CARDIOPULMONARY EFFECTS OF FENTANYL-DROPERIDOL, NITROUS OXIDE, AND ATROPINE SULFATE IN DOGS

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ABSTRACT

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By

Delbert J. Krahwinkel Jr.

The cardiopulmonary effects of droperidol-fentanyl, nitrous oxide, and atropine were evaluated and analyzed in 12 adult male Beagles. The cardiovascular variables measured were: cardiac output, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, central venous pressure, heart rate, stroke volume, total peripheral resistance, and packed cell volume. Respiratory measurements included arterial and venous pH, PO_2 and PCO_2, base deficit, minute volume, respiratory rate, and tidal volume. In addition, analgesia, response to auditory stimuli, and muscle relaxation were subjectively evaluated. All dogs were surgically prepared with a thermistor in the aorta for measuring cardiac output by thermal dilution. Arterial and venous catheters were inserted and a chronic tracheostomy was performed. Each dog served as its own control and data obtained from unanesthetized, unmedicated animals were compared with data recorded following administration of the test drugs.

The dogs were randomly divided into 3 groups of 4 dogs each. Group I was given intravenous droperidol-fentanyl alone; Group II was given droperidol-fentanyl intravenously with 67% nitrous oxide, and

Group III was given atropine sulfate intramuscularly followed by intravenous droperidol-fentanyl and 67% nitrous oxide.

Respiration was depressed in all 3 groups for 3 to 5 minutes following injection of the droperidol-fentanyl. This resulted in a respiratory and metabolic acidosis in all animals.

In addition, droperidol-fentanyl alone caused a decrease in systolic pressure and a slight decrease in heart rate. These dogs were sensitive to auditory stimulation. No cardiovascular changes were noted when nitrous oxide was added in the Group II animals. Analgesia and muscle relaxation were improved over the Group I animals. The premedication of atropine sulfate in Group III resulted in increased cardiac output, heart rate, and diastolic pressure. The subsequent administration of droperidol-fentanyl-nitrous oxide caused a transient increase in mean and systolic pressure. This latter anesthetic regime along with assisted or controlled respiration provides an excellent anesthetic state with minimal cardiopulmonary depression.

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Dedicated to

My God

to Whom belongs the credit
for any and all talents
that I possess

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INTRODUCTION

In 1949, Laborit of France conceived the idea that general anesthesia could be produced without profound depression of all cortical and subcortical centers. He introduced a method of anesthesia based on selective blocking of certain cellular, autonomic, and endocrine responses. This new technique utilized a narcotic-tranquilizer combination to form a "lytic cocktail." When this method, called neuroplegia, was combined with hypothermia, surgery could be performed without the aid of other anesthetic agents. However, this resulted in marked circulatory depression. Consequently, the technique never gained wide popularity.

The term neuroleptanalgesia was introduced in Europe by De Castra and Mudeleer in 1959. They popularized the idea and stimulated interest by using a potent psychomotor sedative with a powerful analgesic.

The search continued for a means of selectively blocking afferent nervous systems involved in surgical stress. With the emphasis on analgesia, Janssen (1963) introduced a series of highly potent meperidine-derived analgesics from which evolved the narcotic, fentanyl. This drug proved to be a very potent analgesic with minimal cortical and cardiovascular depressant effects. Janssen simultaneously developed a group of butyrophenone derivative tranquilizers. These potent tranquilizers induced a state of "neurolepsis" by effectively suppressing subcortical and autonomic activity. Droperidol was one of this group.

When these 2 drugs were administered, a condition resulted in which the patient was completely passive, unresistant to physical stress, and analgesic. This stage was referred to as neuroleptanalgesia (NLA). The combination of droperidol and fentanyl in a 50:1 ratio is the primary neuroleptanalgesic presently used. Innovar-Vet[a] contains 20 mg of droperidol and 0.4 mg of fentanyl per milliliter and is used in animals. Innovar[b] is used in human medicine and contains 2.5 mg of droperidol and 0.05 mg of fentanyl per milliliter. Innovar is used extensively in human surgery for the poor-risk patient who cannot tolerate cardiovascular depression produced by most inhalant anesthetics. Many inconsistencies have been reported in the literature with reference to the cardiopulmonary effects of NLA. Some investigators have reported a significant decrease in blood pressure while others have reported no decrease. Bradycardia was observed by some but not by others. Similar differences have been noted in the effect on respiratory rate and tidal volume.

