar to resting levels (Ferranio, Mc Cubbin and Page, 1969).

ECG Effects

The major rhythm alteration seen with chloralose anesthesia is the conversion of a sinus arrhythmia into a regular sinus rhythm (Cox, 1972a; Hamlin, Smith and Smetzer, 1966; Greisheimer, 1965); the drug does not sensitize the myocardium (Greisheimer, 1965 citing Raymond-Hamet, M., Compt. Rend. 186:101, 1928). Shukla, Agrawal and Srivastava (1962) documented the pattern of the lead II electrocardiogram (ECG) change during an anesthetic period of slightly longer than 90 minutes. They first noted a progressive decrease to about 50 percent of the pre-anesthetic control, and then stabilization with occasional re-instatement of the sinus arrhythmia. No change was apparent in P-R interval or QRS duration. The time sequence of the ECG events was undisturbed from the pre-anesthetic controls which generally corresponds to the expected response in humans undergoing anesthesia. Greisheimer (1965) reported that with chloralose anesthesia there is a slight increase in P-wave, S-wave, and T-wave amplitude (citing Ludany, G. von, Arch. Exptl. Pathol. Pharmakol. 167:717, 1932). Sinus arrhythmia is considered a normal rhythm in resting or sleeping dogs (Hamlin, Smith and Smetzer, 1966) and is the rhythm characteristic of

chloralose-anesthetized dogs (Van Citters, Franklin and Rushmer, 1964). Fluctuations in the vagal efferent activity seems to be predominantly responsible for the occurence of the sinus arrhythmia (Hamlin et al., 1966), although sympathetic efferent activity may contribute (Hamlin, Smith and Smetzer, 1966). In this regard, the pre-anesthetic addition of morphine, a potent vagotonic drug (White, 1971), to chloralose may set the stage for the expression of this characteristic rhythm.

Arterial Blood Pressure

The effect of chloralose on the arterial blood pressure is reported as hypertensive (Korner et al., 1968; Bass and Buckley, 1966; Sardi and Scarselli, 1966; Alvarez-Buylla, 1949; Vincent and Thompson, 1928), hypotensive (Brezenoff, 1973; Sawaza, 1938; Raymond-Hamet, 1928), or as not fluctuating from control values (Danielson et al., 1975; Brown and Hilton, 1956b). Again, the diverse effects reported in chloralose anesthetized animals may be due to differences in methodology. Variation of the blood pressure, in chloralosed models, does provide some insite concerning this drug's effect on autonomic balance and regulatory reflexes.

Under chloralose anesthesia, the blood pressure response was exaggerated when epinephrine was injected (Griesheimer, 1965; Brown and Hilton, 1956a and 1956b; Vincent and Thompson, 1928), but responses to norephinephrine and isoproterenol were minor in dogs (Cox, 1972a). In rats, the pressor response to norepinephrine and reflex bradycardia was potentiated by chloralose although induction caused a transient hypotension and no alteration of the heart rate (Brezenoff, 1973). Cox (1972a) did report that the heart rate response to elevated or depressed blood pressure was exaggerated under chloralose.

Pressoreceptor Effects

Because of the integral relationships required to maintain the arterial blood pressure within a relatively narrow range, the effect of anesthetics on regulatory mechanisms has stimulated some investigation. Early work on the carotid and aortic baroreceptor reflexes using chloralose-anesthetized dogs was done in the 1930's by Heymans and his coworkers (Heymans, Delaunois and Heuvel-Heymans, 1953; Dripps and Dumke, 1943). Chloralose anesthetized animals provided the model for much of this early experimental work (Neil and Redwood, 1949; Schmidt, 1940; Marshall and Rosefield, 1936) but major support for

baroreceptor stability in chloralosed canines came from Koppermann, Brendel and Thauer (1955). In this elaborate study, using chronically instrumented dogs, the carotid sinus reflex was tested for degree of reactivity under different anesthetic agents. It was concluded that the response in chloralosed dogs to unilateral common carotid occlusion with sudden pressure application (200 mmHg, for thirty seconds) was essentially unchanged from the awake controls. This finding was unique to chloralose, as the results with two other anesthetics, hexobarbital and butallylanol, showed no reflex activity under comparably deep anesthetic levels.

In chloralosed anesthetized dogs, Brown and Hilton (1956a) showed that the baroreceptors reacted classically to common carotid artery occlusion. They further concluded that chloralose proved less devastating to baroreceptor regulation than other frequently used anesthetic agents, e.g., pentobarbital, diethyl ether and barbital. In a later study (Brown and Hilton, 1956b), evidence for augmentation of the baroreceptor reflex under chloralose was demonstrated by successively denervating the carotid and aortic baroreceptors, and then comparing the pre-denervation and post-denervation blood pressures with each animal serving as its own control. Others agree that

chloralose at least preserved or even augmented baroreceptor reactivity (Hamed and Jandhyala, 1978; Cox, 1972a; Greisheimer, 1965; Balis and Monroe, 1964; Van Citters, Franklin and Rushmer, 1964; Armstrong, Porter and Langston, 1961).

However, not all investigators accept that baroreceptor integrity is maintained with chloralose anesthesia. Neil and Redwood (1949) reported that carotid sinus nerve (CNS) stimulation elicited a pressor response. Although the dominant effect of chloralose was to inhibit the vasomotor center activity, some dimunition of peripheral baroreceptor sensitivity was shown. The increase in blood pressure seen was attributed to the excitation of the chemoreceptor afferents although no change in heart rate was demonstrated.

Killip (1963) found similar results in cats concluding that chloralose depressed baroreceptor afferents with sinus nerve stimulation to the point that the simultaneous chemoreceptor afferent stimulation was translated into the hemodynamic response typical of chemoreceptor excitation. Further investigations by Neil and Redwood (1949) using chloralosed dogs and rabbits yielded a marked reduction in blood pressure when carotid nerves were stimulated electrically.

When chloralosed cats were subjected to postural changes to evaluate their cardiovascular reflex activity, evidence of diminished vasomotor and peripheral baroreceptor activity was obtained (Hammond, 1971). Similarly, the tilt test in decerebrate rats tested with chloralose showed cardiovascular reflex compensation was impaired but not abolished (Sapru and Krieger, 1979).

Researchers recently have shown that chloralose anesthesia depresses the canine baroreflex response to acute carotid hypotension by nearly 60 percent from non-anesthetized values (Cox and Bagshaw, 1979). In their chronic study, although careful attention was given to preserve the homeostacity of the model, the premedication with morphine and atropine may have contributed to the differences found. In addition, species differences, the diversity in methodology and in experimental conditions undoubtedly contributes to the difference in baroreflex responses reported in chloralose-anesthetized animals.

Effects on Peripheral Resistance

Even though changes in total peripheral resistance are recognized as a cardiovascular regulatory mechanism, very few studies report the direct effect of anesthetics on vascular smooth muscle, and there are only occasional

reports of alterations in peripheral resistance in chloralose preparations. Mauck, Freund and Porter (1965) found that with chloralose anesthesia total peripheral resistance (TPR) varied with the dosage, i.e. in their lightly anesthetized group (53 mg/kg). TPR was more elevated than in the dogs which received a heavier dose, i.e., 98 mg/kg. The contractility of small blood vessels is reported to be normal after the administration of chloralose (Greisheimer, 1965, citing Chouppe, H. Bull. Med., Paris 8:85, 1894). Cox (1972a) reports that chloralose had no discernible direct action on vascular smooth muscle, as evaluated by TPR effects of beta-adrenergic stimulation before and after chloralose anesthesia.

Clark and Mac Cannell (1975) found chloralose to be unique among ten anesthetics tested on rabbit mesenteric portal vein or thoracic aortic strips in vitro. Although no agent exerted much effect on the arterial vessel strips, the inherent spontaneous activity characteristic of the venous specimens was modified by the different anesthetic agents. The rate and amplitude of spontaneous activity was decreased either initially or over time with all of the agents tested except chloralose. This agent increased activity in nine out of fourteen preparations and induced

no change in activity in the remaining five trials. Chloralose did not shift the noradrenaline dose response curves of either arteries or veins and chloralose did not seem to alter venous or arterial basal tone. It is noteworthy, that the concentrations utilized by these investigators were analgous to clinical anesthetic blood levels. In order to ascertain the autonomic contribution that might account for in vivo hemodynamic responses, i.e. peripheral vascular constriction of some agents, the effects of reserpine pre-treatment as well as H^3-noradrenaline washout curves were analyzed. In both cases, chloralose had no effect. These authors believe that the decrease in venous spontaneous activity (seen with all agents except chloralose) could result in venous pooling and be a contributory mechanism of hypotension which often accompanies general anesthesia. Hamed and Jandhyala (1978) found that the resting neurogenic tone of dogs hindlimb vasculature was identical under morphine-chloralose and pentobarbital; the morphine-chloralose dogs exhibited were more reactive vascular reflexes. Miller and Wiegman (1977) report that a urethane-chloralose anesthetic in intact rats seems to have a dual action on the microvasulature. Urethane causes an inhibitory response of the small vessels to norepinephrine, while chloralose, or the

chloralose-urethane combination elicits on "excitatory effect" which acts to functionally block neuronal uptake of norepinephrine. This may be a dominant feature of the urethane component, however, Monroe, Balis and Ebersberger (1963) report that hormone-induced small vessel responses are augmented by chloralose.

Myocardial Effects

The effect of chloralose on myocardial function has not been studied extensively in spite of the fact that it is often the anesthetic preparation of choice when contractility indices are being evaluated (Newell, Schmidt and Higgins, 1979; Grossman et al., 1971; Mehmel, Krayenbuehl and Rutishauser, 1970; Priola and Fulton, 1969; Wildenthal, Mierzwiak and Mitchell, 1969; Ng, Levy and Zieske, 1967; Levy et al., 1966; Degeest, Levy and Zieske, 1965; Veragut and Krayenbuehl, 1965). The data available, however, suggests that chloralose exerts a negative inotropic effect not only in heart-lung preparation (Bass and Buckley, 1966) but also in the intact animal (Parker and Adams, 1978; Leshin et al., 1972).

Attempts to quantify alterations in myocardial function using cardiac output and stroke volume have been numerous (Muir, 1977; Mauck, Freund and Porter, 1965;

Shabetai, Fowler and Hurlburt, 1963; Franklin, Van Citters and Rushmer, 1962; Wiggers, 1944), but not conclusive in the dog (Shabetai, Fowler and Hurlburt, 1963). More recently, left ventricular performance has been quantified by contractility indices measured during the isovolumic (Patterson, Kent and Peirce, 1972) and ejection (Mahler et al., 1975) phases of left ventricular systole. The maximum rate of rise of isovolumic pressure (max dP/dt or peak dP/dt) is a valuable guide to left ventricular inotropic status but can be altered by changes in preload and moderate changes in afterload or chronotropic status (Mason, 1969). However, this parameter is particularly useful in monitoring the changing inotropic state during the course of an experiment (Patterson, Kent and Peirce, 1972; Mason, 1969).

Further quantification of left ventricular contractile state has been accomplished by the maximal velocity of contractile element shortening at zero-load (Vmax). Although some researchers have challenged this parameters' independence from loading factors (Patterson, Kent and Peirce, 1972), it remains one of the most sensitive indicators of myocardial performance (Krayenbuehl, Hess and Turina, 1978; Mason, Spann and Zelis, 1970; Mason, 1969).

The cardiac output measurements under different types of anesthetics vary with the depth and duration of anesthesia (Mauck, Freund and Porter, 1965). Shabetai, Fowler and Hurlburt (1963) could not establish a normal relationship between cardiac output and body weight when dogs were anesthetized with either morphine-chloralose or pentobarbital. The most remarkable hemodynamic difference in the two types of anesthetics was found to be the heart rate response (Shabetai, Fowler and Hurlburt, 1963). Van Citters, Franklin and Rushmer (1964), concluded that pentobarbital had a significant positive chrontropic effect and that chloralose had less effect on baseline ventricular performance. These findings were further quantified by Cox (1972a and 1972b) in trained dogs.

In addition, Cox (1972b), documented that pentobarbital exerted a marginally significant decrease in stroke volume over time, as well as an attenuation to varying-dose isoproterenol challenges, indicating "at least an initial depression of cardiac muscle". His parallel study which substituted chloralose in the same experimental design yielded only transient hemodynamic variations with support for augmented presscreceptor reflexes demonstrated by beta-adrenergic challenge (Cox, 1972a).

Acute Induction Responses

Initially, the hemodynamic response to induction with chloralose is immediate and transient (Cox, 1972a) and includes the abolishment of pre-anesthetic sinus arrhythmia with an increase in heart rate (Cox, 1972a; Strobel and Wollman, 1969; Bass and Buckley, 1966; Greisheimer, 1965). Van Citters, Franklin and Rushmer (1964), however, reported no increase in heart rate, but did observe the same ECG rhythm change in their chronically instrumented dogs.

Since both the Cox (1972a) and Van Citters, Franklin and Rushmer (1964) studies utilized unpremedicated chronically instrumented dogs, the variation in heart rate response may be a function of the anesthetizing dose of chloralose. Van Citters, Franklin and Rushmer (1964) used an average of 60 mg/kg while an initial deeper level may have been accomplished by the 100 mg/kg dose that Cox used. Thus, the inclusion of a morphine premedicant seems to alter the pattern seen with chloralose alone, primarily by the preservation of the sinus arrhythmia (Shabetai, Fowler and Hurlburt, 1963).

Acute experiments reflect the hemodynamic stability of chloralose. Cox (1972a), found that sixty (60) minutes after

induction there was no significant difference between awake control and chloralose-anesthetized hemodynamic parameters. Van Citters, Franklin, and Rushmer (1964) found that chloralose offered a stable hemodynamic status for two hours after induction when they compared control and anesthetized values.

Although an early period of stability is seen after the initial effects dissipate, deterioration of hemodynamic stability has been reported in later stages. Bass and Buckley (1966) documented their most pronounced changes after two and one-half hours of chloralose anesthesia, in that the stroke volume and hence the cardiac output decreased significantly even though the hypertension and tachycardia which they saw from the end of the first hour of anesthesia were sustained. Van Citters, Franklin and Rushmer (1964) also documented a slight deterioration in hemodynamic status with prolonged anesthesia time. Cardiac output was maintained over the three hour anesthetic period, but at the expense of typical reciprocal changes in stroke volume and heart rate. In addition, aortic flow diminished with time, stroke work and power generated by the heart increased with induction but then stroke work decreased to a level slightly lower than that of the controls (Van Citters, Franklin and Rushmer, 1964).

According to Price (1960) these hemodynamic responses could represent compensatory action which preserved cardiac output by decreasing the kinetic work requirement.

A net decrease in cardiac output was observed by Shabetai, Fowler and Hurlburt (1963) in morphine-chloralose anesthetized dogs, but of perhaps more significance, was the finding that wide fluctuations occurred in sequential cardiac output determinations within one hour. (Arfors, Arturson and Malmberg, 1971; Shabetai, Fowler and Hurlburt, 1963). Arfors, Arturson and Malmberg (1971), however, found no net change with supplemented prolonged (6 hours) chloralose anesthesia. Although primary changes in contractility may not be reflected by alterations of cardiac output (Price, 1960), homeostatic compensations may sustain cardiac minute volume "in the face of a failing myocardium" (Price, 1960).

It is apparent that different chloralose anesthetic regimes exert somewhat variable effects in the anesthetized animal. Furthermore, there is undoubtedly some modification of the chloralose response when animals are premedicated with morphine. A biphasic response of the heart rate and blood pressure, i.e., an initial change then stabilization at baseline levels, seems to typify chloralose anesthesia in trained or morphinized dogs (Cox, 1972a;

Harley, Behar and Mc Intosh, 1968; Van Citters, Franklin and Rushmer, 1964; Armstrong, Porter and Langston, 1961). In chloralosed dogs, myocardial function seems to be only minimally altered initially but gradually deteriorates during the anesthetic course (Bass and Buckley, 1966; Van Citters, Franklin and Rushmer, 1964).

Respiratory Effects

The manifestation of quiet spontaneous breathing under chloralose anesthesia (Speakman and Babkin, 1949; Wang and Nims, 1947) supported the belief that chloralose anesthesia does not cause a covert respiratory depression (Strobel and Wollman, 1969; Parker and Adams, 1978; Greisheimer, 1965). The finding that chloralose causes central respiratory depression (Florez and Borison, 1969; Dripps and Dumke, 1943; Schmidt, 1940; Marshall and Rosenfield, 1936) but augments peripheral chemoreceptor activity (Brown and HIlton, 1956a and 1956b; Dripps and Dumke, 1943; Schmidt, 1940) seems to represent the compensatory mechanism which predominates during the anesthetized state.

Respiratory integrity in dogs under the influence of chloralose was evaluated by Koppermann, Brendel and Thauer (1955), by examining the effect of breathing 4 percent

carbon dioxide. These investigators found that chloralose anesthetized animals when compared to awake controls, had an attenuated respiratory response to this powerful central stimulant. Although this phenomena may be related to the anesthetic state (Prys-Roberts, 1980; Dripps and Dumke, 1943), the increased activity of the peripheral chemoreceptors seems to represent a specific action of chloralose (Brown and Hilton, 1956a; Dripps and Dumke, 1943; Schmidt, 1940) that protects the intact anesthetized animal from respiratory depression.

A variable heart rate response to chemoreceptor stimulation has been reported in dogs; spontaneously breathing animals exhibit cardioacceleration while bradycardia accompanies animals that are mechanically ventilated and the carotid bodies are stimulated (Killip, 1963). Haymet and Mc Closkey (1975) found that cardiac slowing occurred when carotid chemoreceptors received stimulation during expiration but elicited no effect on heart rate if administered during inspiration.

The respiratory rate is often used to gauge the depth of anesthesia, despite the known differential effects of general anesthetics. Normal values for respiratory parameters in canines are not well documented, but the established normal range for respiratory frequency is

between ten and forty breaths per minute (Kleinman and Radford, 1964). Arfors, Arturson and Malmberg (1971) suggest that a rising $PaCO_2$ with a decreasing breathing frequency indicate a dynamic change in the depth of anesthesia, and Koppermann, Brendel and Thauer (1955), noted that very deep levels of chloralose anesthesia were associated with deep, periodic respirations. The decrease in respiratory rate was found to be due to a lengthening of the expiratory phase of the respiratory cycle (Florez and Borison, 1969). Florez and Borison (1969) also found that a one mg/kg dose of morphine reduced breathing frequency and that both morphine and chloralose significantly elevated apneic thresholds in decerebrate cats. More specifically, the mechanism responsible for slowing respiratory frequency (pentobarbital anesthetized cats) has been demonstrated to involve diencephalic structures, most prominantly, the anterior hypothalamus (Feldberg and Myer, 1965).

Results due to species differences are described by Dripps and Dumke (1943) suggesting that central respiratory responses are more depressed in cats than dogs. Although the effect of chloralose on respiratory rate and pattern is altered from that in awake animals, the tidal volume apparently is not effected (Florez and Borison, 1969).

A more quantitative measure of respiratory adequacy in the anesthetized model would be the determination of the arterial blood gases which allows the assessment of the adequacy of oxygenation and ventilation. Other methods have been employed (Serendenko, Il'chevich and Bershtein, 1974; Bond, Roberts and Manning, 1973; Garcia and Cherniack, 1968) but examination of the arterial blood gases offers a reliable, readily available standardized method for evaluation of respiratory and acid-base status (Danielson et al., 1975; Feigl and D'Alecy, 1972).

The respiratory and acid-base responses of anesthetized animals vary with the level of anesthesia (Folle and Levesque, 1976), and often times, in the absence of ventilatory support, this can be a labile state compounded by hypoxia. Hypoxia is an all too frequent companion in anesthetized animals and its specific consequences have been thoroughly investigated (Sylvester et al., 1979; Vatner, 1978; Borgia and Horvath, 1977; Morrill, Meyer and Weil, 1975; Carrell and Milhorn, 1971; Krasney, 1971; Koivikko, 1969; Garcia and Cherniack, 1968; Korner et al., 1968; Thilenius, 1966; Kontos et al., 1965; Swank and Foley, 1948). The advantage of assessing oxygenation as well as acid-base status in anesthetized experimental animals cannot be disputed (Bagshaw and Cox, 1975;

Danielson et al., 1975). Thilenius (1966) emphasizes that the normal physiological compensations to hypoxia are "markedly protracted" during anesthesia, because "anesthesia apparently eliminates the initial, rapidly mobilized defenses to this stress".

Many authors report that chloralose anesthesia does not influence normal oxygenation (Arfors, Arturson and Malmberg, 1971; Ledsome, Linden and Norman, 1971; Greisheimer, 1965; Griffith, Emery and Lockwood, 1940). The "normal" range for PaO_2 values in unanesthetized dogs is 80-114 mmHg (Kendrick and Matson, 1979; Danielson et al., 1975; Feigl and D'Alecy, 1972; Ledsome, Linden and Norman, 1972; Fukuma et al., 1970). However, it has been shown that a morphine-chloralose anesthetic regime produces a sustained hypoxia (Folle and Levesque, 1976), which could contribute to a pronounced metabolic alteration (Ledsome, Linden and Norman, 1971) during a long-term course of anesthesia.

Metabolic Effects

The oxygen consumption has been of interest to investigators evaluating pulmonary responses and metabolic interference of depressant drugs. It is used as an index of the metabolic condition (Griffith, Emery and Lockwood,

1940) and is affected by individuality, sex, season of the year and the animal's body temperature, but not affected by the duration of anesthesia. Although Griffith, Emery and Lockwood, (1940) did see a 7 percent increase in oxygen consumption in chloralose anesthetized cats, they concluded that the agent itself was not responsible for significant metabolic disturbance during a four hour anesthetic course. Thilenius (1966) observed that in spontaneously breathing dogs under four-hours of chloralose-urethane anesthesia, oxygen consumption, respiratory minute volume, respiratory rate, systemic blood pressure and heart rate were constant. Arfors, Arturson and Malmberg (1971) similarly found no significant change in oxygen consumption or cardiac index in chloralose anesthetized dogs. However, a 15 percent decrease in the resting metabolic rate of chloralosed dogs has been reported (Sharp and Hammel, 1972). Interestingly, although Serendenko, Il'chevich and Bershtein (1974) found a 16 percent decrease in oxygen consumption when they anesthetized dogs with 60-80 mg/kg alpha-chloralose, they also noted a proportional decrease in arterial oxygen saturation which served to preserve the "balance between oxygen supply and consumption". Bond, Roberts and Manning (1973) attributed the lower oxygen consumption values seen with

chloralose-urethane to the more basal state produced by anesthesia as compared to values characteristic of awake, resting, trained dogs (Bond, Roberts and Manning, 1973).

Thermoregulatory Effects

Kumar et al. (1977) have recently re-itinerated the linear relationship between oxygen consumption and body temperature. Chloralose anesthesia has been associated with both a gradual decrease (Feldberg and Myers, 1965) and with gradually increase in body temperatures (Danielson et al., 1975). The weight of evidence is more supportive of an anesthetic state accompanied by hypothermia (Dripps, Eckenhoff and Vandam, 1972; Blair, 1971; Feldberg and Myer, 1965). If hyperthermia is seen, it may be due to the infusion of warmed chloralose solution which, if dissolved in normal saline must be administered at temperatures greater than room temperature to avoid precipitation (Ledsome, Linden and Norman, 1971; Strobel and Wollman, 1969; Van Citters, Franklin and Rushmer, 1964).

In chloralose anesthetized dogs body temperature often drops to 32°C (normal range = 37° to 38°C) (Blair, 1971). At this level, thermoregulatory activity, cerebral and skeletal muscle blood flow have been found to be depressed while no changes were reported for the activity

of other major organ systems (Blair, 1971). In addition, excessive premedication may directly impair thermoregulation (Blair, 1971). Blair (1971) reports that hypoxia accompanies temperatures within the hypothermic range (0° to 35°C); which if unrecognized and uncorrected could lead to acidosis. The mechanisms that may be involved, according to this author, include: (1) ventilation/perfusion inequality, (b) hypoglycemia, (c) enhanced anesthetic effect by the hypothermic state--which occurs with both morphine and chloralose, and (d) a diminished ability for heat production which accompanies hypoxia and hypercarbia.