The objective of this experiment was to evaluate the cardiovascular and respiratory effects of Innovar-Vet in the dog when used alone and with nitrous oxide and atropine sulfate. The reasons for the study were (1) inconsistencies in the literature both in its effects on man and dogs, (2) a lack of control measurements for comparison, (3) other drugs were used in many experiments which may have affected the results, and (4) a lack of a study using NLA alone and in combination with nitrous oxide and atropine.

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[a]Innovar-Vet[R], Pitman-Moore, Inc., Washington Crossing, N.J.

[b]Innovar[R], McNeil Lab, Ft. Washington, Penn.

REVIEW OF LITERATURE

Effects on Systemic Cardiovascular Dynamics

In order to study some of the basic effects of this combination of drugs, investigations were conducted to evaluate effects of droperidol and fentanyl separately. Yelnosky and Gardocki (1964) stated that each drug exerted its own cardiovascular effect without any well-defined antagonistic or potentiating interaction.

Gardocki and Yelnosky (1964) reported that fentanyl citrate given to dogs anesthetized with pentobarbital produced changes which were dose related. At low doses (0.0025 to 0.005 mg/kg), there was no significant effect on blood pressure, heart rate or ECG. However, when the dose was increased to 0.01 to 0.04 mg/kg, hypotension and bradycardia resulted. The bradycardia responded immediately to 0.1 to 0.5 mg/kg of atropine intravenously. At these high doses, ventricular premature contractions were noted on one occasion and prolongation of the P-R interval occurred during the periods of marked bradycardia. No ectopic pacemaker activity was noted in any of the tests. Bradycardia was not as profound in vagotomized dogs, but there was no significant difference in blood pressure. Hypotension occurred even when the dogs were premedicated with antihistamine or 1 mg/kg IV atropine. However, these agents markedly reduced the depressor effects of histamine and acetylcholine. Response to intravenous epinephrine indicated there was no sign of adrenergic blockade. Femoral artery injections caused a decrease in vascular resistance. The doses of

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fentanyl used in this experiment represent 2 to 4 times the recommended human dose but are much lower than the usual dog dose. This lack of depression has been observed by Morrison (1969). Shepherd (1964) reported that fentanyl tolerant dogs maintained normal myocardial function with a greatly reduced oxygen consumption.

Recently, Dixon *et al.* (1970) found no alteration in ventricular function in an isolated heart preparation. However, total peripheral vascular resistance fell to 73% of control one minute after intravenous administration of Innovar, then returned to 82% of control in 15 minutes. Peripheral vascular capacitance increased moderately.

In a similar experiment by Yelnosky *et al.* (1964), the effects of droperidol were studied. Increasing doses (0.125 to 0.5 mg/kg) produced a sharp drop in blood pressure with complete or partial recovery in one minute. Heart rate was not affected and there were no electrocardiographic abnormalities. The effects on contractile force of the heart were variable and of short duration. Yelnosky and Gardocki (1964) showed that a combination of fentanyl and droperidol decreased blood pressure and heart rate. Both effects occurred in 5 minutes, were maximal in 10 to 20 minutes, and lasted as long as 30 minutes. Effects were similar in vagotomized and intact dogs. This combination also caused a partial blockade of the pressor effect of epinephrine. In most instances, there was an increase in myocardial contractile force. Intra-arterial injections of droperidol caused an immediate transient increase in femoral artery blood flow with little change in perfusion pressure. Doses of 0.5 mg/kg had little or no effect on cardiac output but caused a decrease in blood pressure, total peripheral resistance, and heart rate. Higher doses caused a lowered cardiac output as well.

Morrison (1969) observed a small reduction in pulmonary vascular resistance and pressures in addition to its slight effect on the systemic circulation.

In two separate experiments, Dobkin *et al.* (1966) reported extensive experiments in dogs using the 50:1 combination of droperidol and fentanyl. Since a loss of consciousness was not produced, 66% nitrous oxide was used to provide unconsciousness. This resulted in a slight decrease in systolic and diastolic arterial pressure, mean arterial pressure, and heart rate. Venous pressure rose slightly, and there was no significant alteration in the electrocardiogram.