The hypothermia which is seen in conjunction with chloralose anesthesia has been shown to be related to depressed anterior hypothalamic release of neuroregulatory amines such as 5-HT (Feldberg and Myer, 1965). Although, hypothermia may normally accompany the anesthetic state, a wider variability in temperatures has been noted in dogs anesthetized with chloralose, as compared to pentobarbital anesthesia (Blair, 1971) which tends to support the idea that chloralose specifically alters thermoregulation. Indeed, shivering, which may appear as a late defense in response to hypothermia, is said to be

characteristic of chloralose anesthetized mammals (Halkola, Koivikko and Lansimies, 1974).

Acid-Base Alterations

Many anesthetic agents are responsible for alterations in acid-base status (Bunker, et al., 1951). Chloralose anesthesia does not appear to exert a depressant effect on the oxygenation or oxygen transport function of the blood (Serendenko, Il'chevich and Bershtein, 1974; Chakrabarti, 1956), or on the metabolic status other than conferring a slight (32 C) hypothermia. However, this anesthetic is frequently associated with a non-respiratory acidemia (Arfors, Arturson and Malmberg, 1971; Berglund, Nylen and Wallentin, 1965) in dogs, especially as the length of anesthesia time increases (Danielson et al., 1975 Arfors, Arturson and Malmberg, 1971; Ledsome, Linden and Norman, 1971). In rats, a mild respiratory acidosis compounded by hypoxia accompanied morphine-chloralose anesthesia (Folle and Levesque, 1976). Ledsome, Linden and Norman (1971) contend that the metabolic disturbance with chloralose was attributable to a "dilutional acidosis" (Shires and Holman, 1948) iatrogenically introduced by the use of 0.9 percent NaCl solvent for chloralose. In fact, when these

investigators buffered the solvent, their animals did not develop acidemia (Ledsome, Linden and Norman, 1971).

Arfors, Arturson and Malmberg (1971), however, noted a progressive acidemia irregardless of the solvent utilized, although they did not actually buffer standard solvents (PEG, 0.9 NaCl, borate) as Ledsome and coworkers (1971) did. The major physiological concern should be aroused during long-term anesthesia, when a progressive acidosis can wield significant influence (Arfors, Arturson and Malmberg, 1971). It has been noted that the respiratory compensatory mechanisms remain operative in chloralose anesthetized animals, and the severity of metabolic acidosis has been offset by this defense (Danielson et al., 1975). More profound alterations yielding mixed acid-base disturbances would be expected in the event that this compensatory ability were removed. Premedication, or induction with more rapidly acting drugs such as thiopental or halothane, especially in the spontaneously breathing animal (Bagshaw and Cox, 1975) under chloralose anesthesia compounds the responses seen with chloralose alone.

Mechanical ventilation has become an accepted and predominant adjunct during the course of experimental

investigation (Bagshaw and Cox, 1975), although positive pressure ventilation does have physiological impact (Cox and Bagshaw, 1979).

Many investigators directly measure the base deficit and supplement chloralose anesthesia with the infusion of buffers (Kendrick, Matson and Lalley, 1979; Kendrick and Matson, 1979; Thames et al., 1978; Bagshaw and Cox, 1975). A number of researchers, though, routinely give empiric dosages of buffer solutions throughout the experimental period (Cox and Bagshaw, 1979; Powell and Feigl, 1979; Sedin, 1976) in an effort to combat the expected acidosis when chloralose is the major anesthetizing agent.

Summary

In summary, it is apparent from the literature cited that despite the fact that morphine-chloralose anesthetic preparations are frequently employed in experimental research little is known about the cardiopulmonary stability of this combination. This study seeks to answer questions regarding the stability of four types of morphine-chloralose anesthesia protocols.

CHAPTER III

METHODS AND MATERIALS

The cardiopulmonary consequences of prolonged chloralose anesthesia were investigated in a two-phase study. A total of twenty mongrel dogs (10-25 kg) of either sex, were utilized to assess the dose-related effects of two different chloralose anesthetic maintenance regimes and to assess the need for ventilatory support during long-term chloralose anesthesia.

Experimental Protocol

The induction of anesthesia and intra-operative handling was the same for each regime. Each dog was narcotized with 5 mg/kg of morphine sulfate (subcutaneously) thirty minutes before general anesthesia was induced. An intravenous route was established and kept open throughout the experiment with 5 percent dextrose in water. A slow intravenous infusion of 80 mg/kg of warmed alpha-chloralose was used for the induction of anesthesia. Following induction, each dog was restrained in the dorsal recumbant position and intubated with a cuffed endotracheal tube. After securing the airway, the hair of the animal was

clipped in the appropriate areas to allow bilateral femoral arteriotomies and a right axillary arteriotomy. Stainless steel electrodes were placed in order to continuously record the Lead II electrocardiogram (ECG).

With the right and left femoral arteries isolated, the retrograde catheterization technique allowed placement of 5 Fr. and 6 Fr. Milliar Mikro-tip® pressure transducers (Model No. PC-350 A) in the left ventricle and ascending aorta, respectively. The maximum rate of change of left ventricular pressure was obtained electronically by an R-C differentiator circuit. Right axillary artery cannulation permitted serial blood gas sampling. Patency was insured by the intermittent irrigation with a dilute heparinized 0.9 percent sodium chloride solution.

Experimental Design

Phase I

The ten dogs assigned to this part of the study were designated as either Regime I (five dogs) or Regime II (five dogs). The Regime I dogs received 80 mg/kg of alpha-chloralose as an initial dose (I.D.), followed by the hourly infusion of 16 mg/kg (20 percent I.D.) for twelve hours. These animals were allowed to ventilate spontaneously, breathing room air. Following the same

induction protocol, the Regime II dogs were maintained for the twelve hours by the hourly infusion of an incrementally increasing dose from 16 to 40 mg/kg (20-50 percent I.D.). This group was also allowed to breathe spontaneously.

The general hypothesis tested in Phase I was that a significant difference in the cardiopulmonary stability between chloralose anesthetic maintenance Regimes I and II would be found. The specific differences between Regime I and Regime II were evaluated by comparing the cardiac contractility, cardiovascular and pulmonary parameters of the two Regimes.

Phase II

After the standardized induction with 80 mg/kg of alpha-chloralose, the surgical procedures were carried out as established by the experimental protocol. The ten dogs in this part of the study were maintained throughout the twelve hours by the same total dose of anesthetic that the Regime II dogs received. However, the method of administration was altered from the hourly infusion technique, to a constant infusion technique utilizing a Harvard Apparatus Compact Infusion Pump, Model 975, for the purpose of maintaining a more constant blood level of

the anesthetic drug. In addition, Regime III (five dogs) were allowed to breathe room air spontaneously, while the remaining five dogs, designated Regime IV, were mechanically ventilated on room air throughout the twelve hours. A Harvard Apparatus Dual Phase Control Respirator Pump, Type NSH-34 R-11, was used and ventilatory adjustments were made as necessary to keep the pH $\geq$ 7.3 and the $PaCO_2$ in the 35 to 45 mmHg range.

The hypothesis tested in Phase II was that there would be differences between spontaneously ventilated and mechanically ventilated chloralose anesthetized dogs.

Data Collection

The data recorded hourly included the aortic pressure, left ventricular (LV) pressure and its derivative, the Lead II ECG and the arterial blood gases (ABGs). In addition, the aortic systolic pressure (ASP), aortic diastolic pressure (ADP), pulse pressure (PP), left ventricular fill pressure (LVFP), the maximum rate of rise of LV pressure (peak dP/dt), percent change of max dP/dt, heart rate (HR) and rhythm were analyzed from the hourly records. Changes in cardiac contractility were assessed every other hour by plotting $(dP/dt)/(P \times K)$ vs.

Developed Pressure (Vmax) and by computing the V_{CE} at 40 mmHg developed pressure (V_{40}).

Simultaneous recordings of the cardiovascular parameters were made on an 1858 Honeywell Visicorder, at a paper speed of 200 mm/second, on 1/4 inch electromagnetic tape using A. R. Vetter Tape Recording System (Redersberg, PA). A continuous 12-hour record was recorded at a paper speed of 25 mm/second, on an R-611 Beckman Dynograph (Beckman Instruments, Schiller Park, IL).

A Radiometer BMS-3 MK 2 Blood Microsystem and PHM 71 MK 2 Acid-Base Analyzer were used to measure the hourly pH, $PaCO_2$ and PaO_2. The plasma HCO_3^- level was calculated for each hour by plotting the pH and $PaCO_2$ on a Siggard-Andersen Alignment Nomogram.

Each hour of the experiment was concluded by recording all of the aforementioned cardiac and pulmonary parameters. The data was consistently recorded at the end of expiration for a duration of at least ten cardiac cycles.

Methods for Measurement

Cardiovascular Data

The hourly means for each animal were obtained by averaging measurements from three consecutive cardiac cycles. Vertical calibration factors in mmHg/cm rise were

computed from 100 mmHg reference calibrations documented for each catheter, e.g., aortic and LV, for all regimes. The height in centimeters (cm) of the calibration was divided into 100 to obtain the pressure value represented by each vertical centimeter. The need for recorded hourly reference calibrations was realized after an initial review of the Regime I data revealed a distinct catheter shift apparent in the aortic catheter. Only in the first dog (#39) of Regime I were the calibrations recorded at the beginning of the experiment and the computed vertical calibration factor used throughout. Thereafter, a reference calibration was recorded with each data run so that a vertical calibration factor could be computed hourly.

Along the horizontal axis, time-duration of events was determined by dividing the interval duration by the mm/sec paper speed used during data recordings. The standard recording speed was 200 mm/sec, but it was re-checked manually by measuring the distance between one second time lines and dividing that value into one second. This horizontal calibration factor was useful when determination of the interval duration for an event was needed.

Heart Rate

The three cardiac cycles of longest duration were used in order to obtain the mean end-expiratory hourly heart rate. The distance in centimeters between two consecutive R-waves was divided by the paper speed used during the recording. Heart rate was determined from the R-R interval on the basis of the inverse relationship between HR and R-R (HR = 1/R-R).

Aortic Systolic Pressure

It was necessary to make the assumption that peak ASP was equivalent to peak LV systolic pressure, because of the variability in the aortic Millar catheter. The lowest point of the LV waveform occurring early in the rapid fill phase was used as the baseline (zero) reference point. A straight horizontal line was drawn through this point. LV systolic pressure was determined by measuring a perpendicular to this baseline which was extended through the peak of the LV waveform. ASP was expressed in mmHg by multiplying this value by the LV vertical calibration factor.

Pulse Pressure

The pulse pressure was measured along the perpendicular from the peak of the aortic pressure waveform to a straight horizontal baseline which bisected the lowest point of the aortic waveform just before the generation of pressure. Multiplication of this directly measured value by the hourly aortic vertical calibration factor allowed expression of the pulse pressure in mmHg.

Aortic Diastolic Pressure

This value was calculated by subtracting the raw PP (cm) from the raw ASP (cm) and converting it to a pressure value using the specific hourly aortic vertical calibration factor.

Left Ventricular Fill Pressure

In order to calculate this parameter, the assumption was made that the difference between left ventricular end-systolic and end-diastolic pressures was equivalent to the left ventricular filling pressure. The lowest point of the LV waveform occurring in the rapid fill phase was used as the baseline (zero) end-systolic reference point. A straight horizontal line was drawn through this point.

The point of end-diastole was determined to be at the end of atrial systole, and was identified by drawing a straight vertical line that bisected the peak of the QRS complex. This vertical line was extended to bisect the horizontal baseline and the distance from the baseline to the LV waveform was measured in centimeters and converted, utilizing the LV vertical calibration factor, to express the value in mmHg pressure.

Maximum dP/dt

A measurement from the baseline of the dP/dt tracing to the apex of the waveform constituted max dP/dt in centimeters. In order to determine the rate of rise (mmHg) of LV pressure per unit time, the rate of pressure development was calculated, and this value was then divided by the max dP/dt. This process yielded a 'conversion factor' which served as a standard for the amount of pressure (mmHg) represented by each vertical centimeter of the dP/dt deflection. By multiplying subsequent raw (cm) dP/dt values by the conversion factor, max dP/dt or the rate of rise of LV pressure, was calculated. Each hour the average raw max dP/dt from three cardiac cycles was converted, and an hourly mean max (or peak) dP/dt was recorded.

A 'conversion factor' for the rate of pressure development was determined from measurements of one cardiac cycle for each dog by:

1. A straight line was drawn closely adherent to the ascending limb of the LV waveform.

2. A straight vertical line, bisecting the Visicorder paper, was drawn to the right of this angled line so as to form an acute angle at an arbitrary point above the LV waveform.

3. At the point where the two lines were one centimeter apart, a straight horizontal line was drawn as a baseline.

4. The vertical height in centimeters along the vertical axis from the point of baseline intersection to the point of apex intersection was converted to mmHg pressure using the appropriate LV vertical calibration factor.

5. The horizontal distance between the two lines (predetermined at one centimeter, for ease of calculation) represents the time required to develop peak pressure, and when multiplied by the horizontal calibration factor, yields the time in seconds required for the pressure to develop.

6. Finally, the 'conversion factor' was computed by dividing the time required for pressure development

(mmHg/sec) by the raw max dP/dt value (cm) and expressed as mmHg/cm rise of the dP/dt waveform.

Vmax and V_{40}

Three consecutive cardiac cycles from seven of the twelve hours (hours 1, 2, 4, 6, 8, 10 and 12) were evaluated using contractility indices. The velocity of the contractile element shortening (V_{CE}) was computed from this formula: $(dP/dt)/(P \times K)$, where dP/dt is the rate of pressure development, P is LV developed pressure and K is a constant (28) for the series elastic element. Extrapolation of the V_{CE} at zero load (Vmax) was accomplished by Linear Regression Analysis (Y = 0). The velocity of contractile element shortening at 40 mmHg was likewise retrieved by predicting a Y = 40 value for the Regression line.

The computation of V_{CE} followed this procedure:

1. A straight horizontal line was drawn to bisect the LV waveform at the beginning of isovolumic contraction.

2. A straight horizontal line was drawn through the dP/dt waveform, dividing it into it's positive and negative deflections. These two lines served as the origin for the ensuing vertical measurements for LV and dP/dt, respectively.

3. The point representing a generation of 20 mmHg pressure on the LV waveform was marked and a vertical line bisecting that point was drawn and extended through both the LV and dP/dt waveforms.

4. To the right of this line, twelve parallel lines one mm apart, were drawn so that each line bisected both waveforms.

5. LV developed pressure (DP) was measured from the origin to the point where the vertical line bisected the LV waveform. Hence, for each cardiac cycle (3/hr) thirteen LV DP points were recorded. Similarly, corresponding values for dP/dt were measured along each of the thirteen vertical parallel lines, from its respective baseline. Both of these values were measured in millimeters and converted to centimeters. At a specified pressure, the V_{CE} for the two points could be determined.

Computations:

A. The LV developed pressure value in centimeters was multiplied by the LV vertical calibration factor to yield developed pressure in mmHg/sec.

B. The corresponding raw dP/dt in centimeters (adjusted for lag time*) was treated similarly to yield a value also expressed in mmHg/sec. This was accomplished

by multiplication of the raw dP/dt by the previously calculated dP/dt 'conversion factor', standardized for each dog.

C. *Careful review of the time sequence of the LV and dP/dt records revealed that the LV differentiator circuit exhibited a time lag of about 10 msec. The adjustment was made by shifting all dP/dt measurements to the right 2 millimeters (10 msec). The value for the LV developed pressure was recorded. The corresponding dP/dt value was adjusted for the observed time lag by recording the value 2 millimeters to the right. Thus, a pair of numbers were recorded for calculation of V_{CE}, but their correspondence was adjusted 10 msec.

Pulmonary Data

The blood gas analysis machine was calibrated to the barometric pressure prior to any data collection. Each hour, before the arterial blood gas analysis, the pH, $PaCO_2$ and PaO_2 ranges were recalibrated to insure that the electrodes were accurate and the celophane membranes intact.

Data Analysis

All data was analyzed on the Texas Woman's University Computer System, using the TOPS-20 M IPS Statistical

Program. Mean values for the cardiovascular and pulmonary parameters were evaluated hourly in all regimes by the Student's t Test, using the 'NGROUP' IPS Program. Differences between Regime I and Regime II were evaluated for statistical significance by Student's t analysis of the hourly means. The data for Regime III and Regime IV were analysed hourly by the same statistical method.

The contractility indices, Vmax and V_{40} were computed by entering the V_{CE} values into a Linear Regression Analysis IPS 'REGRES' Program with a predicted Y = 0 and Y = 40, respectively. The regression lines (slopes and intercepts) were then compared between Regime I and Regime II as well as Regime III and Regime IV by the Student's t Test.

CHAPTER IV

RESULTS

The purposes of this study were to quantify cardiopulmonary differences produced by two specific chloralose anesthetic maintenance regimes (Phase I), and to evaluate the effects of mechanical ventilation in a tried chloralose maintenance regime (Phase II). Each phase of the study utilized ten mongrel dogs (either sex) and was further divided into five-member treatment regimes.

In Phase I of this study Regime I (R-I) dogs received 16 mg/kg/hour (20 percent initial dose, I.D.), and Regime II (R-II) animals received 16-40 mg/kg/hour (20-50 percent I.D.). The Phase I animals were allowed to breathe spontaneously.

In Phase II, Regime III (R-III) and Regime IV (R-IV) dogs were maintained by the constant infusion of chloralose at the same dosage schedule as the R-II dogs, but the R-III dogs were allowed to breathe spontaneously and R-IV dogs were mechanically ventilated.

Phase I

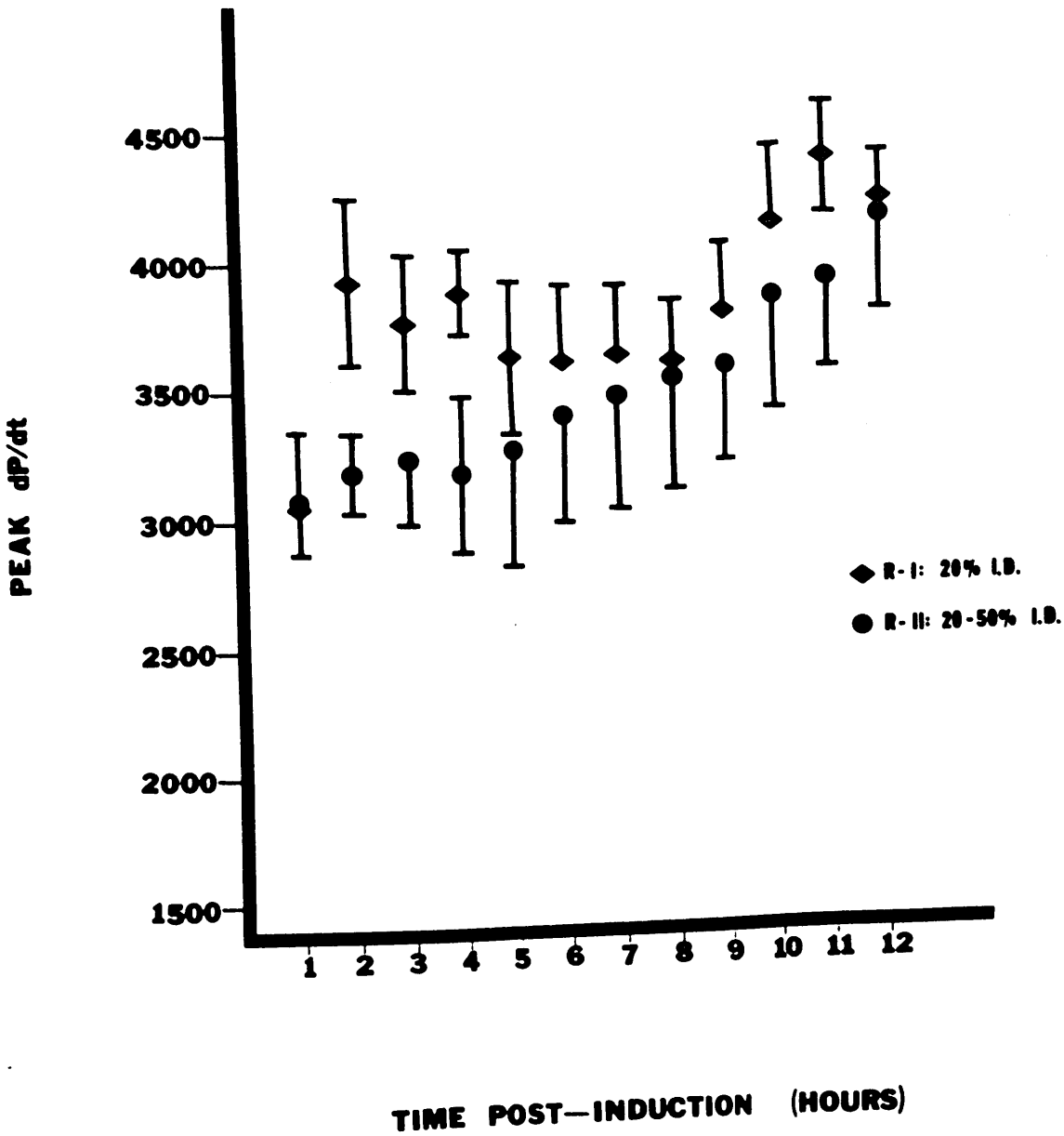
Changes in cardiac contractility were assessed by the hourly comparisons of percent change of the maximum rate of

peak dP/dt, rise of left ventricular pressure (max dP/dt) and every two hourly comparisons of the maximum velocity of contractile element shortening at zero load (Vmax) and velocity of contractile element shortening at 40 millimeters of mercury (mmHg) pressure (V_{40}). The means were compared and in general, no significant differences were noted. However, differences were occasionally noted and trends observed.

The maximum dP/dt or peak dP/dt values of Regime I and Regime II were statistically compared. Although no significant differences were found, an interesting pattern characterized this parameter when different doses of chloralose were used for maintenance of anesthesia. The first hour mean values were not statistically different but thereafter, all of the Regime I mean values exceeded the Regime II mean values. The range for the R-I means was 3072 ± 209 mmHg/sec to 4388 ± 213 mmHg/sec. The Regime II values ranged within 3078 ± 277 mmHg/sec to 4148 ± 364 mmHg. The means gradually increase linearly with time although in Regime I, the 11th hour value is the highest and the 12th hour mean is somewhat decreased from this peak value (Figure 2).

The mean values of percent change of max dP/dt for both R-I and R-II were increased from the initial values,

Figure 2: Peak Rate of Rise of the First Derivative of Left Ventricular Pressure vs. Time Post-Induction.


PEAK dP/dt
4500
4000
3500
3000
2500
2000
1500
1 2 3 4 5 6 7 8 9 10 11 12
R-I: 20% I.D.
R-II: 20-50% I.D.
TIME POST—INDUCTION (HOURS)

so all the means are expressed as positive percent change plus-or-minus the standard error about the mean. The range for the R-I dogs was between +19.0 ± 7.8 and +44.9 ± 9.3, while the R-II dogs ranged from +5.1 ± 11.6 to +36.0 ± 9.7 percent change from initial values. In the first comparison (Figure 3) between these two groups (hour 2) a significant difference ($P < 0.04$) was found and although no other significant differences existed, the mean values for the R-II dogs were consistently lower than those for the R-I animals.

Likewise, Figure 4 and Figure 5 demonstrate that the mean Vmax and V_{40} values in the R-II dogs were consistently lower than those of the R-I animals. The range in Vmax values for R-I encompassed 1.53 ± 0.17 to 1.81 ± 0.19; the V_{40} values for these dogs fell within a 1.52 ± 0.11 to 1.66 ± 0.13 range. In R-II, the Vmax values ranged from 1.59 ± 0.17 to 1.72 ± 0.20 and the V_{40} values ranged between 1.43 ± 0.06 and 1.50 ± 0.08. In both R-I and R-II, a pattern of chronological stability was seen in each of the four contractility parameters measured.

Other cardiovascular parameters evaluated at hourly intervals include heart rate (HR), aortic systolic pressure (ASP), aortic diastolic pressure (ADP), pulse pressure (PP)

Figure 3: Percent Change of Maximum Rate of Rise of the First Derivative of Left Ventricular Pressure vs. Time Post-Induction.