Dobkin *et al.* (1970) used premedication of 0.2 mg atropine subcutaneously followed by Innovar-nitrous oxide anesthesia in 60 human patients. They reported no appreciable change in blood pressure, pulse rate, or ECG. Cardiac index and stroke index decreased 28% and 15%, respectively. Peripheral vascular resistance increased 34% and left ventricular work was reduced 32%. Atropine had no effect on pH, PCO_2, or PO_2, but during anesthesia pH increased and PCO_2 decreased due to hyperventilation. Metabolic acidosis did not develop in any patients.

Hamlin *et al.* (1968) showed that Innovar-Vet, used simultaneously with small doses of pentobarbital, produced a response similar to that found in sleeping dogs. Depression of cardiac output was caused by decreased heart rate, since stroke volume remained unchanged.

Abel and Waldhausen (1968) observed that chronic instrumented dogs had a decreased heart rate, increased stroke volume, and unchanged cardiac output. The addition of pentobarbital caused an increased heart rate and decreased stroke volume.

Moran *et al.* (1972) reported on the cardiovascular effects of Innovar-Vet-nitrous oxide (50%) on chronically prepared dogs. They

found a decrease in mean arterial pressure secondary to a decrease in total peripheral resistance, a nonsignificant increase in cardiac output. Heart rate was not changed but all dogs were premedicated with 0.1 mg of atropine.

Several experiments with these drugs have been carried out in human volunteers as well. In one of these by Corssen *et al.* (1964), the subjects received no premedication and drugs were administered alone or in combination. Fentanyl alone caused a slight decrease in pulse rate, but no consistent change in systolic or diastolic arterial pressure, while droperidol alone caused a slight tachycardia, but no blood pressure changes. When administered together, there was a nonsignificant increase in heart rate and a nonsignificant decrease in systolic blood pressure. Zaunder *et al.* (1965) studied human subjects premedicated with atropine. The results showed an increase in cardiac index and central venous pressure, a decrease in total peripheral resistance, mean arterial pressure and pulse rate; stroke index, stroke work and circulation time remained unchanged. The only statistically significant change was hypotension. In a third human study with atropine premedication, Dobkin *et al.* (1964) found similar changes, except that arterial pressure was less affected. In addition, the electrocardiogram showed no abnormalities.

Grell *et al.* (1970) reported no hypotension, arrhythmias or ECG changes in 584 human patients anesthetized with fentanyl-nitrous oxide. This observation is consistent with that of Heerdt (1970) in patients anesthetized with Innovar-nitrous oxide for open-heart surgery.

In a study of the effects of fentanyl on isolated heart muscle, Goldberg and Padget (1969) showed that fentanyl directly depressed the contractile performance of heart tissue. There were decreases in peak

developed tension (tpd), maximum rates of tension developed (dp/dt), and relaxation (-dp/dt). Eisele and Smith (1972) studied the cardiovascular effects of 40% nitrous oxide in man and found an increase in the catecholamine turnover and a direct depression of myocardial function; mean arterial pressure was not affected since vasoconstriction was present.

Effect on Regional Blood Flow

Gorman and Craythorne (1969) reported that, in contrast to most anesthetics, Innovar caused little or no depression on the hemodynamic aspects of renal function. The increase in renal vascular resistance observed with most anesthetics was not apparent with Innovar.

Freeman *et al.* (1966) reported cerebral blood flow to be increased up to 34% in one experiment utilizing cats. However, this was accompanied by activation of the EEG. Edmonds-Seal and Prys-Roberts (1970) have shown depressant effects on cerebral flow.

As mentioned earlier, Gardocki and Yelnosky (1964) have indicated that droperidol caused an increase in femoral artery flow while Yelnosky *et al.* (1964) reported fentanyl had no effect.

Anti-Arrhythmic Effect

The effectiveness of Innovar, or droperidol alone, in preventing epinephrine induced arrhythmias has been reported by Dobkin and Byles (1966), Hamlin *et al.* (1968), and Yelnosky *et al.* (1964). However, in dog experiments by Dobkin and Byles (1966) arrhythmias were only found after administration of methoxamine, phenylephrine, mephentermine, and metaraminol.

Antifibrillatory action has been attributed to Innovar anesthesia in two studies of open-heart surgical procedures in human beings.

Corssen (1964) reported no ventricular fibrillation in 85 patients. In the second series of 101 subjects, Corssen *et al.* (1964) reported that ventricular fibrillation occurred in 11, but 9 of these were due to occlusion of coronary artery flow and sinus rhythm was restored with a single electroshock.

Effect on Vasoactive Substances

Brown *et al.* (1969) stated that Innovar produces a generalized alpha adrenergic block which is useful in combating the arterial vasoconstriction associated with hypovolemic shock. Chodoff and Domino (1965) have shown that the adrenergic active drug, droperidol, effectively blocks only the alpha effects of epinephrine and not those of norepinephrine. In a study of numerous vasopressors, Dobkin and Byles (1966) found that Innovar blocked the pressor response to norepinephrine and methoxamine, reduced the pressor response to phenylephrine and mephentermine, but had little effect on the response to metaraminol and angiotensin. Shepherd (1964) stated that droperidol blocked the norepinephrine pressor response and protected against traumatic shock. Chodoff and Domino (1965) also found that this drug had no effect on the depressor response of histamine or acetylcholine.

An extensive investigation by Dobkin *et al.* (1965) showed that there was no gross alteration in the blood levels of histamine, serotonin, epinephrine, or norepinephrine during long periods of Innovar-nitrous oxide anesthesia in the dog. In a second study on human surgical patients, Giesecke *et al.* (1967) found a significant increase in the urinary excretion of epinephrine during the anesthetic, surgical, and postsurgical periods, but no significant differences in norepinephrine levels. They further stated that urinary levels paralleled those of blood.

Effects on Respiration

Schotz and Ziegler (1967) reported a respiratory and metabolic acidosis in human patients given Innovar. These were premedicated with atropine and pentobarbital. They theorized this was due to hypoxia and hypercarbia associated with respiratory depression. Tarhan *et al.* (1971) observed significant decreases in PO_2, increases in PCO_2, and acidosis in human patients. Oxygen consumption was also significantly decreased.

Teutenberg *et al.* (1967) reported a decrease in both rate and depth of breathing within 5 minutes following induction with Innovar-nitrous oxide in human patients. These returned to control levels within 15 minutes. Yelnosky *et al.* (1964) showed a decrease in respiratory rate and an increase in tidal volume in dogs given droperidol alone.

Gardocki and Yelnosky (1964) showed a decrease in minute ventilation due to a decrease in both rate and tidal volume when fentanyl was used alone. Maximal depression was seen within one minute with marked recovery in 5 minutes. When the 2 drugs were combined, Yelnosky and Gardocki (1964) found the effects to be similar to those induced with fentanyl alone. That is, decreased respiratory rate and tidal volume followed by recovery in 5 to 30 minutes to near control values.

Dobkin *et al.* (1964) reported apnea in man within 5 minutes following IV administration. Arterial pH decreased in 23 of 24 patients, but the change exceeded 0.1 units in only 3 subjects. PCO_2 increased slightly in 22 of the 24, but all had assisted respirations due to the apnea. Plasma bicarbonate did not change, so that there was no significant evidence of a trend to metabolic acidosis. The PO_2 rose considerably from the administration of 40% oxygen. Cyanosis was

evident in a few subjects before respiration was assisted. In dogs given Innovar with 67% N_2O, Dobkin and Byles (1966) reported a metabolic acidosis which was not statistically significant. This change was accompanied by a drop in PCO_2 and an increase in PO_2 due to controlled respiration. There was no change in hematocrit.

In summary, most NLA investigations have reported a decrease in arterial pressure associated with a decrease in total peripheral resistance. This is attributable to the alpha blocking effects of droperidol. Cardiac output appears to be unchanged in experiments where atropine is used to prevent bradycardia. Without atropine fentanyl induced bradycardia does occur at anesthetic doses. Electrocardiogram changes are minimal with combinations of droperidol and fentanyl. Antiarrhythmic properties have been reported. Nitrous oxide appears to have no cardiopulmonary effect except for a mild vasoconstriction. Respiration is severely depressed by NLA, especially during the first few minutes following IV injection. Metabolic and respiratory acidosis can be prevented by controlling ventilation.