Figure 4: Velocity of Contractile Element Shortening at Zero Load vs. Time Post-Induction.

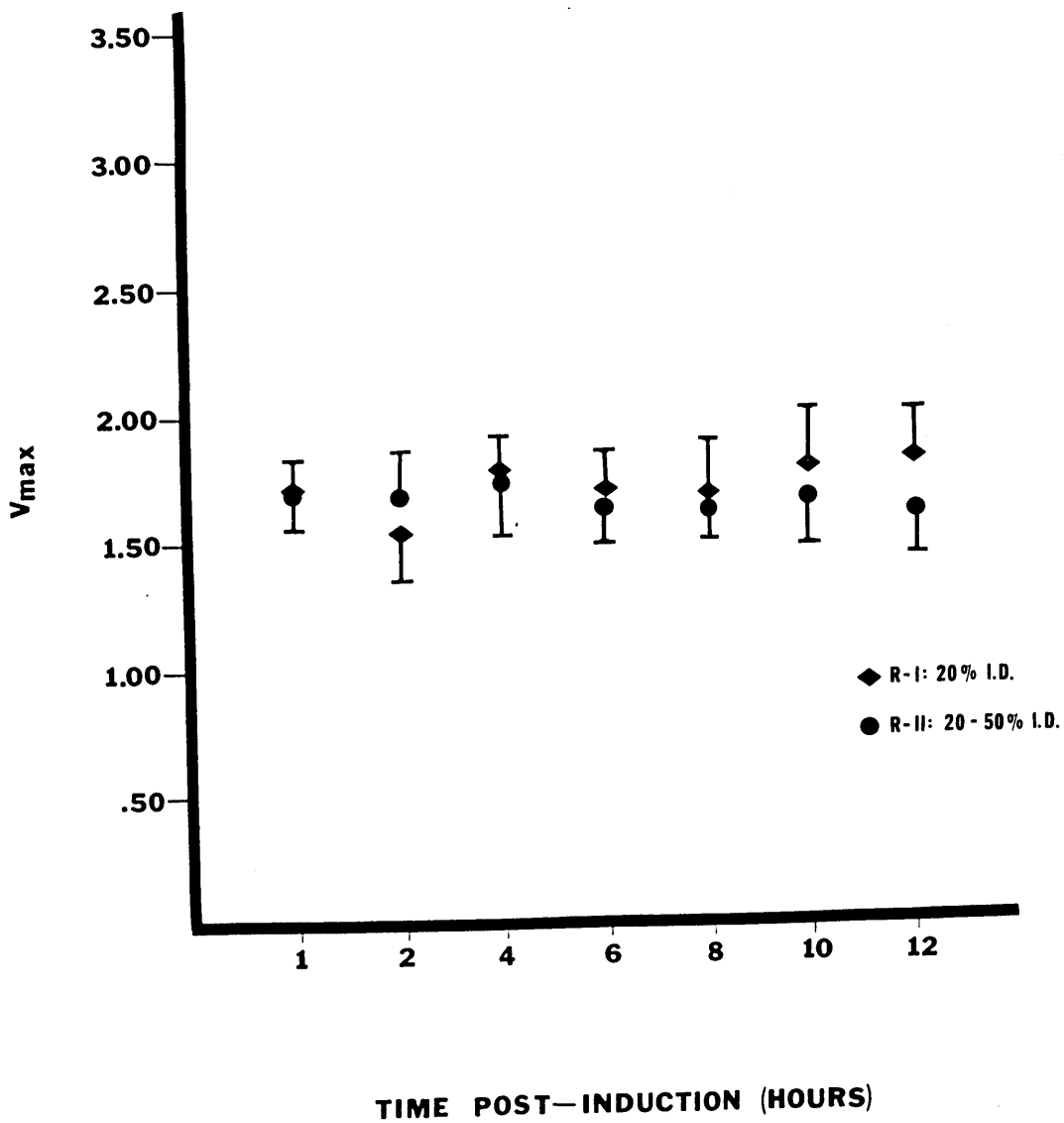
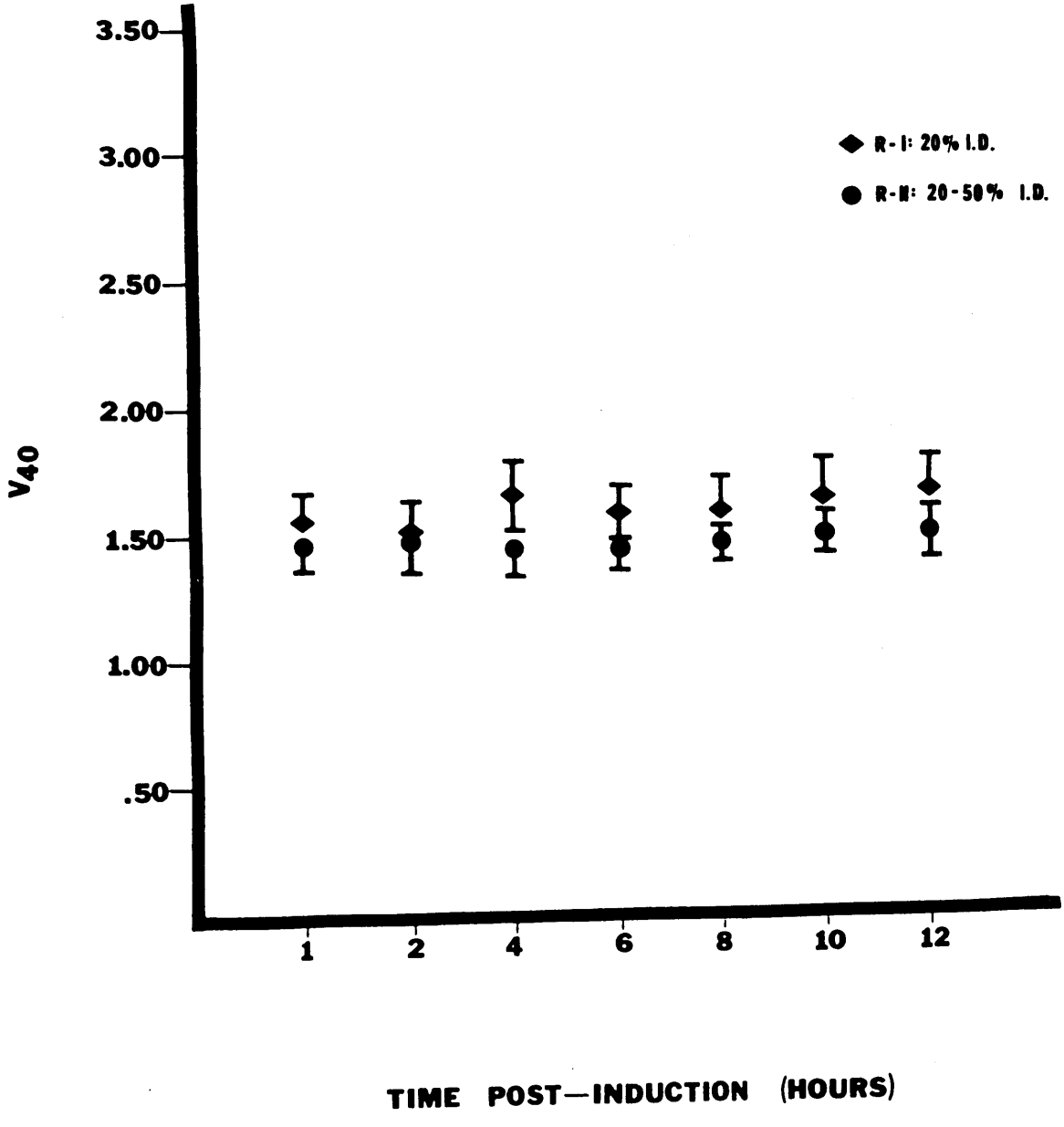

3.50
3.00
2.50
2.00
1.50
1.00
.50
Vmax
1
2
4
6
8
10
12
R-I: 20% I.D.
R-II: 20 - 50% I.D.
TIME POST—INDUCTION (HOURS)

Figure 5: Velocity of Contractile Element Shortening at 40 mmHg Developed Pressure vs. Time Post-Induction.

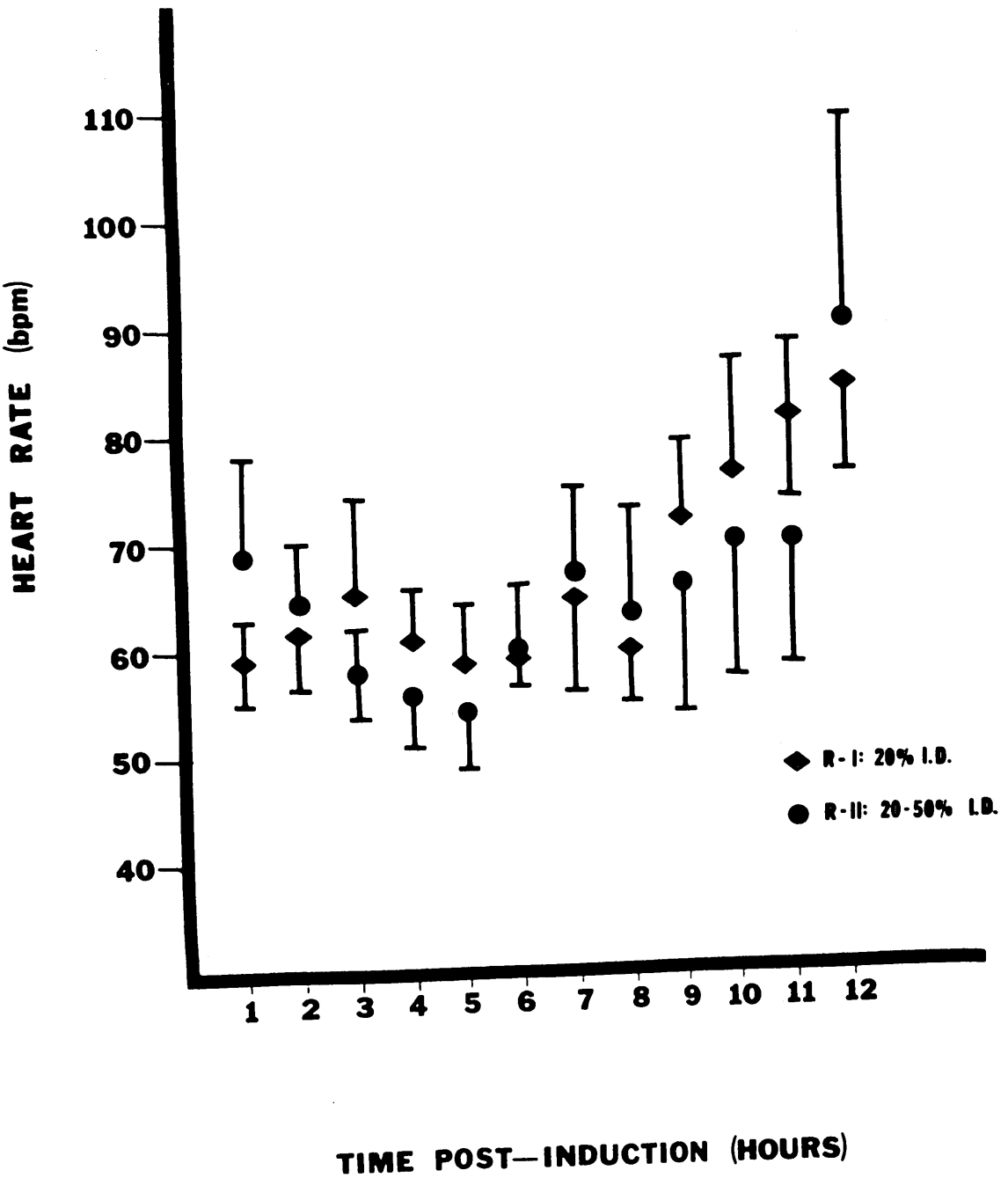

3.50
3.00
2.50
2.00
1.50
1.00
.50
V40
R-I: 20% I.D.
R-II: 20-50% I.D.
1
2
4
6
8
10
12
TIME POST—INDUCTION (HOURS)

and left ventricular fill pressure (LVFP). A simple rhythm analysis was made hourly using the lead II electrocardiogram (ECG).

The heart rate range from 58.4 ± 5.6 to 84.0 ± 8.0 beats per minute (bpm) of R-I dogs and from 54.0 ± 5.5 to 90.2 ± 17.3 bpm of R-II dogs were quite similar, showing no significant differences between the two dosage regimes in any of the twelve hours. Both groups exhibit a similar pattern and gradually developed borderline bradycardia by the fourth-through-sixth hours. Then the heart rates steadily increased until hour ten (Figure 6). By the twelfth hour, a mild tachycardia occasionally was seen in both regimes, although the mean heart rates were in the eighties and nineties.

No statistical comparisons were applied to the ECG data except for HR, rather, analysis was accomplished by careful review of each permanent hourly record. In the R-I dogs, the prevalent ECG rhythm was a sinus arrhythmia (respiratory-heart-rate response) with occasional, intermittent junctional activity, either isolated prematurities or an actual sustained junctional rhythm. The respiratory-heart-rate response (R-HR-R) was always present unless a tachycardia occurred. Occasionally, premature atrial

Figure 6: Heart Rate vs. Time Post-Induction.


HEART RATE (bpm)
110
100
90
80
70
60
50
40
1
2
3
4
5
6
7
8
9
10
11
12
R-I: 20% I.D.
R-II: 20-50% I.D.
TIME POST—INDUCTION (HOURS)

contractions (PACs) were recorded, and only rarely were premature ventricular contractions (PVCs) documented.

There was a lesser incidence of junctional dysrhythmias in R-II dogs: only two of the five animals exhibited junctional activity whereas, four of the five R-I dogs displayed some form of junctional dysrhythmia. No premature or aberrant atrial activity was recorded in any of the R-II dogs, and as in R-I, PVCs were only rarely documented. The predominant basic rhythm of the R-II dogs was also a sinus arrhythmia. These data should be interpreted in light of the fact that continuous ECG recordings were only made on the Beckman Dynograph, which at slow paper speeds obscures accurate ECG rhythm interpretation. Hence, only the brief, end-hourly ECG records were utilized for analysis.

No significant differences were observed in ASP, ADP or PP when R-I animals were compared to R-II animals. The ASP range in R-I was between 123.1 ± 5.0 and 141.2 ± 5.9 mmHg and similarly for R-II was between 128.1 ± 5.0 and 144.3 ± 7.7 mmHg. Figure 7 shows that in both regimes there was a rather sporadic change in ASP from the first hour. R-I mean ADPs ranged from 69.1 ± 6.7 to 89.6 ± 7.2 mmHg, while R-II means encompassed a narrow range from 64.4 ± 8.5 to 77.5 ± 4.7 mmHg (Figure 8).

Figure 7: Aortic Systolic Pressure vs. Time Post-Induction.

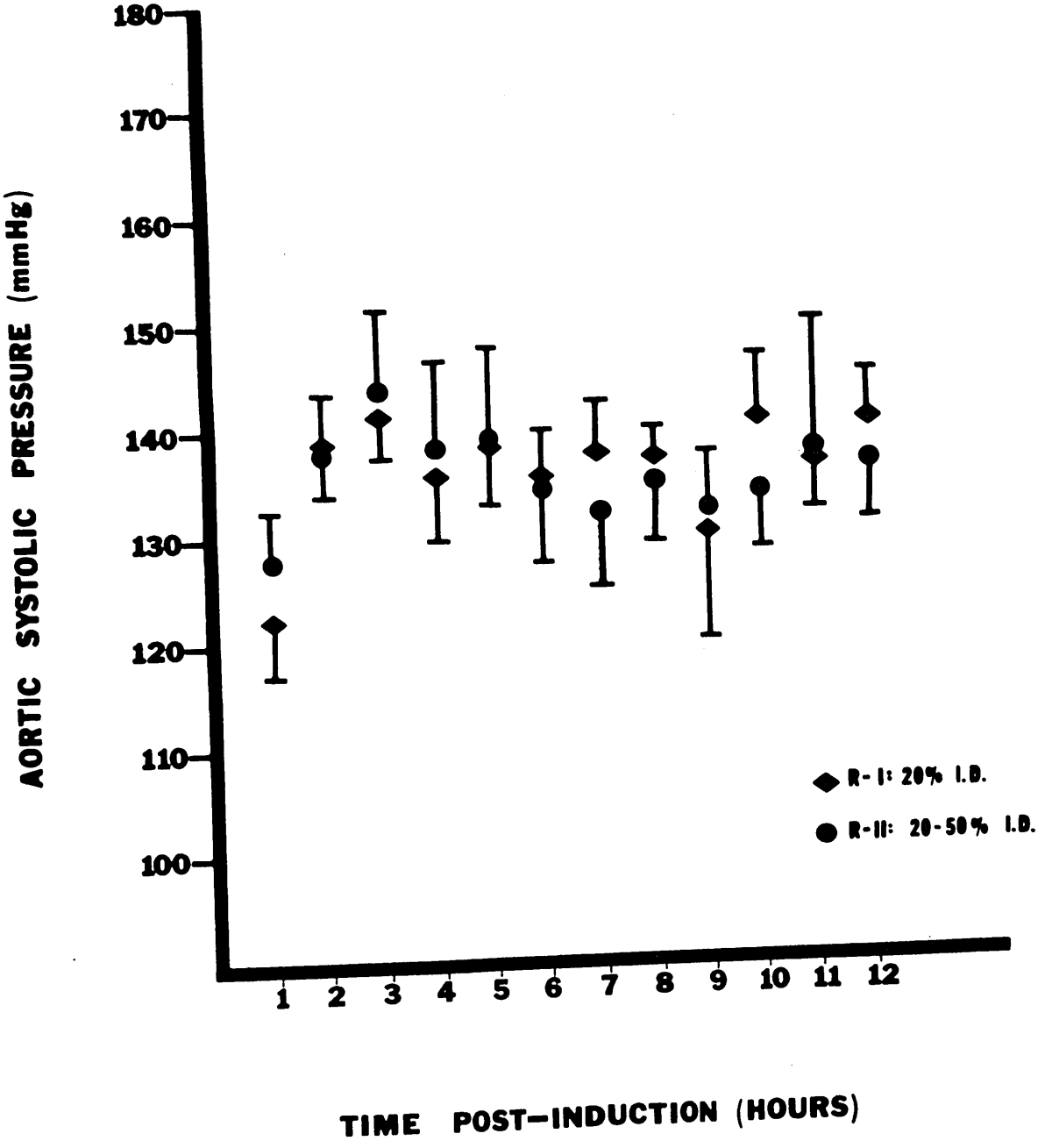

AORTIC SYSTOLIC PRESSURE (mmHg)
180
170
160
150
140
130
120
110
100
1
2
3
4
5
6
7
8
9
10
11
12
R-I: 20% I.D.
R-II: 20-50% I.D.
TIME POST-INDUCTION (HOURS)

Figure 8: Aortic Diastolic Pressure vs. Time Post-Induction.

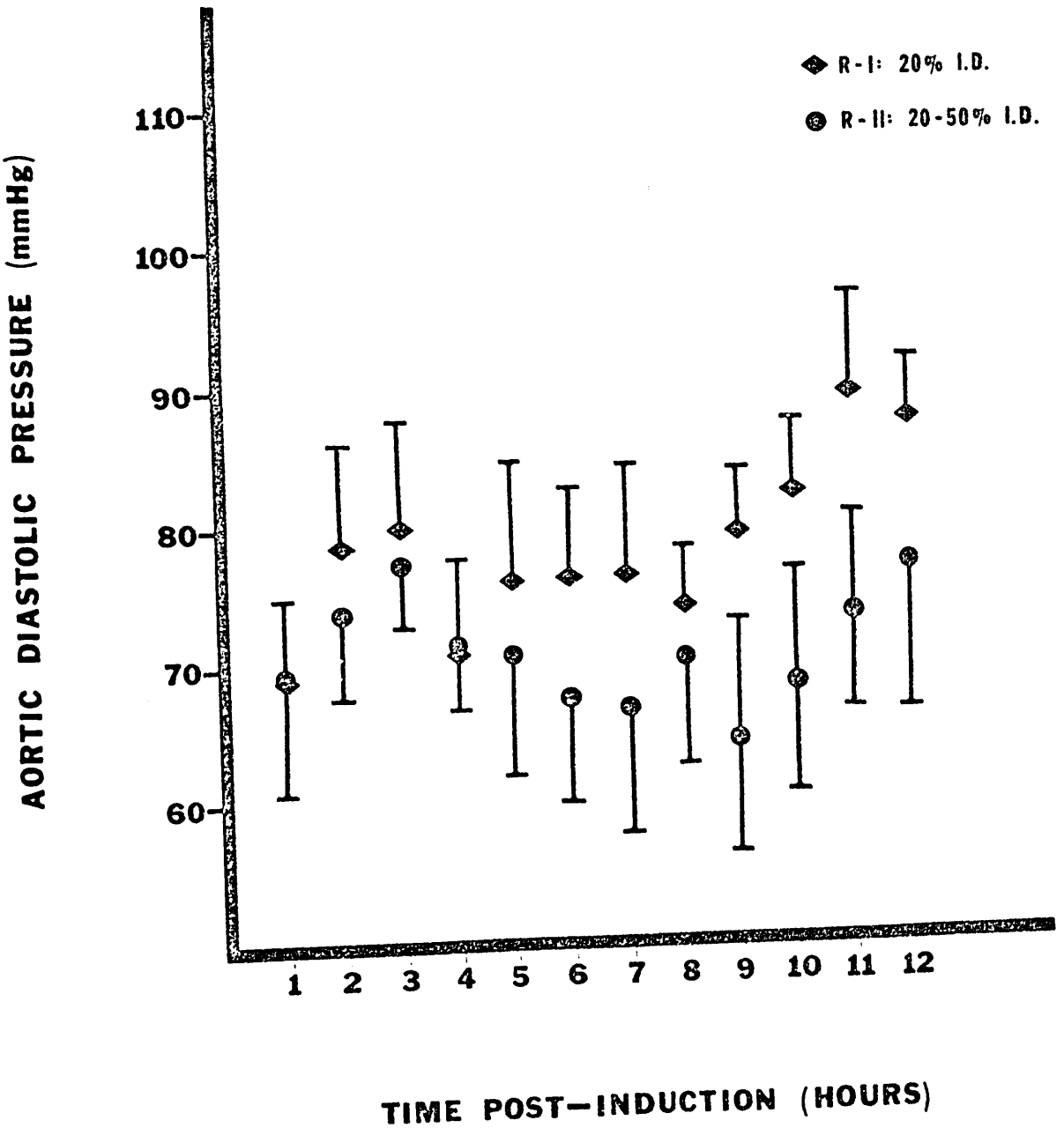

R-I: 20% I.D.
R-II: 20-50% I.D.
AORTIC DIASTOLIC PRESSURE (mmHg)
110
100
90
80
70
60
1
2
3
4
5
6
7
8
9
10
11
12
TIME POST-INDUCTION (HOURS)

Figure 9 demonstrates that the variance in PP values between the two regimes was minimal. The R-I dogs exhibited mean values between 53.2 ± 2.2 and 64.7 ± 3.5 mmHg, and the R-II means ranged between 58.6 ± 3.2 and 68.3 ± 7.6 mmHg.

A comparison of R-I and R-II mean LVFPs showed a significant difference in the ninth hour ($P < 0.05$) (See Figure 10). Although no other difference was found, it is notable that all of the R-I means were higher than the R-II means, except in hour twelve. The R-I means encompassed an 8.1 ± 1.0 to 10.4 ± 1.2 mmHg range and the R-II values fell within 6.5 ± 0.9 to 8.9 ± 0.7 mmHg.

The pulmonary response as well as alterations in acid-base balance during these two long-term chloralose anesthetic regimes were assessed by comparing the hourly mean values of the arterial blood gases. No significant differences were found between the heavy and light dosage regimes, but definite trends were observed.

Figure 9: Pulse Pressure vs. Time Post-Induction.