MATERIALS AND METHODS

Animals

Twleve, male, 1- to 2-year-old, conditioned Beagles (*Canis familiaris*) weighing 9 to 12 kilograms were obtained from a laboratory animal dealer.[a] These dogs were housed in individual concrete cages and exercised twice daily in accordance with Public Law 89-544 (The Animal Welfare Act). Cages were cleaned twice daily and dogs fed[b] once daily. Fresh water was provided *ad libitum*. All animals were vaccinated against rabies, distemper and hepatitis and were free from internal and external parasites.

Standardization and Training

One week prior to experimentation, blood was collected from each dog and examined. Tests included total leukocyte count, differential leukocyte count, hemoglobin, packed cell volume, total protein, blood urea nitrogen, and serum glutamic pyruvic transaminase. All values were within normal limits as reported by Michaelson *et al.* (1966) for the normal Beagle.

Two days before surgical preparation, each dog was brought to the laboratory and a neck bandage applied as a conditioning procedure.

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[a]Laboratory Research Enterprises, 6251 S. Sixth Street, Kalamazoo, Mich. 49001.

[b]Ken-L-Ration Meal, Quaker Oats Co., Chicago, Ill. 60651.

Subsequently no dog bothered his implanted catheters postsurgically.

All dogs were trained to lie on a table in right lateral recumbency to minimize excitement and anxiety during control recordings. This 15-minute daily training was initiated 7 days prior to experimentation. Most dogs were unaccustomed to handling and objected to this procedure for the first 2 or 3 days. With one exception, all dogs had adjusted to lying quietly on the table with a technician scratching the ears. One experimental run was postponed for 3 days until further training was accomplished.

Materials

Silicone rubber tubing,[a] 1.01 mm ID x 2.16 mm OD, was used for venous catheters to be placed in the right atrium. These were 75 cm long and had small silastic[b] blebs placed 15 cm from one end to provide anchorage within the jugular vein (Figure 1).

A double lumen, 100 cm, number 10 French, cardiac catheter[c] was used for the arterial pressure and cardiac output determinations (Figure 1). The end-hole lumen was used to obtain arterial pressures and blood for analysis. A calibrated thermistor[d] was mounted in the side-hole position with epoxy cement by a local laboratory[e] for measurement of cardiac output by the thermal dilution technic as described by Evonuk *et al.* (1961).

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[a]Medical Grade Silastic Tubing, Dow Corning Corp., Midland, Mich.

[b]Silastic Medical Adhesive, Dow Corning Corp., Midland, Mich.

[c]Corunand Double Lumen Catheter, U.S. Catheter and Instrument Co., P.O. Box 787, Glen Falls, N.Y. 12801.

[d]Veco 32A7, Victory Engineering Corp., Victory Road, Springfield, N.J. 07081.

[e]Dept. of Physiology, Michigan State University, East Lansing, Mich.