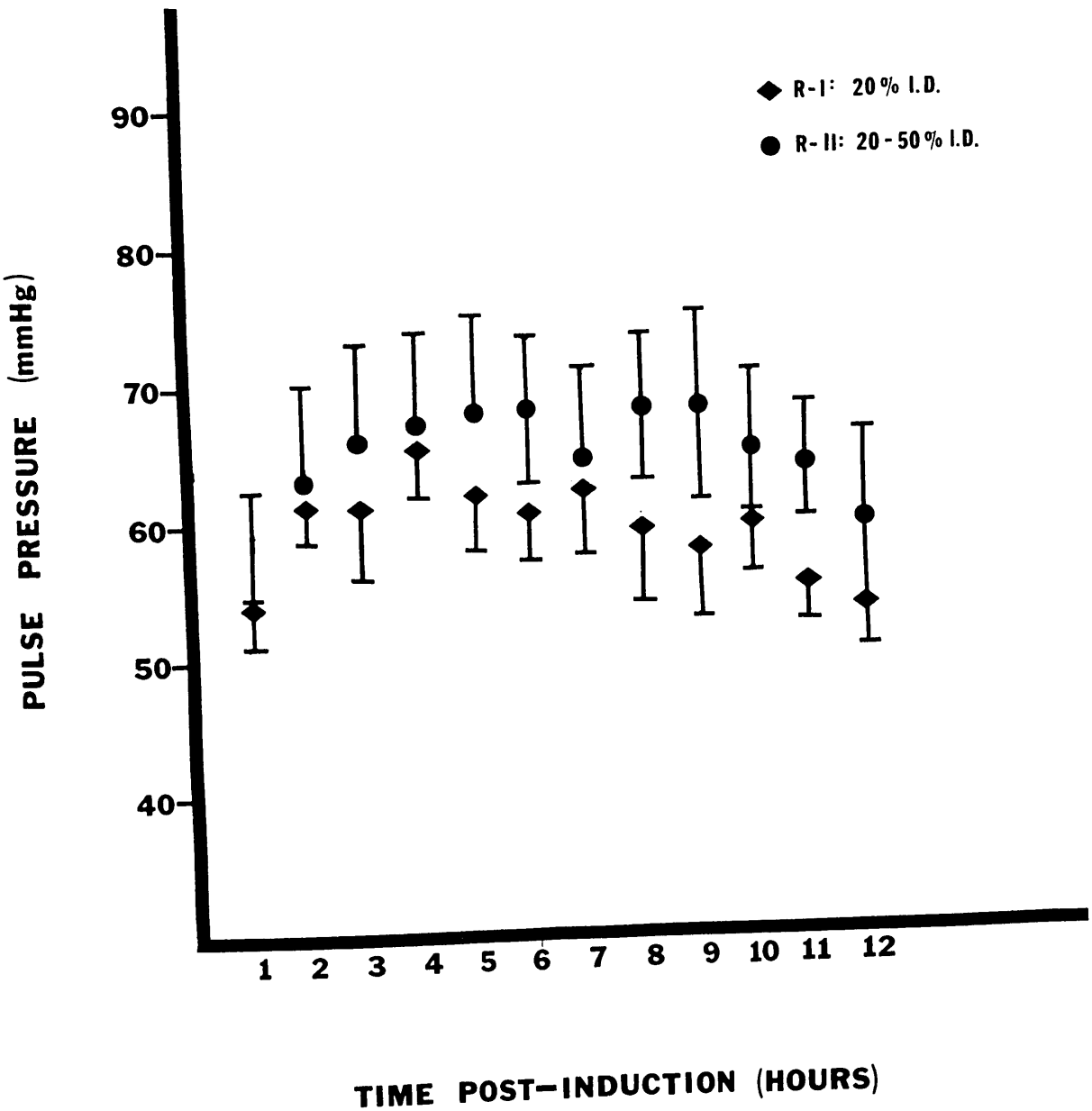
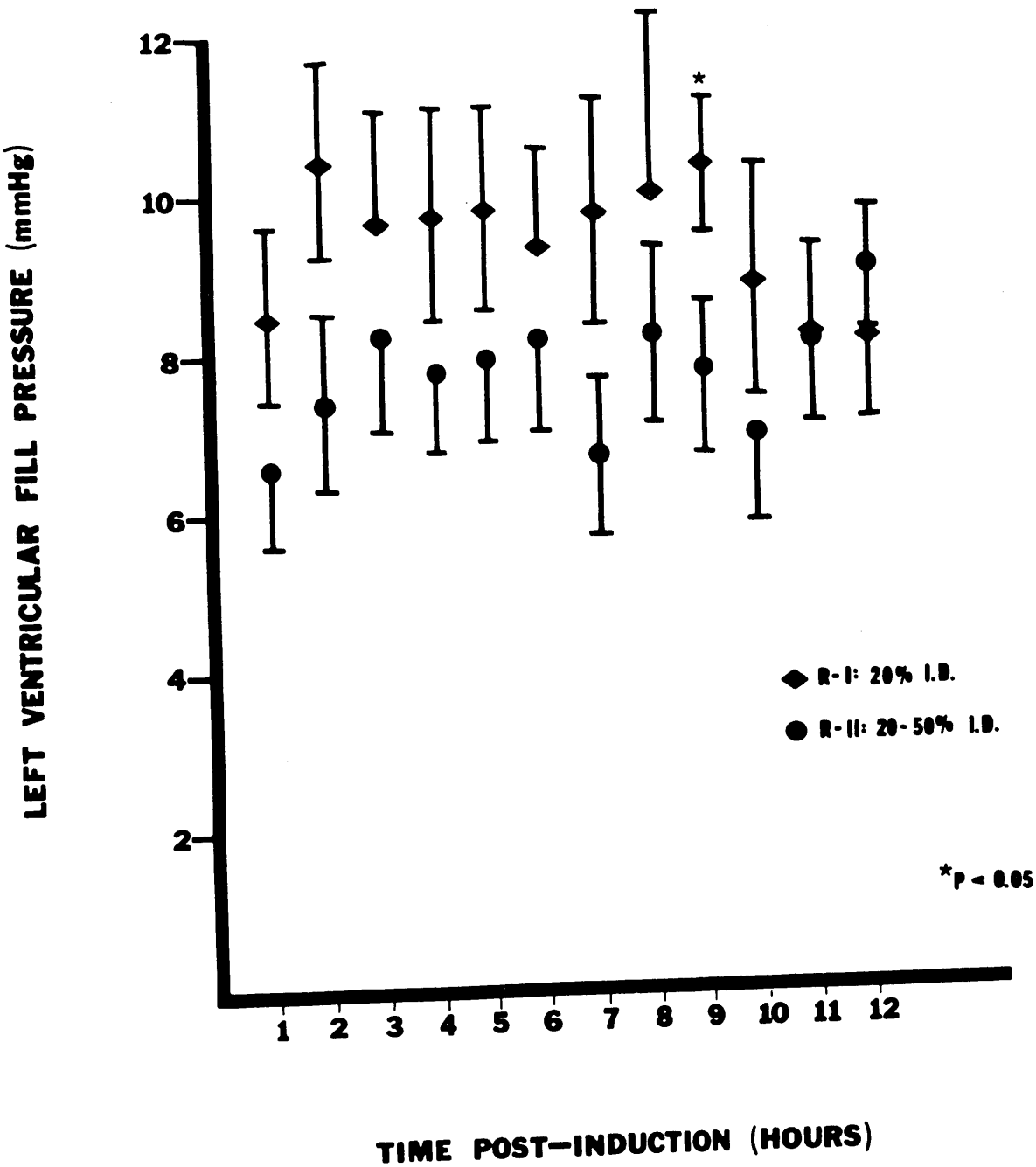

R-I: 20% I.D.
R-II: 20-50% I.D.
90
80
70
60
50
40
PULSE PRESSURE (mmHg)
1
2
3
4
5
6
7
8
9
10
11
12
TIME POST-INDUCTION (HOURS)

Figure 10: Left Ventricular Fill Pressure vs. Time Post-Induction.


LEFT VENTRICULAR FILL PRESSURE (mmHg)
12
10
8
6
4
2
1
2
3
4
5
6
7
8
9
10
11
12
*
R-I: 20% I.D.
R-II: 20-50% I.D.
*P < 0.05
TIME POST-INDUCTION (HOURS)

In both groups, a respiratory acidemia and a profound hypoxemia was seen throughout the experiment. In the latter five hours of the anesthetic course, both R-I and R-II dogs exhibited a metabolic component to the acidemia. In R-I, the $PaCO_2$ values during this latter portion of the anesthetic course were in the low normal range. The elevation of the $PaCO_2$ in R-II was of lesser magnitude in the latter five hours, than in the preceding hours of the experiment.

In the first hour, the R-II dogs showed a higher pH (7.29 ± 0.03) than the R-I dogs (7.26 ± 0.01). The inverse situation ($pH_{R-I} > pH_{R-II}$) was documented for the remainder of the anesthetic course. Figure 11 illustrates that statistical significance was approached in the last two hours, but was not attained. The pH range for R-I was between 7.26 ± 0.01 and 7.42 ± 0.01 and for R-II was between 7.28 ± 0.02 and 7.33 ± 0.04. In both groups, the pH tended to improve during the twelve hours.

The $PaCO_2$ ranged from 34.4 ± 1.7 to 51.4 ± 1.4 mmHg in R-I dogs. These dogs initially exhibited high $PaCO_2$ values which smoothly declined to the low values in the twelfth hour (Figure 12). The R-II means steadily increase for the first three hours, but then the $PaCO_2$ declined

Figure 11: Arterial pH vs. Time Post-Induction.

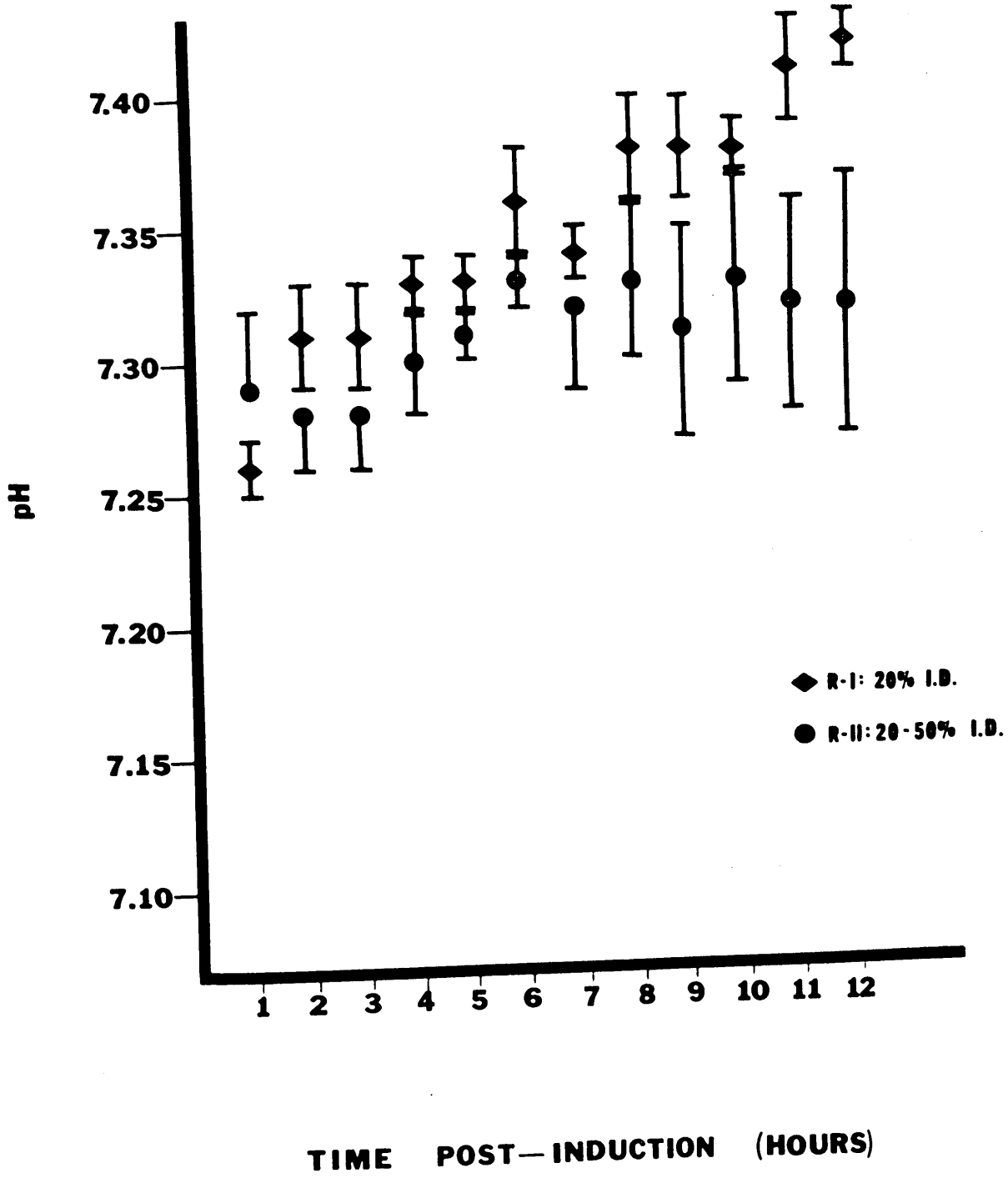
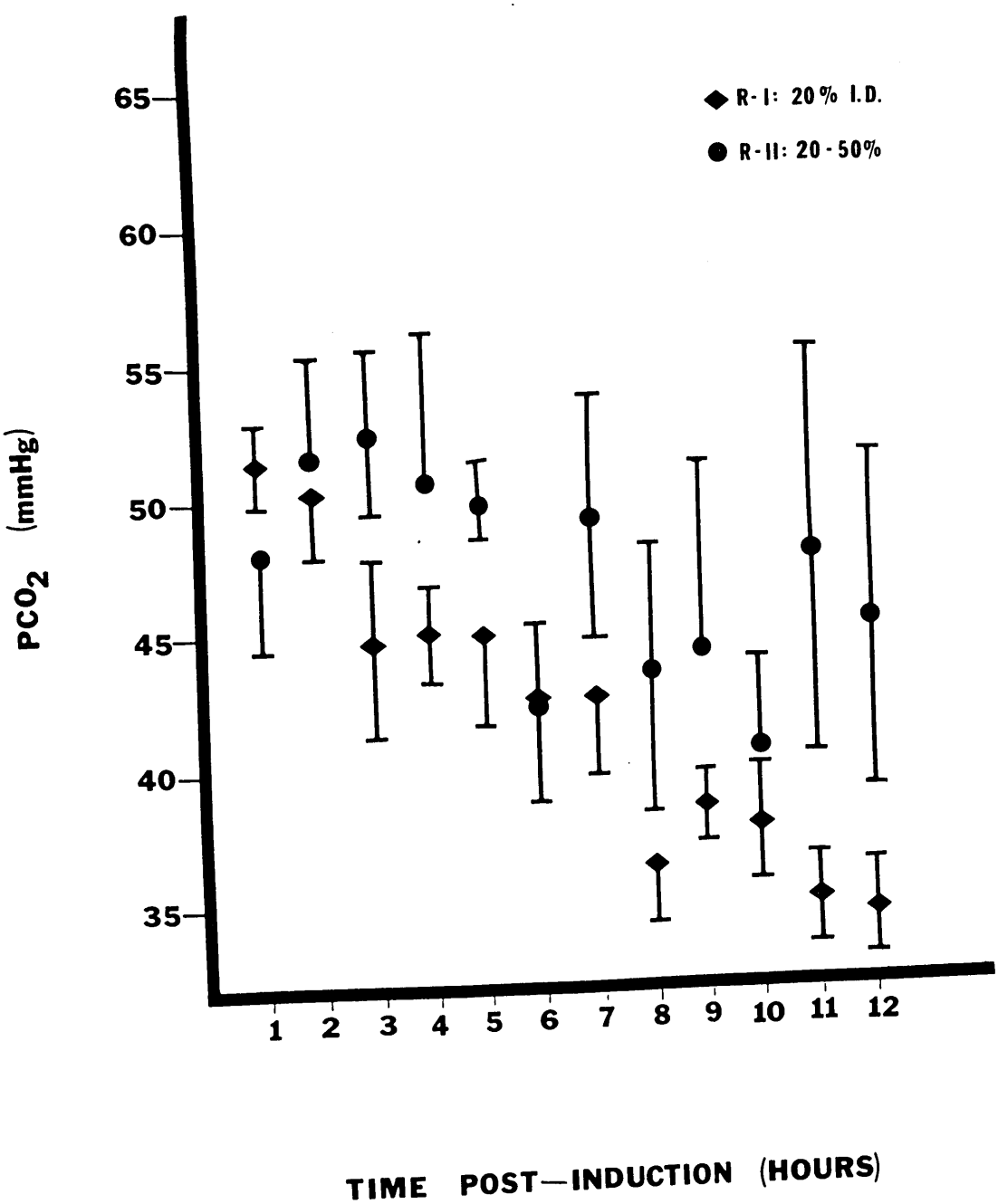

7.40
7.35
7.30
7.25
7.20
7.15
7.10
pH
1
2
3
4
5
6
7
8
9
10
11
12
R-I: 20% I.D.
R-II: 20-50% I.D.
TIME POST—INDUCTION (HOURS)

Figure 12: Arterial Carbon Dioxide Tension vs. Time Post-Induction.


R-I: 20% I.D.
R-II: 20-50%
65
60
55
50
45
40
35
PCO_2 (mmHg)
1
2
3
4
5
6
7
8
9
10
11
12
TIME POST—INDUCTION (HOURS)

sporadically from the high, 52.4 ± 3.0 mmHg to a low value of 40.6 ± 3.2 mmHg.

All the plasma bicarbonate (HCO_3^-) levels fell within a narrow range, between 21.6 ± 1.1 and 25.4 ± 1.0 mEq/L for R-I, and between 21.0 ± 1.7 and 25.1 ± 0.8 mEq/L for R-II. Figure 13 shows that in hour six, the R-I value was greater than the R-II value (23.7 ± 0.4 as compared to 21.2 ± 1.2 mEq/L, respectively). The last five hours of the experiment showed generalized depression of the mean HCO_3^- values in both regimes.

Figure 14 depicts the pattern which characterized the PaO_2 changes in the R-II dogs: the values rose gradually until the fourth hour, then decreased to a plateau until the seventh hour when PaO_2 again rose, peaking at 69.2 ± 4.3 mmHg in the tenth hour. The PaO_2 values for R-I ranged from 55.1 ± 5.7 to 63.8 ± 6.0 mmHg and for R-II ranged from 53.1 ± 2.4 to 69.2 ± 4.3 mmHg.

Phase II

As in Phase I, the mean percent change of maximum dP/dt, the mean Vmax and the V_{40} were compared between the spontaneously breathing and mechanically ventilated dogs. No significance was observed between R-III and R-IV in any of these indices, yet specific trends did emerge.

Figure 13: Arterial Bicarbonate Level vs. Time Post-Induction.

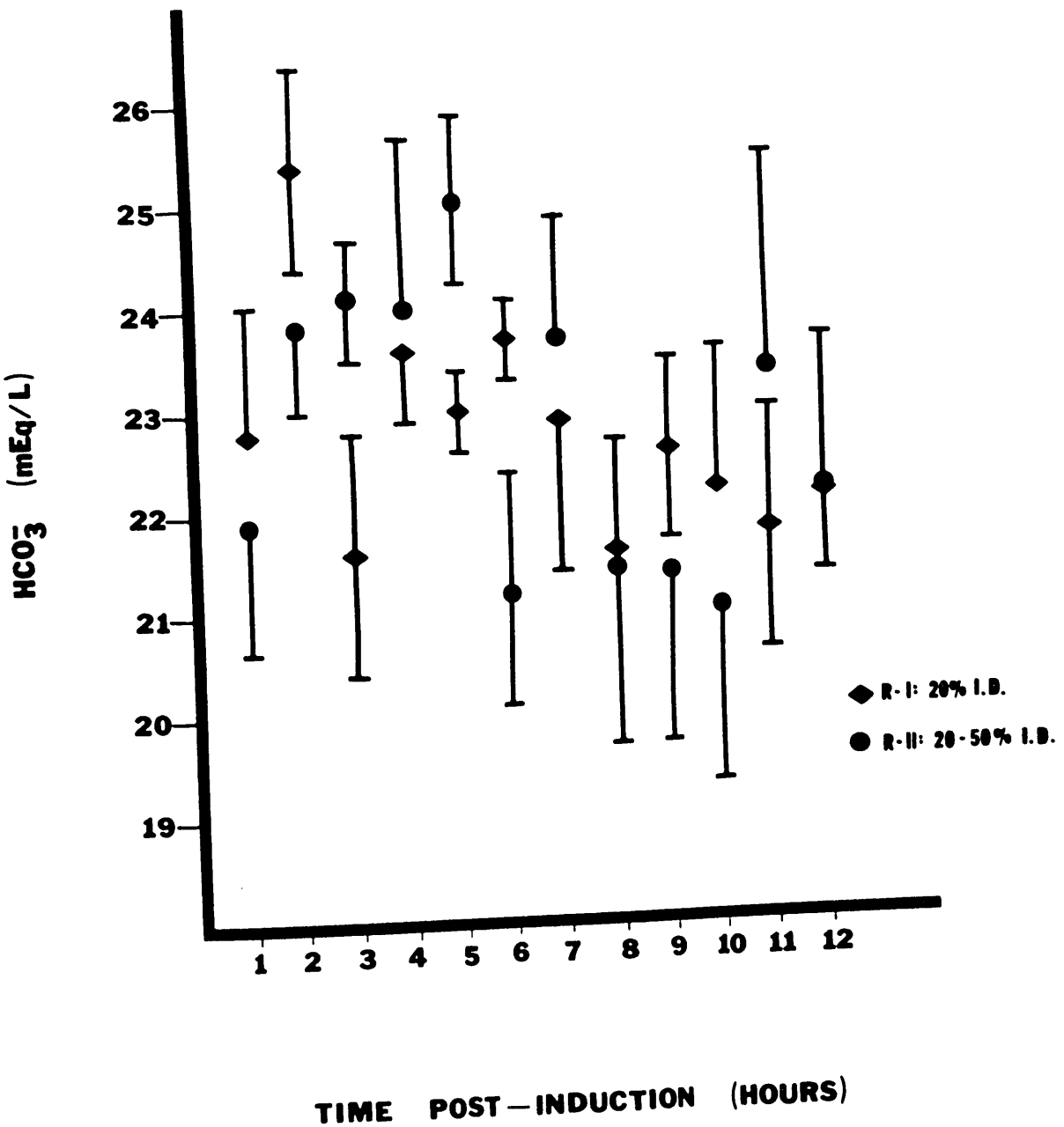
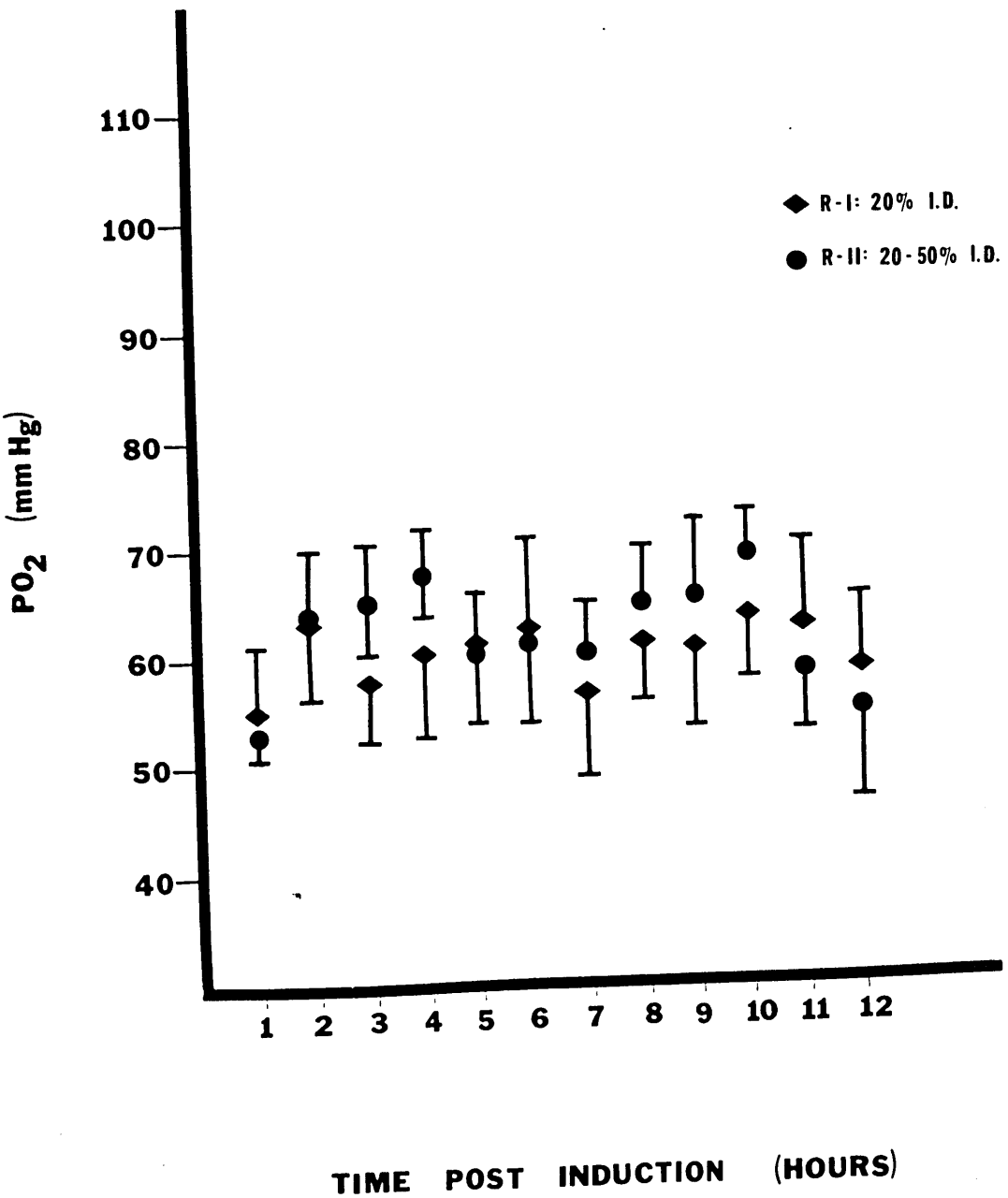

26
25
24
23
22
21
20
19
HCO_3^- (mEq/L)
1 2 3 4 5 6 7 8 9 10 11 12
TIME POST—INDUCTION (HOURS)
R-I: 20% I.D.
R-II: 20-50% I.D.

Figure 14: Arterial Oxygen Tension vs. Time Post-Induction.


110
100
90
80
70
60
50
40
PO_2 (mm Hg)
R-I: 20% I.D.
R-II: 20-50% I.D.
1
2
3
4
5
6
7
8
9
10
11
12
TIME POST INDUCTION (HOURS)

The peak dP/dt showed statistically significant variability between Regime III and Regime IV (See Figure 15). Regime III values ranged from 3256 ± 312 mmHg/sec to 3906 ± 483 mmHg/sec and the values seemed to increase only very gradually in an oscillatory pattern. The 1st hour value was the lowest and the highest value was observed in the 10th hour. In R-IV the means ranged between 1735 ± 161 mmHg/sec in the tenth hour to 2764 ± 370 mmHg/sec in the second hour. Generally, the R-IV values were seen to increase slightly then decrease sharply and remain depressed from initial values throughout the 12 hours, although slight recovery was observed by the eleventh and twelfth hours.

In Phase II, the percent change of mean max dP/dt fluctuated in both positive and negative directions from the 'standard' first hourly values. Except for the low fifth hour value in R-III (-0.9% ± 12.4%), the mean percent changes in these animals were increased from initial values (Figure 16). In contrast, negative mean percent changes from initial values were seen in the R-IV dogs. The magnitude of percent change in R-IV was greater in all but the tenth and eleventh hours.

The first comparison of Vmax between R-III and R-IV showed a significant difference ($P < 0.04$) and although no

Figure 15: Peak Rate of Rise of the First Derivative of Left Ventricular Pressure vs. Time Post-Induction.

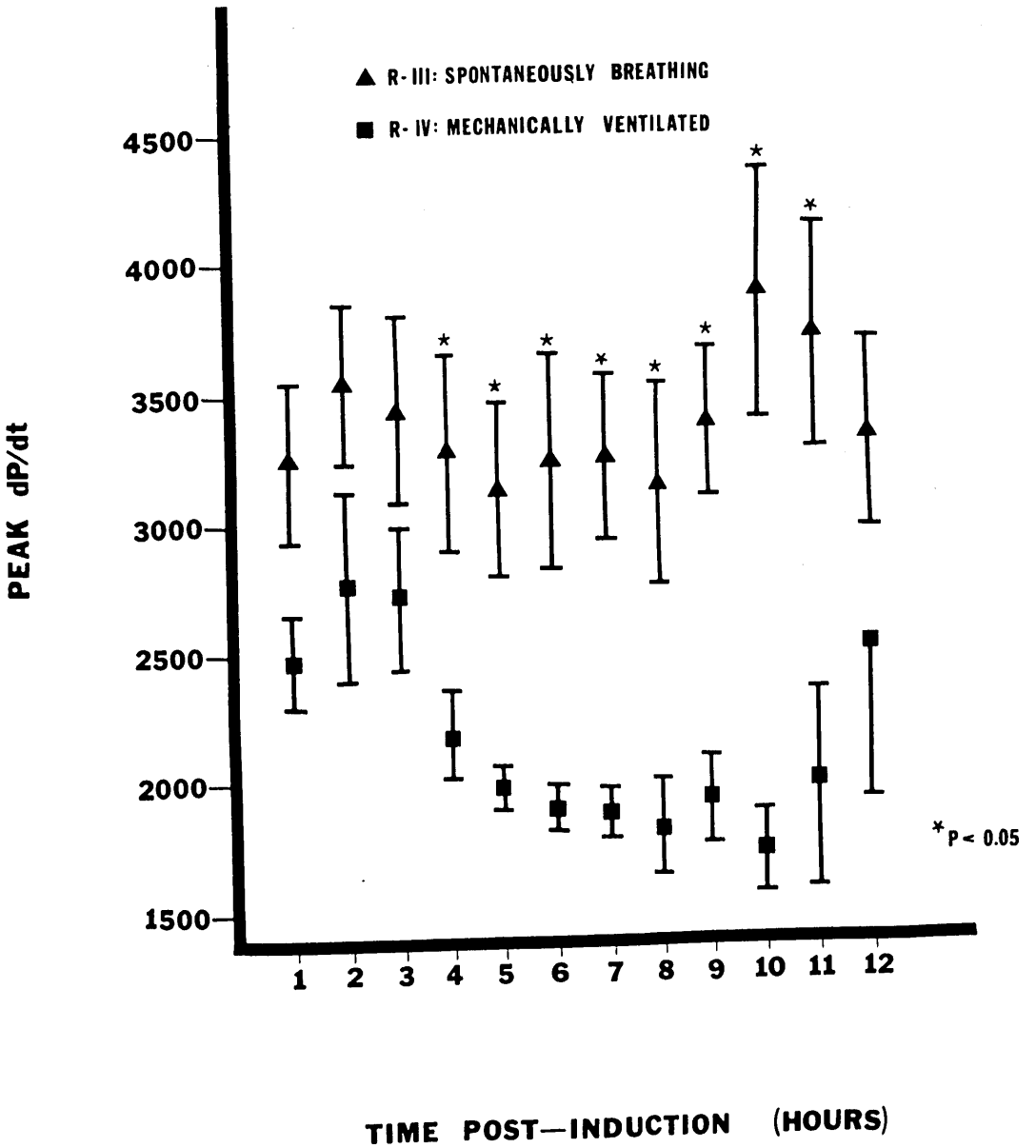
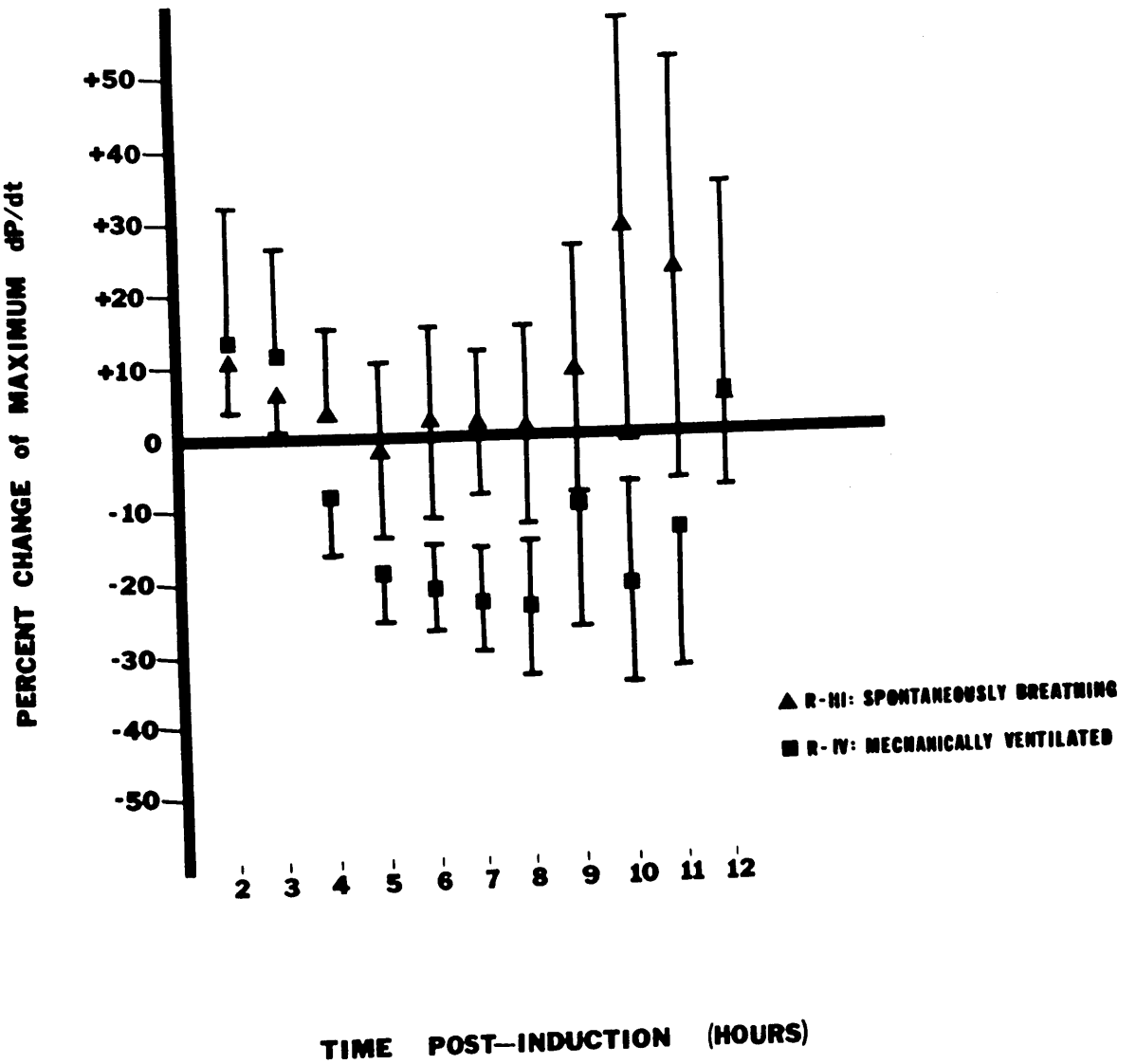

▲ R-III: SPONTANEOUSLY BREATHING
■ R-IV: MECHANICALLY VENTILATED
PEAK dP/dt
4500
4000
3500
3000
2500
2000
1500
1 2 3 4 5 6 7 8 9 10 11 12
*P < 0.05
TIME POST—INDUCTION (HOURS)

Figure 16: Percent Change of Maximum Rate of Rise of the First Derivative of Left Ventricular Pressure vs. Time Post-Induction.


PERCENT CHANGE of MAXIMUM dP/dt
+50
+40
+30
+20
+10
0
-10
-20
-30
-40
-50
2
3
4
5
6
7
8
9
10
11
12
▲ R-III: SPONTANEOUSLY BREATHING
■ R-IV: MECHANICALLY VENTILATED
TIME POST-INDUCTION (HOURS)

other differences were observed, Figure 17 displays distinct trends. All the R-IV Vmax means exceed the R-III means. The Vmax values peaked the second hour, thereafter generally declined in both regimes. This is loosely associated with the intra-regime pattern in the percent change of max dP/dt for both regimes. The Vmax range for R-III was from 1.41 ± 0.32 to 2.09 ± 0.68 and for R-IV was from 2.32 ± 0.26 to 2.92 ± 0.42.

Hourly means for V_{40} values in R-III ranged from 1.38 ± 0.20 to 1.71 ± 0.36 while the R-IV values were seen between 1.40 ± 0.14 and 1.98 ± 0.29. Figure 18 demonstrates that the twelfth hour again showed a greater mean value in R-IV as compared to the R-III mean V_{40} value.

Generally, no significant differences were found when HR, ASP and ADP were compared between R-III and R-IV. The R-III HR range was from 48.4 ± 4.3 to 79.7 ± 17.3 bpm, and R-IV means corresponded closely showing a 50.0 ± 2.8 to 89.8 ± 19.7 bpm span.

In both R-III and R-IV a sinus rhythm with a respiratory-heart-rate-response was the predominant rhythm. Junctional rhythms were documented in two of the five R-IV dogs, but were not seen at all in the R-III animals. Junctional aberrancies, however, were evident in R-III. Infrequent atrial aberrancies were seen in both R-III and

Figure 17: Velocity of Contractile Element Shortening at Zero Load vs. Time Post-Induction.

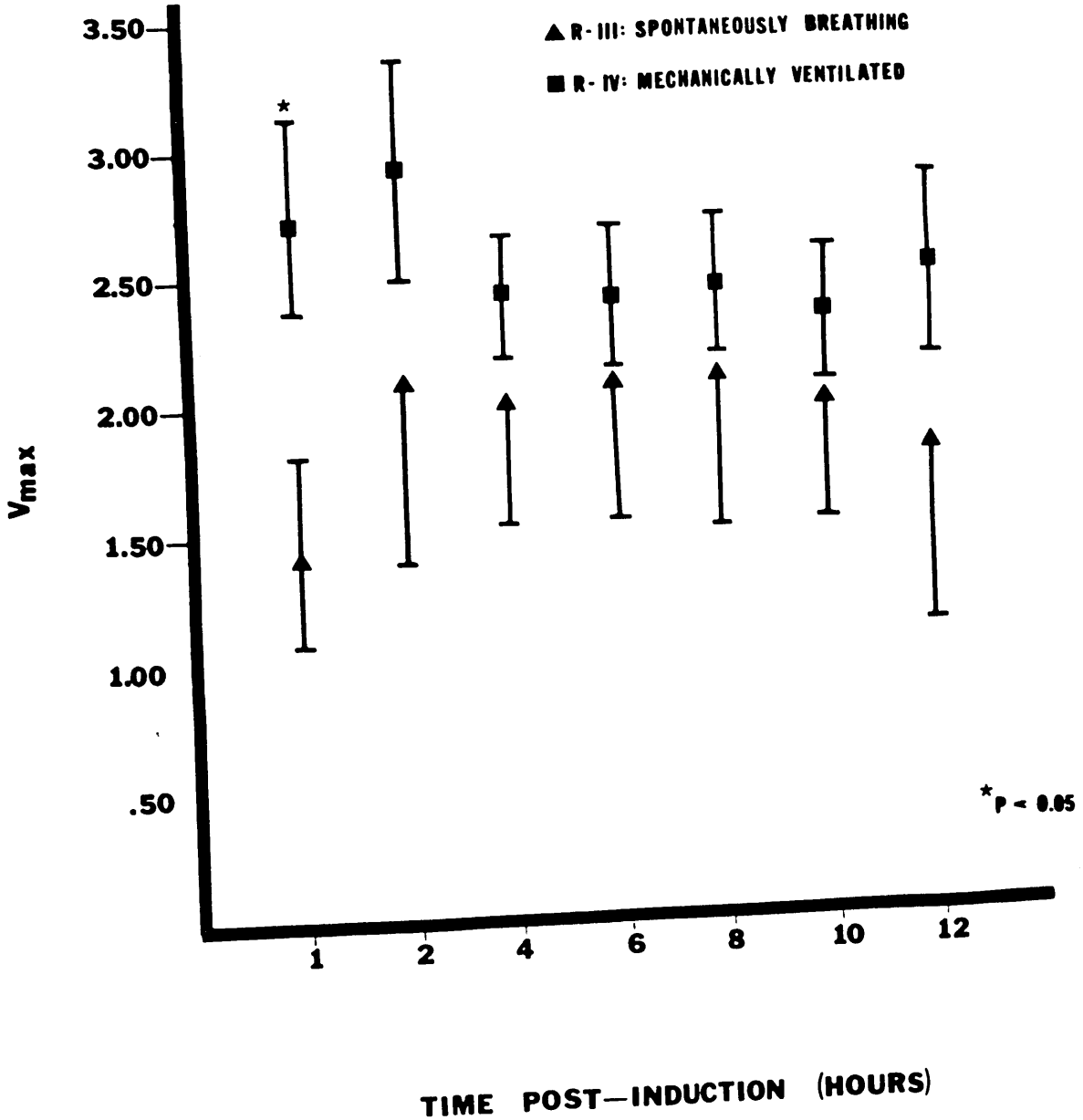
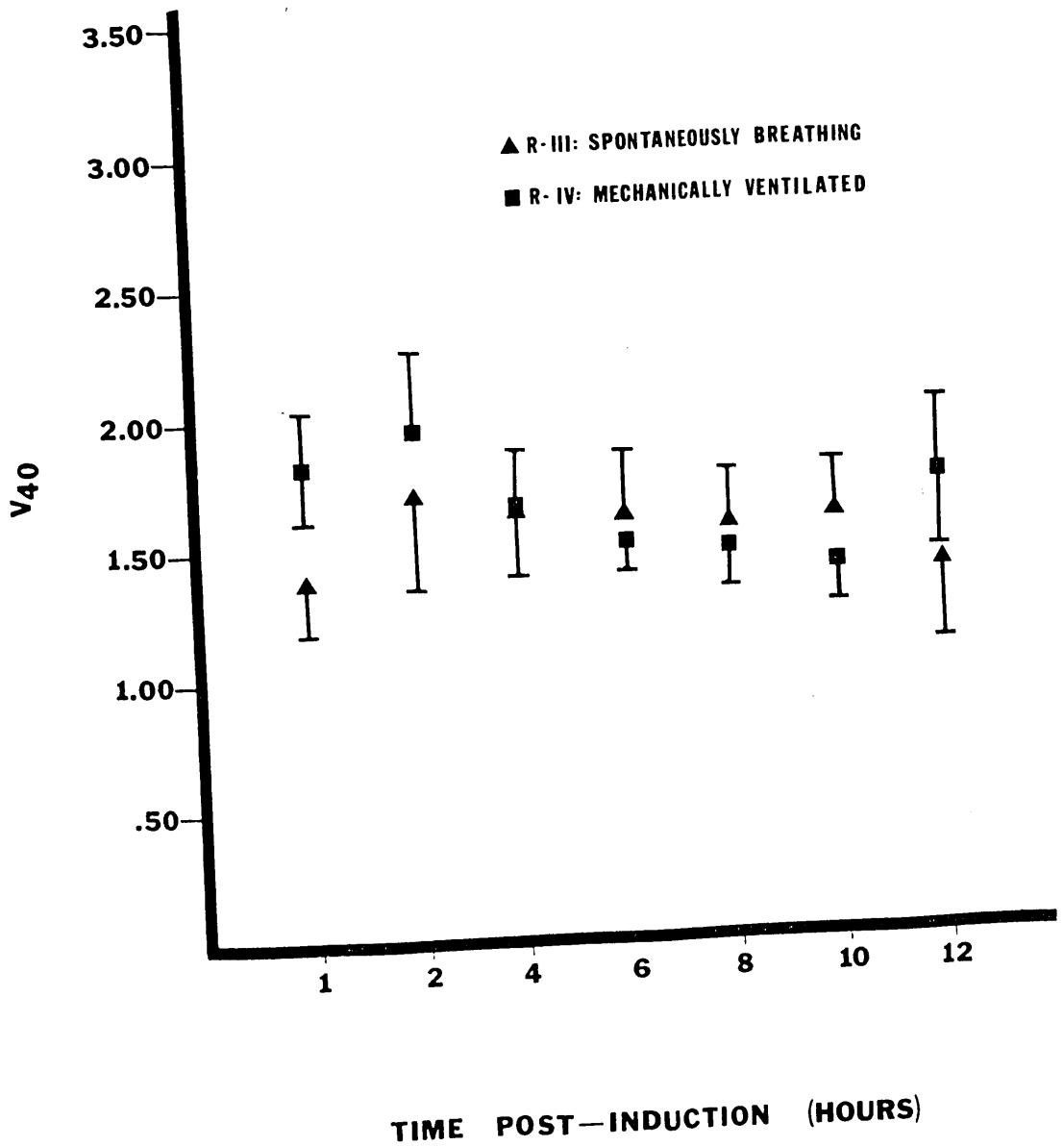

▲ R-III: SPONTANEOUSLY BREATHING
■ R-IV: MECHANICALLY VENTILATED
3.50
3.00
2.50
2.00
1.50
1.00
.50
V_{max}
*
*P < 0.05
1
2
4
6
8
10
12
TIME POST—INDUCTION (HOURS)

Figure 18: Velocity of Contractile Element Shortening at 40 mmHg Developed Pressure vs. Time Post-Induction.


3.50
3.00
2.50
2.00
1.50
1.00
.50
V40
▲ R-III: SPONTANEOUSLY BREATHING
■ R-IV: MECHANICALLY VENTILATED
1
2
4
6
8
10
12
TIME POST—INDUCTION (HOURS)

R-IV. PVCs were more prevalent in R-III than in R-IV (one out of five dogs). Coupling and short bouts of ventricular tachycardia were observed in two of the R-III dogs but no malignant irritability was recorded in the R-IV group.

Three out of five of the R-III dogs demonstrated ST-elevation, and this non-specific change was noted in only one of the R-IV dogs. R-IV did contain one animal that developed an R-R' during the last half of the experiment. Another R-IV animal, without any documented dysrhythmias or other aberrancies, exhibited a depressed T-wave throughout the twelve hours. No pattern emerged relating time-duration of anesthesia with the appearance of dysrhythmias; the early appearance (0-6th hour) of irregularities were equivalent to those which occurred late (7-12th hour). Generally, if dysrhythmias occurred, they persisted throughout the experimental period.

The range of ASP in R-III dogs was between 130.5 ± 14.4 and 157.2 ± 23.1 mmHg; in R-IV, the mean ASP values ranged from 108.1 ± 10.1 to 130.5 ± 8.6 mmHg. A significant difference ($P < 0.04$) was seen in the second hour, and even though no further significant differences were found, all of the R-III values were higher than the R-IV values. The highest mean value of R-III was recorded

in the tenth hour (157.2 ± 23.1). This unusually high mean can be attributed to one dog which suddenly presented with hypertension (237.9 mmHg). In this small sample size, the bizarre value had substantial impact on the hourly mean (averaged from five values). In addition, small sample size contributes to a wide standard error, which may provide an explanation for the absence of statistical significance in view of such an aberrant, albeit isolated, finding. The range of ADP means in R-III was from 62.2 ± 7.8 to 89.6 ± 26.4 mmHg and comparatively, the range of R-IV means was between 62.1 ± 2.5 and 82.8 ± 7.4 mmHg. The widest diversity of the mean values occurred in the tenth hour, which reflects the episodic hypertension seen in one animal.