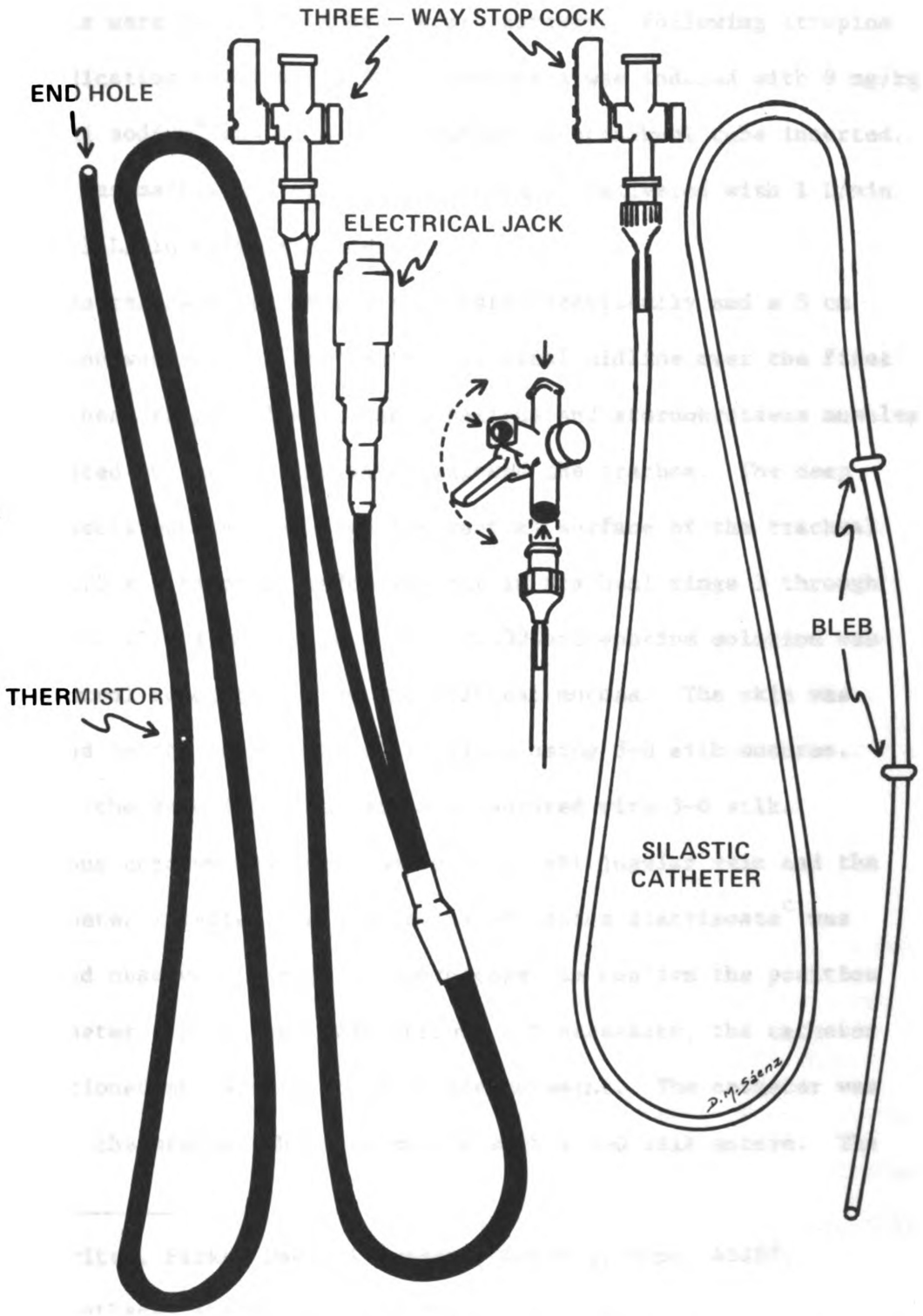

Figure 1. Catheters used for recording cardiac output and arterial and venous pressure. A double lumen 100 cm cardiac catheter (left) with thermistor for measuring cardiac output and arterial pressure. A 75 cm silastic catheter (right) for venous sampling and injection. Blebs were used to secure the catheter within the jugular vein.

Surgical Implantation and Preparation

Animals were fasted 12 hours before surgery. Following atropine sulfate medication (0.02 mg/lb SQ), anesthesia was induced with 9 mg/kg of thiamylal sodium[a] and an 8 mm ID cuffed endotracheal tube inserted. Anesthesia was maintained with 1.0% halothane[b] delivered with 1 L/min oxygen and 1 L/min nitrous oxide.

The ventral cervical area was prepared aseptically and a 5 cm skin incision was made on the ventral cervical midline over the first 6 to 8 tracheal rings. The sternocephalicus and sternohyoideus muscles were separated on the midline which exposed the trachea. The deep cervical fascia was removed from the ventral surface of the tracheal rings. A 1.5 x 2 cm oval window was cut in tracheal rings 3 through 6 using a No. 11 scalpel blade. A 1:10,000 epinephrine solution was used to control hemorrhage from the tracheal mucosa. The skin was then sutured to the severed tracheal rings using 3-0 silk sutures. The ends of the skin incision were also sutured with 3-0 silk.

A venous cutdown was performed on the left jugular vein and the venous catheter inserted. A 5 ml bolus of sodium diatrizoate[c] was injected and observed through a fluoroscope[d] to confirm the position of the catheter tip in the right atrium. If necessary, the catheter was repositioned and secured to preclude movement. The catheter was anchored to the sternocephalicus muscle with a 3-0 silk suture. The

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[a]Surital, Parke, Davis & Company, Detroit, Mich. 48207.

[b]Fluothane, Ayerst Lab, New York, N.Y. 10017.

[c]Hypaque 50%, Winthrop Lab, New York, N.Y.