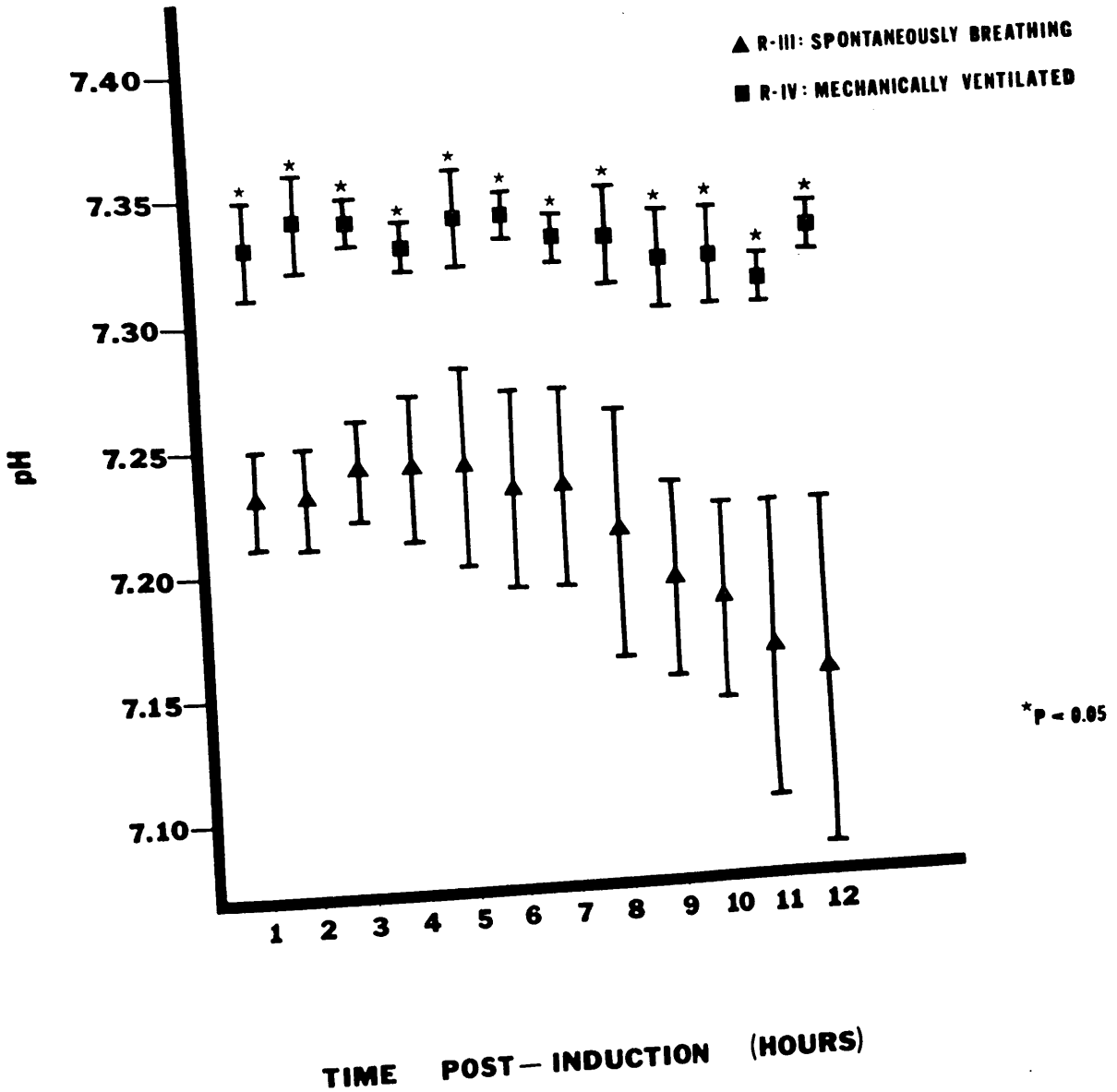
The range in mean PP for the R-III dogs was 56.8 ± 5.6 to 73.3 ± 10.7 mmHg, while the R-IV means varied from 35.9 ± 4.8 to 57.7 ± 7.4 mmHg. The R-III means initially increased and then plateaued at this elevated level, but a marked high-to-low linear decent was observed over the twelve hours of the R-IV mean PP values. In all but the first comparison, R-III values for mean PP exceeded R-IV values. The fourth, sixth and ninth hours all approached significance, culminating in the eleventh and twelfth hours with P values of less than 0.04 and 0.05,

respectively. The R-III LVFP range of means were between 7.4 ± 0.9 and 10.2 ± 1.4 mmHg, which was higher than the range for the R-IV LVFP means (3.1 ± 1.0 to 4.8 ± 1.7 mmHg). All of the R-III means were greater than the corresponding R-IV means, with statistical significance in the third, fourth, fifth, sixth, ninth, tenth, eleventh and twelfth hours.

Alterations in the pulmonary status and acid-base balance were markedly different in R-III and R-IV. Generally, R-III exhibited trends similar to those seen in the Phase I dogs, i.e., a mixed respiratory and metabolic acidemia with severe hypoxemia. In R-IV a marginal metabolic acidemia existed throughout the twelve hours when ventilatory manipulation maintained a relatively constant $PaCO_2$ (35-45 mmHg). In the following section, these trends and differences are discussed.

The mean pH values for R-III fell within a 7.15 ± 0.07 to 7.24 ± 0.03 range, while a consistently higher and more narrow range, 7.31 ± 0.01 to 7.34 ± 0.02 contained all of the R-IV means (See Figure 19). Highly significant differences ($P < 0.005$) were evident during the first two hours and significant differences ($P < 0.05$) were noted for the ensuing hours.

Figure 19: Arterial pH vs. Time Post-Induction.


▲ R-III: SPONTANEOUSLY BREATHING
■ R-IV: MECHANICALLY VENTILATED
7.40
7.35
7.30
7.25
7.20
7.15
7.10
pH
1 2 3 4 5 6 7 8 9 10 11 12
TIME POST—INDUCTION (HOURS)
*P < 0.05

R-III $PaCO_2$ means between 62.3 ± 6.0 and 48.4 ± 2.4 mmHg were consistently higher than the R-IV means, which were mechanically controlled between 37.3 ± 1.0 and 39.6 ± 2.0 mmHg (Figure 20). Highly significant differences ($P < 0.005$) occurred every hour but the fourth hour ($P < 0.01$). There was only a marginal difference in the range of plasma bicarbonate between R-III and R-IV. The mean bicarbonate range for R-III was 18.9 ± 2.7 to 22.4 ± 1.8 mEq/L. Similarly, the R-IV HCO_3^- mean values ranged from 18.5 ± 0.8 to 21.1 ± 1.3 mEq/L. In all but the first hour, the unventilated animals displayed slightly higher means than the ventilated group. Figure 21 demonstrates no difference between the two regimes although the P values steadily decreased with time.

The hypoxemia exhibited in Phase I dogs also predominated in the unventilated R-III animals, whose oxygen tensions ranged from 51.2 ± 8.4 to 71.1 ± 8.1 mmHg. The ventilated regime had a higher level of mean values, and exhibited a range from 78.9 ± 4.3 to 97.1 ± 9.4 mmHg. Differences in hours four, five, six and eight were close to significant, and significant differences were found in the latter part of the experiment (See Figure 22).

Figure 20: Arterial Carbon Dioxide Tension vs. Time Post-Induction.

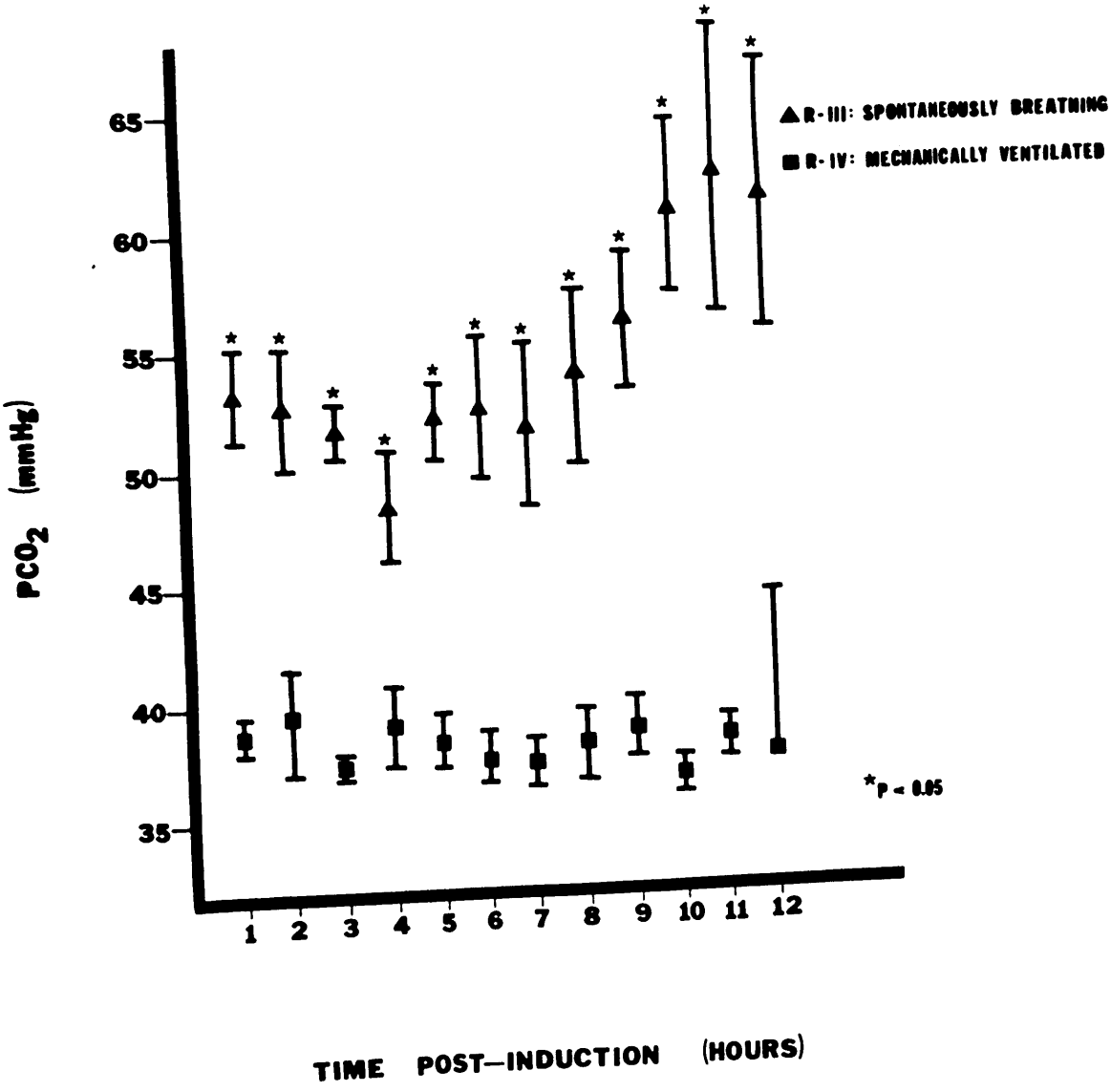

▲ R-III: SPONTANEOUSLY BREATHING
■ R-IV: MECHANICALLY VENTILATED
*P < 0.05
PCO_2 (mmHg)
65
60
55
50
45
40
35
1 2 3 4 5 6 7 8 9 10 11 12
TIME POST-INDUCTION (HOURS)

Figure 21: Arterial Bicarbonate Level vs. Time Post-Induction.

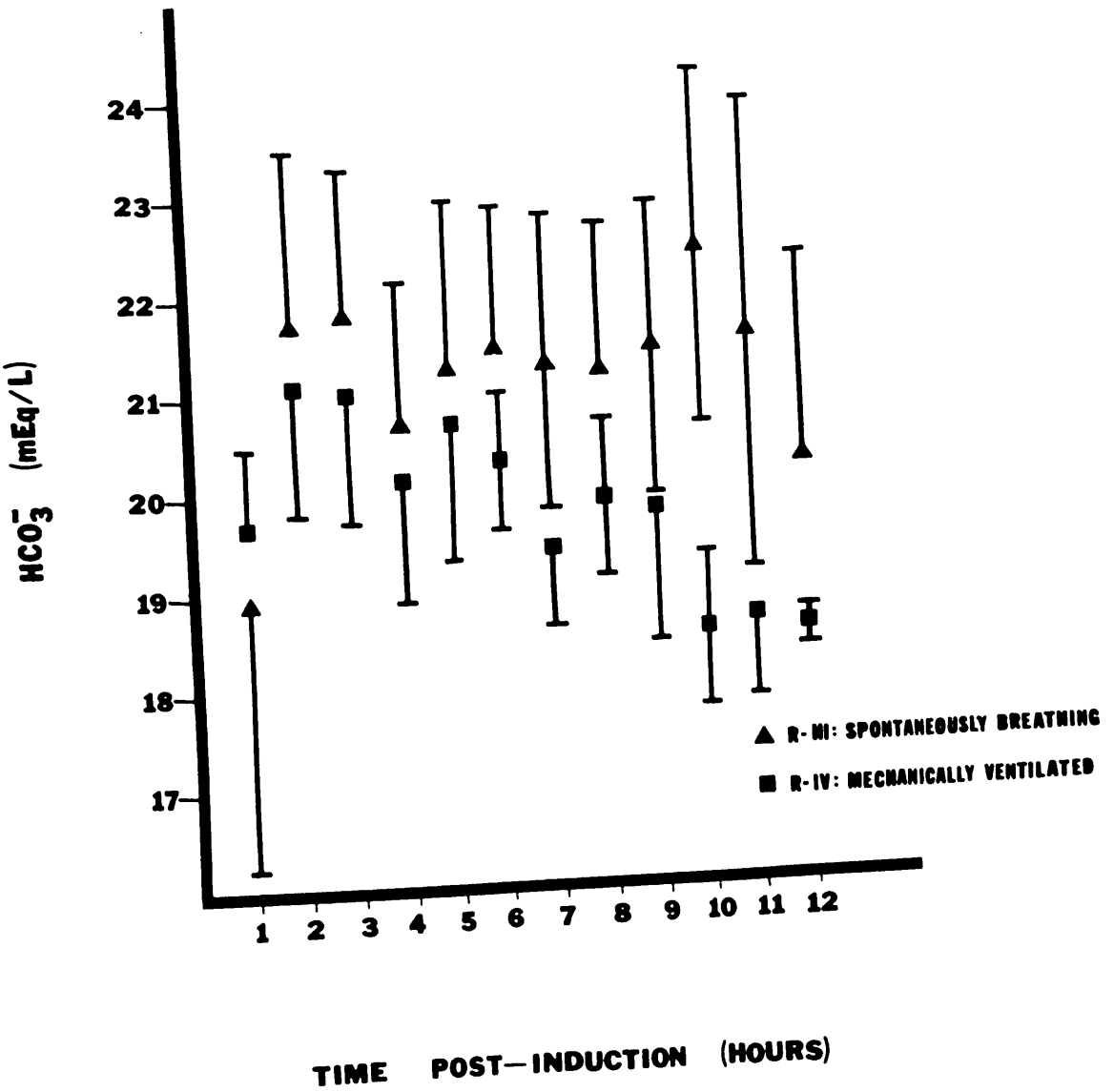
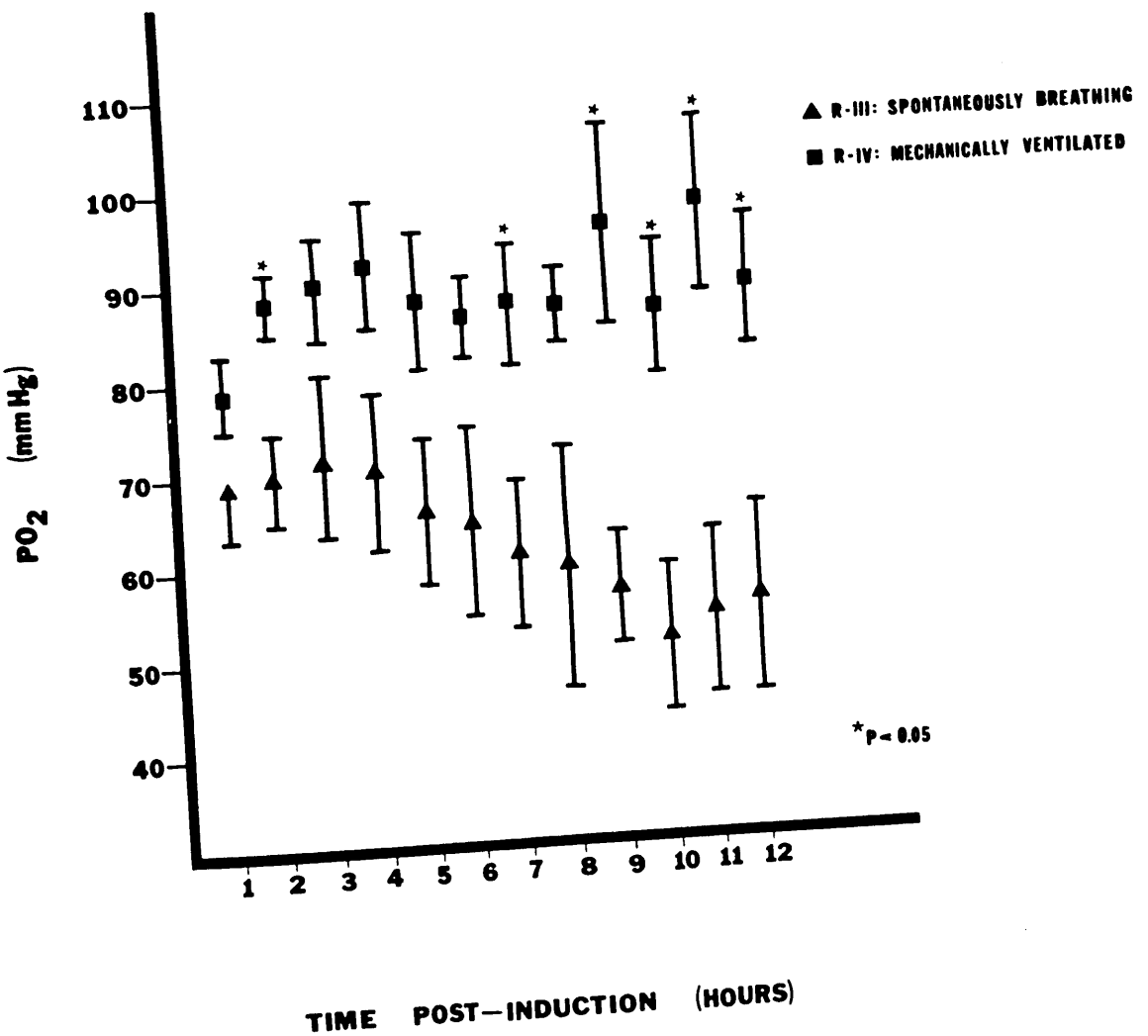

24
23
22
21
20
19
18
17
HCO_3^- (mEq/L)
1 2 3 4 5 6 7 8 9 10 11 12
TIME POST—INDUCTION (HOURS)
R-III: SPONTANEOUSLY BREATHING
R-IV: MECHANICALLY VENTILATED

Figure 22: Arterial Oxygen Tension vs. Time Post-Induction.


110
100
90
80
70
60
50
40
PO_2 (mm Hg)
1 2 3 4 5 6 7 8 9 10 11 12
TIME POST—INDUCTION (HOURS)
▲ R-III: SPONTANEOUSLY BREATHING
■ R-IV: MECHANICALLY VENTILATED
*P < 0.05

Additional Findings

From the total of seven dogs that were unacceptable for inclusion in this study, a 'series' of three dogs emerged because each manifested some physiological alteration during the course of the experiment that warranted exclusion from this study. These findings included hyperthermia, elevated parasympathetic tone, and a ventilation perfusion defect. Four animals were not included in this study because of technical difficulties encountered while maintaining the animals during the twelve hour anesthetic period.

CHAPTER V

DISCUSSION OF RESULTS

Recently, physiologists have been more cognizant of the impact of anesthetic drug effects on experimental results. (Chenoweth and Van Dyke, 1969; Mushin, 1964). The degree of physiological alteration and depression with different anesthetic agents, as well as the documented species variability can contribute to misinterpretation of data (Dripps, Eckenhoff and Vandam, 1972) unless the drug effects are well known in the species utilized. Alpha-chloralose is a laboratory anesthetic used frequently in physiological investigations (Bagshaw and Cox, 1975). Despite its popularity with cardiovascular physiologists, the literature is sparse concerning the dose-dependent or time-duration cardiopulmonary effects of this agent (Cox, 1972a; Bass and Buckley, 1966; Balis and Monroe, 1964).

The study was divided into two parts, designated as Phase I and Phase II. Phase I compared 'light' and 'deep' levels of chloralose anesthesia. The 'light' (Regime-I) dose dogs received 16 mg/kg (or 20 percent of the initial dose of 80 mg/kg) of alpha-chloralose every hour as a bolus injection for the twelve hours of the experiment. The 'heavy' (Regime-II) dose dogs received 16-40 mg/kg

(or 20-50 percent of the initial dose of 80 mg/kg) of alpha-chloralose every hour as a bolus injection for the twelve hour maintenance period. The general hypothesis tested was that a significant difference in the cardiopulmonary effects between chloralose anesthesia maintenance regimes I and II would be found.

Phase II was an extension of the initial study because of the profound mixed acidemia and hypoxemia which occurred at both dosage ranges in Phase I. Phase II compared the differences between spontaneously breathing (Regime III) and mechanically ventilated (Regime IV) chloralose anesthetized dogs. All ten animals in this phase of the study received the same total dosage as the 'heavy' dose dogs of Phase I although the type of administration was changed to a constant infusion rather than hourly bolus injections in order to obtain a more constant blood level of the anesthetic. However, the animals in Phase II were experimentally treated in like manner except that one group was mechanically ventilated and the other group was allowed to breathe spontaneously. The hypothesis tested by this phase of the study was that significant differences would be found in the cardiopulmonary stability between spontaneously breathing and mechanically ventilated dogs undergoing a twelve hour morphine-chloralose anesthetic.

Therefore, the purpose of this study was to provide quantitative information on the long-term, dose-dependent cardiopulmonary effects of morphine-chloralose anesthesia in dogs.

Phase I

The cardiovascular data obtained in both dosage regimes of alpha-chloralose was similar to that reported for resting awake dogs (Ferranio, Mc Cubbin and Page, 1969; Harley, Behar and Mc Intosh; 1968). The tachycardia and hypertension reported by others (Charney, Bass and Buckley, 1970; Bass and Buckley, 1966; Greisheimer, 1965; Vincent and Thompson, 1928) was not found in either of the two dosage regimes studied. The vagotonic influence of the morphine premedication (Stanley, 1979) may have countered the frequently reported vagolytic effects of chloralose (Harley, Behar and Mc Intosh, 1968; Bass and Buckley, 1966). However, Cox (1972a) in unpremedicated dogs, recorded only transient hemodynamic changes during induction which returned and stabilized at preanesthetic values. This cardiovascular stability may reflect acclimatization (Ferranio, Mc Cubbin and Page, 1969), but when acute studies were undertaken, the combination of morphine premedication

and chloralose anestheisa did offer a preparation that minimally influenced hemodynamic parameters.

The hemodynamic parameters did, however, reveal some trends that may characterize a twelve hour chloralose anesthetic period. The heart rate was stable in both regimes but gradually slowed to a borderline bradycardia during the middle of the experiment, rising again in both regimes by the end of twelve hours. This fourth-through-eighth hour "depression" may represent a time of maximal drug plasma concentration of chloralose. A contributation to the "recovery" of the heart rate at the end of the experiment may be secondary to the dissipation of the morphine's potent vagotonic effect. Other factors contributing to the rise in the mean heart rate and the slight tachycardia noted in some individual animals in both dosage regimes, would include the decreasing depth of anesthesia with attendent increase in sympathetic nervous system activity.

The stability of the systolic and diastolic blood pressure after the first hour and for the remaining eleven hours concurs with current reports, although no studies heretofore encompass longer than eight hours (Cox, 1972a; Ledsome, Linden and Norman, 1971; Bass and Buckley, 1966; Van Citters, Franklin and Rushmer, 1964; Shabetai, Fowler

and Hurlburt, 1963). It is unlikely that the baroreceptor reflex is implicated in our findings of normotensive animals with slow heart rates since neither hypertension nor hypotension was a consistent finding. Mauck, Freund and Porter (1965), showed a significant increase in systemic vascular resistance with time and with the depth of chloralose/urethane anesthesia in dogs, but it is questionable whether chloralose alone (Clark and Mac Cannell, 1975) or morphine-chloralose alters this parameter (Hamed and Jandhyala, 1978). The consistently higher left ventricular fill pressures and aortic diastolic pressures with narrower pulse pressures of the Regime I animals, more likely represent an increase preload, an increased afterload, or a decrease stroke volume in the lightly anesthetized group.

This apparent preload difference may reflect a difference in sympathetic nervous system activity resulting in an increase in venous return (Guyton, 1976). In addition to this mechanism another hypothesis to be considered, is that chloralose anesthesia decreases preload in a dose-related manner. Normal canine values for left ventricular end-diastolic pressures have not been established, but reported "control" values encompass a range from 0 to 15 mmHg pressure (Mahler et al., 1975; Grossman et al., 1972;

Taylor et al., 1967). A significant difference ($P < 0.05$) in LVFPs was seen only in the ninth hour. This isolated finding may bespeak the small sample sizes utilized (Schefler, 1979) but the differences in LVFP between the two dosage regimes does suggest a dose-related effect of this anesthetic.

Early stability of the maximum dP/dt has been reported with only transient induction-related depression with chloralose (Cox, 1972a; Van Citters, Franklin and Rushmer, 1964). This parameter has been used in acute loading and contractility studies of chloralose but no long-term study has evaluated the effect of morphine-chloralose on myocardial contractility. The initial peak dP/dt mean values of Regime I and Regime II are nearly the same, but thereafter, R-I means exceed R-II means in every comparison. By examining the percent change from the initial values, a comparison of the magnitude of change in the peak dP/dt values can be made. Both groups of animals exhibited positive percent changes from the control value. The first comparison (at the end of the second hour) showed a significant difference ($P < 0.04$) between the two dosage regimes. While this may signify a difference in the initial contractile state of the two groups, this is unlikely. It may represent the time of greatest difference in contractile

response of the two regimes. No other significant differences occurred, but the Regime I reflected greater percent change throughout the twelve hours. The Regime II dogs showed a slight recovery, i.e., less depression, during the last six hours. Regime I dogs showed an initial large percent change which was diminished in magnitude in the fifth through eighth hours.

A gradual increase over time was observed in both percent change of maximum dP/dt and peak dP/dt in both maintenance regimes. Overall, it appears that dogs in both dosage regimes become more contractile with increasing duration of chloralose anesthesia. However, the anesthetizing dose of chloralose is being distributed from the plasma during the first hour of anesthesia time. The value from which the percent change of the maximum dP/dt was calculated was obtained at the conclusion of the hour following the heaviest dose (80 mg/kg) of chloralose, thus it might be expected that contractility would improve throughout the course, as the plateau concentration in the plasma gradually falls. The most interesting finding, however, is the difference between the two dosage regimes; the R-II animals showed a relative depression in peak dP/dt and percent change of maximum dP/dt as compared to R-I animals.

The parameter, maximum dP/dt has been cited to be preload dependent, e.g., when preload is increased by increases in end-diastolic volume and pressure, the rate of rise of the isovolumic LV pressure is elevated (Mason, 1969). Similarly, if afterload or aortic diastolic pressure increases, the peak dP/dt rises (Mason, 1969) because peak pressure is reached momentarily before the semilunar valves open and opening would be delayed at high diastolic pressures (Mason, 1969). In addition, dP/dt is directly related to the heart rate. While this parameter allows prediction of the direction of change, Vmax and V_{40} have been accepted as contractility indices that are independent of these loading factors, as well as independent of heart rate and rhythm changes (Davidson et al., 1974; Siegel et al., 1969).

Vmax values, although not significantly different between R-I and R-II lent the most substantial support to the trend that was developed in LVFP, peak dP/dt and percent change of maximum dP/dt. In all but the second comparison, R-I Vmax means exceeded R-II values, suggesting that a dose-related depression of contractility accompanies chloralose anesthesia in intact animals. The Vmax and V_{40} values were very similar in both groups, but over all, the R-I means were higher than the R-II means although not

significantly. Less hourly fluctuation was seen than with the dP/dt measurements, and these indices of contractility displayed quite stable values from the first through the twelfth hours. Regression lines drawn from the Vmax values of the two groups would be nearly parallel, however, the R-II Y-intercepts are all significantly lower than the R-I values. This further accents the trend exhibited in the other measures of contractility.

It is known that chloralose depresses contractility in heart-lung preparations (Bass and Buckley, 1966) as well as in intact dogs (Bond, Roberts and Manning, 1973; Cox, 1972a; Phillips, Priano and Traber, 1972; Mauck, Freund and Porter, 1965; Van Citters, Franklin and Rushmer, 1964). Mauck, Freund and Porter (1965) were the only investigators to report dose-related effects on indices of contractility. They showed that a progressive decline in cardiac output and simultaneous progressive increase in systemic vascular resistance accompanied chloralose/urethane anesthesia in dogs, with significant depression in their heavier dose group.

Theoretically, the Regime II animals should have higher blood plasma concentrations, yet no significant differences between the two groups was apparent with respect to hemodynamic parameters or contractility indices. With the wide

margin of safety associated with chloralose (Balis and Monroe, 1964), this is not totally unexpected, because the R-II dogs received only a gradual increase (3 percent I.D./hour) in the maintenance dosage over the amount prescribed for the R-I animals. It is apparent, though, from the data presented that left ventricular performance is depressed in the heavier dosage regime when compared to the lighter dose regime. Furthermore, it seems evident in the two dosage regimes tested that morphine-chloralose offers a hemodynamically stable preparation for twelve hours.

The arterial blood gases were remarkedly revealing of concurrent, yet silent events which accompanied the long-term chloralose anesthetic course. The dogs of both dosage regimes sustained a respiratory acidemia and profound hypoxemia. Normal arterial blood gases have been suggested in dogs to be within the following ranges:

pH:	7.33 - 7.42	(Danielson et al., 1975; Arfors, Arturson and Malmberg, 1971; Glick, Plauth and Braunwald, 1964; Dill et al., 1932)
$PaCO_2$:	32 - 45 mmHg	(Danielson et al., 1975; Feigl and D'Alecy, 1972; Glick, Plauth and Braunwald; 1964)
PaO_2:	71 - 114 mmHg	(Hammill et al., 1979; Danielson et al., 1975; Feigl and D'Alecy, 1972).

Plasma HCO_3^-:	22.6 mEq/L	(Ledsome, Linden and Norman, 1971)
Base excess:	-1 to -2.8 mEq/L	(Arfors, Arturson and Malmberg, 1971; Ledsome, Linden and Norman, 1971).

The improvement in the $PaCO_2$ and pH in both regimes during the latter part of the experiment probably reflects (1) metabolic degradation of morphine in conjunction with (2) the gradual increase in sympathetic activity as the level of anesthesia lightened. Recovery was more evident in Regime I as compared to Regime II, and nearly significant differences were seen by the eleventh and twelfth hours respectively. This concurs with findings by Mauck, Freund and Porter (1965), in that the direction of change of the pH and $PaCO_2$ was the same, but the magnitude of change was much greater in our series. Only minimal alterations in pH, $PaCO_2$ and PaO_2 during the two and one-half anesthesic period were observed by Mauck, Freund and Porter (1965). Although their "heavy-dose" (98 mg chloralose/978 mg urethane) group received amounts of chloralose only slightly greater than our animals the differences in pulmonary responses may be in part due to animal size (Krantz and Cascorbi, 1969; Kleinman and Radford, 1961), methodology, anesthetic maintenance and most particularly, to the drug used to establish anesthesia. Chloralose used in conjunction

with a morphine pre-operative medication is a different drug than chloralose-urethane combination and exhibits divergent physiological effects (Strobel and Wollman, 1969; Greisheimer et al., 1957).

During the latter portion of the experiment, the plasma bicarbonate (HCO_3^-) levels decreased to initial levels. In view of the establishment of near normal pH values in both regimes in the last five hours of the experiment, the change may reflect an improvement in ventilation and relaxation of compensatory conservation of HCO_3^-. The direction of change, though, is also consistent with a gradually developing metabolic acidosis, which is expected when tissue hypoxia is sustained (Price and Wilson, 1978; Alberti, 1971). In part, the metabolic component may reflect "dilutional acidosis" (Shires and Hollman, 1948) an adverse effect associated with chloralose anesthesia in dogs (Arfors, Arturson and Malmberg, 1971; Ledsome, Linden and Norman, 1971)

Profound hypoxemia accompanied both anesthetic dosage protocols for the entirety of the experiment. Although ventilation improved in both groups (i.e., $PaCO_2$ values decreased to within normal limits), the anesthetized animals were unable to overcome the concommittent hypoxemia. Spontaneous ventilation in the anesthetized animals may lead

to hypoventilation reflecting drug-induced central respiratory effects (Prys-Roberts, 1980; Bagshaw and Cox, 1975). In addition, the reaction to central hypoxia is diminished in anesthetized animals (Giese et al., 1978). Chloralose has been shown to decrease the central response to carbon dioxide, although peripheral chemoreceptor activity is relatively unaltered (Dripps and Dumke, 1943). A static position during anesthesia, even with occasional hyperinflation contributes to ventilation/perfusion inequality (Wahrenbrock et al., 1970) especially if the animal is breathing spontaneously. Spontaneous breathing which results in hypercapnia is always accompanied by hypoxemia (West, 1965; Dripps, Eckenhoff and Vandam, 1972). The presence of arterial hypoxia after compensatory correction of hypercapnia in the spontaneously breathing dog suggests either a ventilation/perfusion inequality, the development of a significant shunt or alveolar-capillary block (Murray, 1976) or a combination of these mechanisms. Although the presence of a pulmonary lesion seems apparent in both groups, a dose-related effect was observed between the two regimes. The ability of the Regime I dogs to recover more completely than the heavier-dosed Regime II dogs is evident. Although no significant differences were

recorded, this dose-related depression extends the observations and trends of the cardiac contractility data.

Interestingly, in spite of rather severe hypoxemia, the dogs in this portion of the study showed rather consistent hemodynamic stability. Hypoxia is known to exert significant effects on the cardiovascular system and on the heart (Muir, 1977; Thilenius, 1966). The ECG changes were not remarkable in either group. Without the measure of the arterial blood gases, the coexistence of hypoxemia and acidosis would have been undetected in our series, since cyanosis is known to be a late finding and an unreliable index of the degree of unsaturated hemoglobin (Widmann, 1970).

It is evident that during prolonged morphine-chloralose anesthesia in spontaneously breathing dogs the acid-base status and the degree of oxygenation requires close monitoring. Classical signs of hypoxia such as tachycardia, hypertension, dysrhythmias, increased cardiac output in the presence of skeletal muscle vasodilation and falling stoke volume (Hammill et al., 1979; Bing et al., 1969; Glick, Plauth and Braunwald, 1964) were only subtle, if even identifiable in our dogs that were thoroughly monitored. Mild to moderate hypercarbia is thought to increase plasma noradrenalin initially, and only later, to increase adrenalin

levels (Morris and Millar, 1962). Acidosis, if severe may cause decreased cardiac contractility (Downing, Talner and Gardner, 1965). However, while autonomic nervous system "balance" may be accomplished by these opposing compensations, the value of an in vivo model with these ongoing responses becomes extraordinarily complex and hence, the interpretation of research data may be totally invalid (Mushin, 1964).

The arterial blood gas data from both dosage regimes identified an area which required further study. To more fully assess the effects of chloralose maintenance regimes over extended anesthesia times, we elected to evaluate a mechanically ventilated regime and compare the results to an equal-dose but spontaneously breathing regime. The results of Phase II of this study are discussed in the next section.

To summarize, the results of the comparison of two maintenance protocols of chloralose anesthesia conflict with some of the long-held beliefs about this drug (Strobel and Wollman, 1969; Greisheimer, 1965). However, the results apparently concur with the underlying notion that more aggressive, albeit it often times empiric, management during the anesthetic course is warranted (Bagshaw and Cox, 1975). In both dosage regimes, a hypoxemia and acidemia occurred in

lieu of any pronounced hemodynamic or autonomic symptomatology. From these findings the importance of monitoring was established, at the least, standard cardiovascular and pulmonary parameters. In the long-term anesthetic maintenance regimes, inclusion of fluid and electrolyte status would be warranted (Bagshaw and Cox, 1975). In addition, the results from Phase I of this study suggested that marked respiratory embarrassment may accompany prolonged chloralose anesthesia in morphinized dogs.

Phase II

As in the Phase I dogs, the unventilated animals in Phase II of the study exhibited marked hypoxemia in the presence of an initial respiratory acidemia. Some of the trends observed in this phase of the study differed from the trends that characterized Regimes I and II. The hypoxemia. that was evident at the outset in both groups of Phase II was adequately compensated by the Regime IV dogs, but progressively deteriorated in the Regime III animals. Significant differences in PaO_2 between the two groups were noted at the end of the second, seventh, and ninth through twelfth hours.

The first hour appearance of hypoxemia, even in the ventilated series contradicts the belief that this drug

combination is benign with regard to the respiratory system (Danielson et al., 1975; Stobel and Wollman, 1969; Parker and Adams, 1978; Greisheimer, 1965). Dripps and Dumke (1943) documented decreased central chemoreceptor activity when chloralose is used, but showed that the peripheral chemoreceptors remain active, even augmented in their ability to react to lowered PaO_2 or increased $PaCO_2$ values. In the R-III dogs, it would seem that peripheral chemoreceptor activity was impaired or overridden.

In Phase I of the study, ventilation was initially depressed, then improved over the course of the experiment. In the Regime III animals, however, ventilation did not improve with time: it is unlikely that this is related to maintenance dosage, because cumulative hourly doses paralleled the Phase I, Regime II animals. The major difference between Regime II and Regime III dogs was the method of infusion; Regime III animals received a constant infusions whereas, the Regime II animals received bolus injections each hour. Hence, the constant infusion of anesthetic drug may offer a more stable blood level of anesthetic, with accompanying anesthetic plateau and thus avoidance of the "catch-up but overshoot" labile course associated with intermittent doses given empirically or "when the animals show signs of lightness".

The presence of arterial hypoxemia signifies concurrent tissue hypoxia in intact animals (Alberti, 1977; Bagshaw and Cox, 1975). Respiratory impairment, as denoted by the significantly elevated $PaCO_2$ values in Regime III, lead to the persistence of a significant acidemia in this group. The plasma bicarbonate (HCO_3^-) values of Regime III were all (except for the first comparison) greater than those of Regime IV, which may exemplify metabolic compensation in the hypercarbic, acidotic regime. Notably though, the bicarbonate values for both Regime III and Regime IV were generally lower than the accepted "normal" of 22.6 mEq/L (Ledsome, Linden and Norman, 1971). An underlying acidosis may accompany chloralose anesthesia, possibly due to the solvent, normal saline (Ledsome, Linden and Norman, 1971; Shires and Hollman, 1948), but may be a characteristic of chloralose (Arfors, Arturson and Malmberg, 1971). The rather low bicarbonate levels found in both Regime III and Regime IV may represent a summation of contributing factors; the finding that the HCO_3^- levels were slightly higher in the hypoxic Regime III animals than in the Regime IV dogs, does support this idea. It was evident from this phase of the study that chloralose anesthesia in morphinized dogs significantly impairs respiratory function and that

mechanical ventilation during the anesthetic course offers an effective means to overcome the problem. Additionally, a slight metabolic acidosis was uncovered using this anesthetic preparation when hypercarbia and hypoxemia were controlled.

Despite the coexistence of hypoxemia and severe mixed acidosis in Regime III and the mild-to moderate but stable metabolic acidosis in Regime IV, the hemodynamic variables exhibited remarkable independence and stability. The hemodynamic parameters monitored were similar in both regimes. The heart rates were slow and the electrocardiogram rhythms were generally stable in both regimes. The aortic systolic and diastolic blood pressures were similar in both groups although some differences were apparent. The Regime III dogs had higher systolic pressures, and although not quite as consistently, lower diastolic pressures than the Regime IV dogs. Generally, the Regime III animals exhibited wider pulse pressures which were significant from the Regime IV values in the last two hours of the data collection period. The classical effects of hypoxia may account in part for the hemodynamic trends demonstrated between these two regimes. Left ventricular fill pressure (LVFP), an index of preload, was higher in every comparison of Regime III and Regime IV, with statistical differences apparent by the

third hour and continuing through the entire anesthetic period. This possible decrease in preload in the ventilated group may be secondary to intrathoracic pressure alterations and decrease in venous return that accompanies positive pressure ventilation. Alternately, the preload of the Regime III dogs may be increased, and in view of the wider pulse pressures noted in these animals, stroke volume and hence cardiac output may be elevated.

Left ventricular contractility was different between the two regimes and was also apparently modified in each regime with time. In this phase of the study, peak dP/dt was greater in Regime III and significantly greater from Regime IV in the third through the eleventh hours. When the percent change of the maximum dP/dt was compared, the Regime III values changed in a positive direction while Regime IV values in the fourth through eleventh hours, decreased from initial values. In all but the tenth and eleventh hours, the variability from initial values was greater for the Regime IV animals, although no statistically significant differences were observed in the percent change of maximum dP/dt between the two regimes. The initial values from which calculations were made were nearly significant indicating that some variation existed in the contractile state between the two groups by the end of the

first hour. The only difference between these two groups was the manner in which ventilation was allowed. Hence, the apparent difference in contractility may represent either a compromise secondary to the mechanics of artificial respiration or a physiological response of the anesthetized animal to acidosis and hypoxemia. It is explainable that contractility increases initially in response stressors like hypoxemia and acidemia (Hammill et al., 1979; Bing et al., 1969; Boniface and Brown, 1953), as illustrated by the Regime III values. The differences in preload (LVFP) seen between the two regimes may be predominantly responsible for the differences in the peak dP/dt and the percent change of maximum dP/dt values, since preload variability does effect the rate of rise of the left ventricular pressure (Mason, 1969).

The development of depression in left ventricular peak dP/dt and percent change of maximum dP/dt with time in the mechanically ventilated dogs with normal acide-base status and adequate oxygenation, seems to be a change in the wrong direction. Simultaneously, however, it is seen from the hemodynamic data that during the second through twelfth hours, pulse pressures steadily decline in Regime IV, as the diastolic pressures rise and the systolic pressures gradually decrease. Heart rate is relatively

uneffected, and preload (LVFP) does exhibit a gradual decline, albeit quite gradual.

LVFP values for Regime IV were significantly depressed when compared to Regime III. The trend in both of these dP/dt indices suggests that mechanical ventilation may be indirectly responsible for a diminution in dP/dt. These within group changes may represent a gradually developing inability to compensate for the hemodynamic consequences of mechanical ventilation. The narrowing pulse pressure exhibited, parallelled the fourth through eleventh hour depression in dP/dt in the Regime IV dogs. This may reflect diminution in the cardiac output, or at the least, compromise of the anesthetized cardiovascular responsiveness. Cardiac output is known to be decreased when mechanical ventilation is instituted (Dripps, Eckenhoff and Vandam, 1972), however, this has been challenged in the morphinized dog anesthetized with chloralose (Krasney, 1971).

Further examination of contractility indices the Vmax and V_{40} did not magnify the trends in the dP/dt parameters. A more stable 'within group' pattern emerged for both regimes. In the Vmax parameter, all of the R-IV values were higher than the R-III values and a significant difference occurred in the first comparison. This may signal

a difference in initial contractility between the ventilated and spontaneously breathing animals. The Regime III dogs had increased peak dP/dt values, positive percent change of maximum dP/dt with only slight fluctuations from initial values, decreased Vmax and slightly fluctuating V_{40} mean values, compared to the Regime IV dogs.

Preload (LVFP) was significantly higher, and pulse pressures were wider in the Regime III dogs which might influence the dP/dt parameters (Krayenbuehl, Hess and Turina, 1978; Braunwald, 1977). Because of the dependence of this paramter (dP/dt) on muscle mass (Mason, 1969) it is a less than optimal comparative measure between animals, rather is better limited to sequential assessments of the same animal. Vmax and V_{40}, utilizing developed pressure (Grossman et al., 1972) have been found to be relatively independent of loading factors as well as valuable tools to assess myocardial contractile status among individuals (Krayenbuehl, Hess and Turina, 1978). From these data, especially the Vmax index, it is concluded that myocardial contractility was greater in Regime IV than Regime III throughout the experiment. However, an initial increase, followed by a progressive decline in the Vmax values of Regime IV suggests some decreased contractility over time in chloralose anesthetized, ventilated dogs. Regime III

contractility seems to increase from initial measurements, plateau for several hours and finally decrease in the last hours of the experiment, although not to levels below the initial state. Thus, the known myocardial depressant effects of chloralose anesthesia (Bass and Buckley, 1966; Van Citters, Franklin and Rushmer, 1964) may have been reflected in the ventilated regime but seemed additative in the hypoxic, profoundly acidotic animals.

However, several technical considerations should be made regarding Vmax and V_{40} measurements in this study. The differentiated dP/dt waveform was found to have a 0.01 second lag time when compared to the left ventricular pressure waveform. In addition, the inclusion of these pairs of data, x and y, was determined by the plotted slope of the lines such that x and y values fell between the peak pressure attained, and the rapid break (roughly equivalent to aortic diastolic pressure) in the curve. If the Y values exhibited a "dip" as pressure was developing, these data points were excluded. If V_{CE} waivers as left ventricular pressure develops, until the peak pressure is reached and ejection occurs, a technical error in computation probably exists. However, by including all the data points that could realistically reflect the relationship of V_{CE} and developed left ventricular pressure the technical

difficulties are minimized so that Vmax, V_{40} and the lines of best fit between the two regimes could be compared.

Overall, the Regime IV animals appeared to be more contractile than the Regime III animals. The most notable finding in contractile status in both groups, however, is the initial increase and then decline of peak dP/dt, the percent change of maximum dP/dt, Vmax and V_{40} indices. These data suggest that there may be a deterioration in contractility with time during prolonged chloralose anesthesia; and further, that the magnitude of the deterioration in cardiac contractility is increased in the presence of sustained hypoxemia and acidemia. Although our study was extended over a longer time (12 hours) these results concur with the findings of several others (Bass and Buckley, 1966; Mauck, Freund and Porter, 1965; Van Citters, Franklin and Rushmer, 1964) although not unanimously (Arfors, Arturson and Malmberg, 1971).

In summary, the spontaneously breathing animals sustained pathological hypoxemia and hypercarbia which progressed without adequate compensation. A metabolic component to the acidemia was identifiable in both groups; a finding that has been previously reported (Arfors, Arturson and Malmberg, 1971; Ledsome, Linden and Norman,

1971). In addition, our data suggest that chloralose anesthesia may exert a time-dependent depressant effect on myocardial contractility and that the coexistence of hypoxemia and acidemia may worsen left ventricular performance during long-term chloralose anesthesia.

CONCLUSIONS

The prevalent use of chloralose anesthesia to facilitate physiological research (Gabshaw and Cox, 1975) evokes the careful delineation of anesthetic drug effect from experimental intervention. The purpose of this study was twofold:

1. To determine if there were significant differences in cardiopulmonary performance between two alpha-chloralose anesthetic maintenance regimes, and

2. To assess the need for ventilatory support during prolonged alpha-chloralose anesthesia.

Phase I of this study did provide quantitative information of different dosage maintenance protocols on the cardiopulmonary status in morphinized dogs receiving chloralose anesthesia. Although no significant differences were seen between the two groups, the following conclusions were drawn:

1. No significant difference in arterial blood gases was found between regimes; however, in both regimes the changes in the pH and $PaCO_2$ were in the same direction.

2. No significant difference in the contractility indices was found between regimes; however, in general, Regime II mean values for left ventricular fill pressure,

aortic diastolic pressure, the percent change in dP/dt, peak dP/dt, Vmax and V_{40} were lower than in Regime I.

3. These data suggest that alpha-chloralose may have a dose-dependent effect on the cardiopulmonary status of anesthetized dogs.

4. More extensive investigation of different dose regimes and maintenance protocols is necessary in order to evaluate the cardiopulmonary stability of prolonged chloralose anesthesia.

Phase II of this study was an investigation to evaluate the effects of mechanical ventilation during long-term maintenance of chloralose anesthesia in morphinized dogs. When comparisons between the spontaneously breathing and mechanically ventilated regimes were undertaken significant differences in the arterial blood gases and in some of the contractility indices were found. From these data, the following conclusions were drawn:

1. There was a significant depression in pH and a significant elevation in $PaCO_2$ in the spontaneously breathing group.