[d]Model HRT, General Electric Co., Medical Systems Division, Detroit, Mich. 48219.

catheter was filled with a heparinized saline solution (100 μ/ml) and the stopcock closed. An antibiotic[a] saturated gauze sponge was placed over the tracheostomy and the catheter loosely coiled around the neck. A gauze and tape bandage was applied to the neck to keep the dog from damaging the catheters. The dog was placed in a padded cage for recovery.

Aqueous penicillin, 200,000 units, and streptomycin, 250 mg, were administered once daily for the next 7 days. The bandage was changed and the venous catheter flushed with the heparinized saline every 48 hours.

On the day of the study, the dogs were placed on a padded table in right lateral recumbency and the right femoral area was surgically prepared. The skin and subcutaneous area over the femoral artery was infiltrated with 1 ml of 0.5% lidocaine hydrochloride[b] solution. A femoral artery cutdown was performed and the double lumen catheter implanted as described by Rawlings *et al.* (1970).

Equipment

An 8-channel, photographic write-out recorder[c] was used for data recording. Thermal dilution cardiac output curves were obtained by connecting the arterial thermistor to a pressure preamplifier via a Wheatstone bridge. The thermistor was also connected to an electronic thermometer[d] by a two-way switch for measurement of blood temperatures. Lead II of the electrocardiogram was recorded using an ECG preamplifier.

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[a]Furacin Ointment, Norwich Pharmacal Co., Norwich, N.Y. 13815.

[b]Xylocaine, Astra Pharmaceutical, Worcester, Mass.

[c]Model DR-8, Electronics for Medicine, White Plains, N.Y.

[d]Model 41TF, Yellow Springs Instrument Co., Yellow Springs, Ohio.

Pressure transducers[a] were calibrated before each experiment by use of integrated resistors within the recorder. Arterial and venous catheters were connected to the transducers and then to preamplifiers. Electronic averagers were used to obtain mean values.

Arterial and venous blood gases were determined using a blood gas analyzer[b] which was calibrated prior to each study. Calibration was performed using known PO_2, PCO_2 and pH.

Respiratory measurements were obtained by the use of a vane spirometer[c] and stopwatch. Minute volume along with respiratory rate and the tidal volume were calculated.

Oxygen, nitrogen and nitrous oxide were delivered from an anesthetic machine[d] to which was attached a non-rebreathing valve.[e] The concentrations of these gases were confirmed by the use of an oxygen analyzer[f] which was calibrated utilizing room air and 100% oxygen.

The dogs were placed on a water blanket[g] to minimize hypothermia. Arterial hematocrit values were obtained using the centrifuged micro-hematocrit method.

Data Measurement Technic

Cardiac output was determined by injection of 3 ml of room temperature saline into the right atrium via the implanted venous

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[a]Model P23Db, Statham Transducers, Inc., Hato Rey, Puerto Rico.

[b]Model 72 EMD-RUPVEJ, Radiometer Copenhagen, Copenhagen, Denmark.

[c]Volumeter, North American Drager Co., Telford, Penn.

[d]Model Rotameter, The Foregger Co., New York, N.Y.

[e]Stephen-Slater Valve, Ohio Medical Products, Madison, Wisc.

[f]Oxygen Analyzer, IMI Division, Becton Dickinson & Co., New Port Beach, Calif.

[g]Model K-13, Gorman-Rupp Industries Co., Bellville, Ohio.

catheter. The thermal curve was recorded by the thermistor in the aortic arch, as reported by Evonuk *et al.* (1961). A 3 ohm resistor built into the Wheatstone bridge was used to produce a 0.1 C standardization deflection. The cardiac output was determined by using a modified Stewart-Hamilton formula as worked out by Evonuk *et al.* (1961).

$$\text{C.O. (L/min)} = \frac{KV_i\ (T_b - T_i)f}{A}$$

where:

K is calibration factor of the thermistor (mm deflection per 0.1 C)

V_i is volume of the injectate (ml)

T_b is temperature of the blood (C)

T_i is temperature of the injectate (C)

f is recorder paper speed (cm/min)

A is area under the curve (sq.cm)

Heart rate was obtained by counting the pressure pulses on the arterial pressure tracing. Stroke volume was calculated by dividing the cardiac output by the heart rate.