2. The PaO_2 was reduced in the spontaneously breathing animals and was significantly lower than the mechanically ventilated group during the latter part of the experiment.

3. There were no consistent significant differences in heart rate, systolic and diastolic pressure; however, the pulse pressures and left ventricular fill pressures were consistently lower in the Regime IV dogs when compared to the R-III dogs.

4. There seemed to be inconsistent differences in the contractility indices, but overall, the R-IV animals appeared more contractile. A time-dependent depression in contractility indices may accompany prolonged chloralose anesthesia in dogs.

5. These data suggest that in the long-term chloralose maintenance regime specified, a pronounced hypoxemia, acidemia and hypercapnia occur in spontaneously breathing animals.

6. Ventilatory support is recommended during prolonged anesthetic maintenance if the co-existence of hypoxemia and acidemia would disfavorably alter the experimental results.

Therefore, in this study it was apparent that consequential pathology could accompany prolonged morphine-chloralose anesthesia, without detection by frequent assessment of standard cardiovascular parameters such as the blood pressure, the heart rate and the electrocardiogram.

It was also apparent that mechanical ventilation could significantly alter the respiratory depression that characterized the spontaneously breathing animals. Further, this study serves to emphasize the necessity of incorporating a specific anesthetic maintenance protocol into the experimental design, and monitoring cardio-pulmonary parameters during the anesthetic course.

APPENDIX A

PHASE I

REGIME I AND REGIME II

TABLE 1: MEAN VALUES OF PEAK dP/dt

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	3072 ± 209	3078 ± 277	.987
2	3921 ± 326	3187 ± 151	.075
3	3761 ± 272	3242 ± 244	.193
4	3885 ± 154	3179 ± 310	.075
5	3628 ± 303	3273 ± 406	.503
6	3611 ± 289	3386 ± 412	.667
7	3628 ± 263	3478 ± 453	.783
8	3600 ± 237	3520 ± 414	.872
9	3791 ± 252	3575 ± 377	.646
10	4144 ± 282	3847 ± 415	.570
11	4388 ± 213	3910 ± 340	.268
12	4231 ± 180	4148 ± 364	.844

TABLE 2: PERCENT CHANGE IN MEAN MAXIMUM dP/dt

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
2	27.5 ± 6.3	5.4 ± 6.7	.042*
3	21.8 ± 3.8	7.4 ± 9.7	.207
4	25.7 ± 8.4	5.1 ± 11.6	.187
5	19.0 ± 7.8	8.3 ± 14.2	.526
6	19.9 ± 6.4	10.9 ± 11.5	.515
7	20.3 ± 11.4	25.6 ± 18.3	.811
8	19.1 ± 10.1	15.0 ± 11.1	.791
9	25.3 ± 10.6	17.7 ± 12.0	.646
10	36.6 ± 10.2	26.1 ± 11.5	.512
11	44.9 ± 9.3	27.9 ± 7.6	.196
12	39.9 ± 9.6	36.0 ± 9.7	.780

* significant difference ($P < 0.05$)

TABLE 3: MEAN VALUES OF Vmax

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	1.70 ± .12	1.66 ± .14	.816
2	1.53 ± .17	1.68 ± .17	.535
4	1.78 ± .14	1.72 ± .20	.828
6	1.70 ± .14	1.62 ± .13	.671
8	1.69 ± .16	1.61 ± .11	.693
10	1.78 ± .22	1.66 ± .16	.684
12	1.81 ± .19	1.59 ± .17	.429

TABLE 4: LINEAR REGRESSION

Hour	Y = A + BX Regime I	Regime II	Equality of Slopes P <	Equality of Intercepts P <
1	1.858+(-.001)x	1.629+(-.004)x	NS	0.001**
2	1.705+(-.002)x	1.662+(-.006)x	0.05*	0.001**
4	1.789+(-.005)x	1.597+(-.006)x	NS	0.001**
6	1.731+(-.004)x	1.697+(-.007)x	NS	0.001**
8	1.855+(-.006)x	1.708+(-.006)x	NS	0.001**
10	1.805+(-.005)x	1.733+(-.006)x	NS	0.01 *
12	1.876+(-.005)x	1.514+(-.002)x	NS	0.001**

* significant difference ($P < 0.05$)
** highly significant difference ($P < 0.001$)
NS = no significant difference

TABLE 5: MEAN VALUES OF V_{40}

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	1.57 ± .09	1.47 ± .09	0.438
2	1.52 ± .11	1.47 ± .10	0.725
4	1.65 ± .13	1.44 ± .10	0.233
6	1.58 ± .10	1.43 ± .06	0.222
8	1.59 ± .13	1.45 ± .05	0.320
10	1.63 ± .15	1.50 ± .08	0.467
12	1.66 ± .13	1.49 ± .10	0.346

TABLE 6: MEAN VALUES OF HEART RATE

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	59.2 ± 3.9	69.0 ± 9.0	.346
2	61.0 ± 4.8	64.6 ± 5.5	.634
3	65.2 ± 9.2	57.8 ± 3.8	.477
4	60.8 ± 4.5	55.4 ± 4.7	.433
5	58.4 ± 5.6	54.0 ± 5.5	.590
6	59.0 ± 2.2	59.4 ± 6.2	.953
7	64.2 ± 8.7	67.0 ± 8.3	.822
8	59.4 ± 4.8	62.8 ± 10.2	.766
9	71.8 ± 7.2	65.6 ± 11.9	.667
10	76.0 ± 10.7	69.4 ± 12.4	.698
11	80.8 ± 7.9	72.6 ± 11.5	.572
12	84.0 ± 8.0	90.2 ± 17.3	.754

TABLE 7: MEAN VALUES OF AORTIC SYSTOLIC PRESSURE

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	123.1 ± 5.0	128.1 ± 5.0	.503
2	139.0 ± 4.8	137.5 ± 3.7	.803
3	141.4 ± 3.3	144.3 ± 7.7	.741
4	135.6 ± 5.9	138.6 ± 8.1	.775
5	138.1 ± 5.3	139.0 ± 8.7	.930
6	136.6 ± 4.2	135.9 ± 6.9	.933
7	138.4 ± 5.4	131.7 ± 6.4	.444
8	137.8 ± 3.2	135.1 ± 5.8	.698
9	130.6 ± 10.0	132.7 ± 5.2	.852
10	141.2 ± 5.9	134.3 ± 5.7	.418
11	137.9 ± 13.1	137.9 ± 4.9	.998
12	140.5 ± 4.6	136.6 ± 5.8	.613

TABLE 8: MEAN VALUES OF AORTIC DIASTOLIC PRESSURE

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	69.1 ± 6.7	69.5 ± 5.4	.962
2	78.6 ± 7.3	73.8 ± 6.4	.631
3	80.2 ± 7.8	77.5 ± 4.7	.772
4	70.9 ± 4.7	71.4 ± 6.2	.948
5	76.2 ± 8.6	70.7 ± 8.3	.659
6	76.0 ± 6.7	67.7 ± 7.2	.427
7	76.3 ± 7.5	67.4 ± 8.3	.446
8	74.2 ± 4.2	70.0 ± 7.8	.649
9	79.4 ± 4.2	64.4 ± 8.5	.153
10	82.1 ± 5.4	68.7 ± 8.0	.201
11	89.6 ± 7.2	73.5 ± 7.3	.154
12	87.3 ± 4.6	76.4 ± 10.8	.379

TABLE 9: MEAN VALUES OF PULSE PRESSURE

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	54.0 ± 2.9	58.6 ± 3.2	.325
2	61.7 ± 2.6	63.7 ± 6.9	.795
3	61.2 ± 4.8	66.3 ± 6.0	.527
4	64.7 ± 3.5	67.1 ± 6.3	.741
5	61.8 ± 3.9	68.3 ± 7.6	.473
6	60.6 ± 3.5	68.2 ± 5.2	.262
7	62.0 ± 4.8	64.3 ± 6.0	.778
8	59.5 ± 5.7	68.3 ± 5.8	.312
9	57.8 ± 4.9	68.1 ± 6.8	.255
10	59.9 ± 3.9	65.6 ± 5.2	.400
11	54.9 ± 1.9	64.4 ± 4.0	.068
12	53.2 ± 2.2	60.3 ± 6.2	.315

TABLE 10: MEAN VALUES OF LEFT VENTRICULAR FILL PRESSURE

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	8.5 ± 1.1	6.5 ± 0.9	.200
2	10.4 ± 1.2	7.4 ± 1.1	.095
3	9.6 ± 1.5	8.2 ± 1.2	.467
4	9.7 ± 1.3	7.7 ± 0.9	.244
5	9.8 ± 1.2	7.8 ± 1.0	.229
6	9.3 ± 1.2	8.1 ± 1.1	.459
7	9.7 ± 1.4	6.7 ± 1.0	.115
8	10.0 ± 2.2	8.2 ± 1.0	.470
9	10.3 ± 0.8	7.6 ± 0.9	.054*
10	8.8 ± 1.4	6.8 ± 1.0	.254
11	8.2 ± 1.1	8.1 ± 1.0	.969
12	8.1 ± 1.0	8.9 ± 0.7	.563

* significant difference ($P < 0.05$)

TABLE 11: MEAN VALUES OF ARTERIAL pH

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	7.26 ± .01	7.29 ± .03	.336
2	7.31 ± .02	7.29 ± .02	.454
3	7.31 ± .02	7.28 ± .02	.204
4	7.33 ± .01	7.30 ± .02	.143
5	7.33 ± .01	7.31 ± .01	.301
6	7.36 ± .02	7.33 ± .01	.153
7	7.34 ± .01	7.32 ± .03	.352
8	7.38 ± .02	7.33 ± .03	.174
9	7.38 ± .02	7.31 ± .04	.167
10	7.38 ± .01	7.33 ± .04	.280
11	7.41 ± .02	7.32 ± .04	.073
12	7.42 ± .01	7.32 ± .05	.068

TABLE 12: MEAN VALUES OF ARTERIAL PCO_2

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	51.4 ± 1.4	48.0 ± 3.4	.382
2	50.2 ± 2.3	51.6 ± 3.6	.760
3	44.7 ± 3.5	52.4 ± 3.0	.135
4	45.0 ± 1.8	50.6 ± 5.3	.349
5	44.9 ± 3.3	49.7 ± 1.5	.219
6	42.5 ± 2.6	42.0 ± 3.3	.894
7	42.4 ± 2.8	49.1 ± 4.4	.240
8	36.2 ± 2.1	43.3 ± 4.9	.223
9	38.4 ± 1.3	44.2 ± 6.8	.420
10	37.7 ± 2.1	40.6 ± 3.2	.471
11	34.9 ± 1.7	47.7 ± 7.4	.128
12	34.4 ± 1.7	45.2 ± 6.2	.133

TABLE 13: MEAN VALUES OF ARTERIAL HCO_3^-

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	22.8 ± 0.5	21.9 ± 1.2	.474
2	25.4 ± 1.0	23.8 ± 0.8	.231
3	21.6 ± 1.2	24.1 ± 0.6	.095
4	23.6 ± 0.7	24.0 ± 1.7	.852
5	23.0 ± 1.0	25.1 ± 0.8	.144
6	23.7 ± 0.4	21.2 ± 1.2	.076
7	22.9 ± 1.5	23.7 ± 1.2	.702
8	21.6 ± 1.1	21.4 ± 1.7	.894
9	22.6 ± 0.9	21.5 ± 1.4	.520
10	22.2 ± 1.4	21.0 ± 1.7	.620
11	21.8 ± 1.2	23.4 ± 2.1	.521
12	22.2 ± 0.7	22.2 ± 1.5	.xxx

TABLE 14: MEAN VALUES OF ARTERIAL PO_2

HOUR	REGIME I	REGIME II	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	55.1 ± 5.7	53.1 ± 2.4	.771
2	63.1 ± 6.8	63.7 ± 1.7	.939
3	57.4 ± 5.3	65.3 ± 4.9	.302
4	60.1 ± 7.9	67.7 ± 4.3	.481
5	61.2 ± 4.9	60.1 ± 6.1	.899
6	62.6 ± 8.0	60.9 ± 7.1	.878
7	56.4 ± 8.3	60.3 ± 4.7	.694
8	61.1 ± 5.8	64.8 ± 5.4	.653
9	60.8 ± 7.8	65.3 ± 7.3	.685
10	63.8 ± 6.0	69.2 ± 4.3	.484
11	62.4 ± 7.7	58.0 ± 5.8	.655
12	58.4 ± 7.6	54.4 ± 9.7	.757

APPENDIX B

PHASE II

REGIME III AND REGIME IV

TABLE 15: MEAN VALUES OF PEAK dP/dt

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	3256 ± 312	2480 ± 180	.063
2	3552 ± 300	2764 ± 370	.136
3	3445 ± 376	2731 ± 284	.168
4	3290 ± 376	2198 ± 171	.030*
5	3146 ± 336	1970 ± 90	.010*
6	3249 ± 415	1902 ± 85	.013*
7	3260 ± 318	1880 ± 99	.003**
8	3159 ± 319	1820 ± 193	.007*
9	3392 ± 288	1939 ± 174	.003**
10	3906 ± 483	1735 ± 161	.003**
11	3723 ± 449	2013 ± 341	.016*
12	3341 ± 379	2538 ± 606	.294

* significant difference ($P < 0.05$)

** highly significant difference ($P < 0.001$)

TABLE 16: PERCENT CHANGE IN MEAN MAXIMUM dP/dt

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
2	10.8 ± 7.7	14.2 ± 19.2	.873
3	5.9 ± 4.4	12.4 ± 14.6	.682
4	3.1 ± 12.2	- 8.2 ± 8.7	.473
5	- 0.9 ± 12.4	-18.9 ± 6.7	.235
6	2.0 ± 13.2	-21.8 ± 6.1	.142
7	2.2 ± 10.0	-22.5 ± 7.0	.078
8	1.2 ± 16.3	-24.6 ± 9.5	.207
9	9.2 ± 17.6	- 9.7 ± 18.1	.475
10	28.8 ± 28.6	-20.9 ± 14.2	.159
11	23.1 ± 27.9	-13.5 ± 19.7	.315
12	5.1 ± 12.9	5.7 ± 29.3	.984

TABLE 17: MEAN VALUES OF Vmax

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	1.41 ± .32	2.72 ± .41	.037*
2	2.09 ± .68	2.92 ± .42	.329
4	2.01 ± .44	2.43 ± .23	.426
6	2.08 ± .53	2.41 ± .27	.606
8	2.08 ± .57	2.44 ± .28	.582
10	1.98 ± .45	2.32 ± .26	.532
12	1.79 ± .67	2.50 ± .35	.377

* significant difference ($P < 0.05$)

TABLE 18: LINEAR REGRESSION

Hour	Y = A + BX Regime III	Regime IV	Equality of Slopes P <	Equality of Intercepts P <
1	2.034+(-.010)x	2.588+(-.020)x	0.01*	NS
2	2.617+(-.016)x	2.785+(-.021)x	NS	NS
4	2.548+(-.017)x	2.310+(-.017)x	NS	0.001**
6	2.653+(-.018)x	2.300+(-.020)x	NS	0.001**
8	2.595+(-.019)x	2.296+(-.022)x	NS	0.001**
10	2.235+(-.011)x	2.249+(-.022)x	0.001**	0.001**
12	2.166+(-.012)x	2.051+(-.012)x	NS	NS

* significant difference ($P < 0.05$)
** highly significant difference ($P < 0.001$)
NS = no significant difference

TABLE 19: MEAN VALUES OF V_{40}

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	1.38 ± .20	1.82 ± .21	.174
2	1.71 ± .36	1.98 ± .29	.578
4	1.63 ± .23	1.63 ± .14	.987
6	1.61 ± .24	1.51 ± .11	.707
8	1.57 ± .19	1.47 ± .15	.676
10	1.59 ± .20	1.40 ± .14	.450
12	1.41 ± .31	1.73 ± .29	.469

TABLE 20: MEAN VALUES OF HEART RATE

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	70.9 ± 9.5	66.2 ± 2.3	.645
2	68.4 ± 9.6	76.6 ± 23.0	.749
3	53.1 ± 3.7	70.6 ± 12.6	.221
4	48.4 ± 4.3	56.5 ± 3.1	.163
5	51.3 ± 4.6	54.7 ± 4.7	.614
6	52.7 ± 3.9	50.0 ± 2.8	.595
7	59.6 ± 6.9	53.7 ± 5.0	.512
8	55.9 ± 6.3	55.6 ± 5.9	.975
9	57.2 ± 8.6	59.3 ± 4.1	.830
10	75.1 ± 17.0	58.3 ± 3.7	.361
11	79.7 ± 17.3	77.8 ± 7.6	.924
12	75.3 ± 21.2	89.8 ± 19.7	.630

TABLE 21: MEAN VALUES OF AORTIC SYSTOLIC PRESSURE

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	130.5 ± 14.4	124.0 ± 10.9	.729
2	147.1 ± 7.2	123.3 ± 6.3	.037*
3	144.5 ± 5.4	130.3 ± 4.8	.085
4	147.4 ± 10.7	127.9 ± 8.9	.195
5	140.5 ± 9.7	130.5 ± 8.6	.416
6	139.2 ± 8.9	127.3 ± 6.6	.313
7	137.9 ± 8.6	120.9 ± 7.7	.179
8	134.1 ± 9.5	117.8 ± 7.4	.214
9	133.0 ± 7.6	113.2 ± 7.8	.107
10	157.2 ± 23.1	110.3 ± 7.1	.088
11	141.0 ± 13.3	108.1 ± 10.1	.083
12	132.1 ± 7.3	123.7 ± 13.4	.597

* significant difference ($P < 0.05$)

TABLE 22: MEAN VALUES OF AORTIC DIASTOLIC PRESSURE

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	62.3 ± 4.2	66.3 ± 5.5	.584
2	80.4 ± 6.1	69.4 ± 5.7	.224
3	74.9 ± 4.1	82.0 ± 5.7	.343
4	74.2 ± 3.5	80.3 ± 8.3	.512
5	70.4 ± 5.8	82.0 ± 8.4	.292
6	66.7 ± 5.4	75.3 ± 5.4	.292
7	70.2 ± 6.9	69.4 ± 5.6	.929
8	63.0 ± 4.2	68.3 ± 3.7	.365
9	62.2 ± 7.8	65.5 ± 3.8	.717
10	89.6 ± 26.4	62.1 ± 2.5	.331
11	71.8 ± 14.4	68.3 ± 3.4	.818
12	67.7 ± 8.7	82.8 ± 7.4	.222

TABLE 23: MEAN VALUES OF PULSE PRESSURE

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	56.8 ± 5.6	57.7 ± 7.4	.927
2	64.8 ± 8.8	53.2 ± 4.4	.269
3	67.6 ± 9.1	51.9 ± 5.6	.181
4	73.3 ± 10.7	47.6 ± 6.7	.077
5	70.1 ± 10.0	48.5 ± 6.4	.106
6	70.4 ± 10.3	48.3 ± 3.5	.077
7	67.7 ± 10.1	51.5 ± 5.8	.201
8	71.1 ± 9.7	49.5 ± 6.2	.098
9	70.7 ± 9.4	47.7 ± 4.9	.062
10	67.7 ± 11.0	48.1 ± 6.8	.169
11	69.1 ± 8.4	39.8 ± 8.5	.040*
12	64.4 ± 11.6	35.9 ± 4.8	.052*

* significant difference ($P < 0.05$)

TABLE 24: MEAN VALUES OF LEFT VENTRICULAR FILL PRESSURE

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	7.5 ± 1.4	4.7 ± 0.8	.123
2	7.5 ± 0.9	4.8 ± 1.7	.204
3	7.4 ± 0.9	4.0 ± 0.9	.032*
4	8.9 ± 0.8	4.3 ± 0.9	.004**
5	7.6 ± 0.6	3.9 ± 1.1	.015*
6	7.7 ± 0.9	4.6 ± 0.8	.039*
7	8.3 ± 1.8	4.0 ± 0.9	.063
8	8.3 ± 1.6	4.8 ± 1.1	.107
9	8.1 ± 1.5	3.4 ± 0.6	.019*
10	9.8 ± 2.1	4.0 ± 0.9	.032*
11	10.2 ± 1.4	3.1 ± 1.0	.003**
12	8.5 ± 1.5	3.6 ± 1.5	.047*

* significant difference ($P < 0.05$)
** highly significant difference ($P < 0.001$)

TABLE 25: MEAN VALUES OF ARTERIAL pH

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	7.23 ± .02	7.33 ± .02	.004**
2	7.23 ± .02	7.34 ± .02	.003**
3	7.24 ± .02	7.34 ± .01	.010*
4	7.24 ± .03	7.33 ± .01	.016*
5	7.23 ± .04	7.34 ± .02	.013*
6	7.23 ± .04	7.34 ± .01	.014*
7	7.23 ± .04	7.33 ± .01	.041*
8	7.21 ± .05	7.33 ± .02	.043*
9	7.20 ± .04	7.32 ± .02	.020*
10	7.18 ± .04	7.32 ± .02	.019*
11	7.16 ± .06	7.31 ± .01	.051*
12	7.15 ± .07	7.33 ± .01	.035*

* significant difference ($P < 0.05$)

** highly significant difference ($P < 0.001$)

TABLE 26: MEAN VALUES OF ARTERIAL PCO_2

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	53.2 ± 2.0	38.8 ± 0.8	.001**
2	52.6 ± 2.6	39.6 ± 2.0	.004**
3	51.6 ± 1.1	37.4 ± 0.3	.001**
4	48.4 ± 2.4	39.0 ± 1.7	.012*
5	51.9 ± 1.6	38.3 ± 1.1	.001**
6	52.5 ± 3.0	37.5 ± 0.3	.001**
7	51.7 ± 3.5	37.3 ± 1.0	.004**
8	53.7 ± 3.7	38.0 ± 1.5	.004**
9	56.0 ± 2.9	38.7 ± 1.3	.001**
10	60.8 ± 3.6	36.6 ± 0.7	.001**
11	62.3 ± 6.0	38.2 ± 0.9	.004**
12	61.3 ± 5.7	37.4 ± 6.8	.003**

* significant difference ($P < 0.05$)

** highly significant difference ($P < 0.001$)

TABLE 27: MEAN VALUES OF ARTERIAL HCO_3^-

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	18.9 ± 2.7	19.7 ± 0.8	.794
2	21.7 ± 1.8	21.1 ± 1.3	.809
3	21.8 ± 1.5	21.0 ± 1.3	.698
4	20.7 ± 1.2	20.1 ± 1.2	.747
5	21.2 ± 1.5	20.7 ± 1.4	.787
6	21.4 ± 1.5	20.3 ± 0.7	.510
7	21.3 ± 1.5	19.4 ± 0.8	.279
8	21.2 ± 1.5	19.9 ± 0.8	.458
9	21.4 ± 1.5	19.7 ± 1.3	.419
10	22.4 ± 1.8	18.5 ± 0.8	.087
11	21.5 ± 2.4	18.6 ± 0.8	.302
12	20.2 ± 2.1	18.5 ± 0.2	.434

TABLE 28: MEAN VALUES OF ARTERIAL PO_2

HOUR	REGIME III	REGIME IV	P <
	MEAN ± S.E.M.	MEAN ± S.E.M.	
1	68.8 ± 5.3	78.9 ± 4.3	.168
2	69.6 ± 6.6	88.2 ± 3.9	.042*
3	71.1 ± 8.1	89.4 ± 5.9	.105
4	70.1 ± 8.6	91.9 ± 7.2	.088
5	65.6 ± 8.8	88.3 ± 7.6	.088
6	64.0 ± 10.7	86.2 ± 4.5	.091
7	60.7 ± 8.3	87.3 ± 4.4	.022*
8	59.1 ± 13.3	87.2 ± 6.9	.086
9	56.5 ± 6.5	95.4 ± 10.8	.015*
10	51.2 ± 8.4	86.2 ± 7.8	.016*
11	53.5 ± 9.3	97.1 ± 9.4	.011*
12	54.8 ± 10.1	88.6 ± 7.5	.027*

* significant difference ($P < 0.05$)

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