Total peripheral vascular resistance was calculated and expressed as PVR units using the following formula:

$$\text{PVR} = \frac{\text{mean arterial pressure}}{\text{cardiac output}}$$

Arterial pressures were recorded as pulsatile and mean pressures. Venous pressure was recorded only as the mean.

One milliliter arterial and venous blood samples were collected in heparinized 3 ml plastic syringes. Within 1 minute, PO_2, PCO_2 and pH were determined. Capillary tubes were filled with arterial blood for hematocrit determinations. Base deficit was calculated from pH and PCO_2 using a Siggaard-Andersen nomogram.

Degree of analgesia was determined by clamping a rear digit with an Allis tissue forcep. Withdrawal of the leg was recorded as a 1+ reaction, withdrawal of the leg and raising the head as a 2+ reaction, and additional movement as a 3+ reaction. Response to auditory stimuli was determined by dropping an Allis tissue forceps from 30 cm onto a Mayo stand 75 cm from the dog's head. Opening of the eyes was recorded as a 1+ reaction, raising of the head as a 2+ reaction, and additional movement as a 3+ reaction.

Recording of Control Data

Following calibration of equipment, the dogs were connected to the recording devices (Figure 2).

The thermistor was connected to the electronic thermometer and recorder. The arterial pressure catheter was flushed with heparinized saline (100 μ heparin/ml saline) and connected to a transducer. The neck bandage was removed, the venous catheter flushed with heparinized saline, and connected to a second transducer. Four limb ECG leads were attached and secured with tape. The tracheostomy was cleaned with saline and an 8 mm tracheostomy tube[a] lubricated with an anesthetic jelly[b] inserted. The cuff was inflated to prevent leakage and connected to the anesthetic machine and spirometer via the non-rebreathing valve. The dogs were then given 15 minutes to rest before control measurements were taken.

A set of control values was recorded with the animals relaxed and breathing room air. Air was delivered through the respiratory apparatus

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[a]Portex Division, Smith Industries, Woburn, Mass.

[b]Xylocaine Jelly, Astra Pharmaceuticals, Worcester, Mass.

by removing the breathing bag. Then each animal was given a mixture of 33% oxygen in nitrogen delivered from the anesthetic machine for 15 minutes. A second set of control values was then taken with the dogs breathing the increased oxygen concentration (Table 1).

Drug Evaluation

Following control recordings, Group I dogs were given 1 ml of Innovar-Vet per 25 lb (11.4 kg) body weight diluted to 10 ml with normal saline. This was given through the right atrial catheter over a 1-minute period. All variables were measured every 10 minutes following injection until recovery was apparent by the analgesia test. Thirty-three percent oxygen in nitrogen was continued for the entire anesthetic period (Table 1).

Group II dogs were administered the same dose of Innovar-Vet as Group I, but nitrous oxide was substituted for nitrogen. Measurements were made as in Group I with nitrous oxide being administered for the anesthetic period (Table 1).

Group III dogs had 2 sets of control measurements, after which 0.044 mg/kg of atropine sulfate was injected intramuscularly. Fifteen minutes later, the third set of control measurements was taken. They were then given Innovar-Vet intravenously and oxygen-nitrous oxide mixture by the same protocol as followed in Group II. Measurements were made every 10 minutes until recovery was apparent (Table 1).

Data Analysis

Data analysis was accomplished utilizing the facilities and a computer program of Michigan State University. Variables with significant change ($P<0.05$) were determined by the use of Snedecor's F-test as explained by Lewis (1966). These variables were then

Table 1. Experimental design for the research project

	CONTROL MEASUREMENTS (On different breathing mixtures)					EXPERIMENTAL MEASUREMENTS (Min. after administration of drugs)					
GROUP	AIR	O_2	Medication	2nd O_2	Medication	10	20	30	40	50	60
I (4 dogs)	X	X	Innovar-Vet			X	X	X	X		
II (4 dogs)	X	X	Innovar-Vet & N_2O			X	X	X	X	X	
III (4 dogs)	X	X	Atropine	X	Innovar-Vet & N_2O	X	X	X	X	X	X

Each parameter was measured at the times indicated by an X.

analyzed by the Student's t-test to determine where the changes occurred within the experimental design.

Means and standard errors were calculated for each variable within the 3 groups. Data accumulated with the dogs breathing 33% oxygen were used as control measurements.

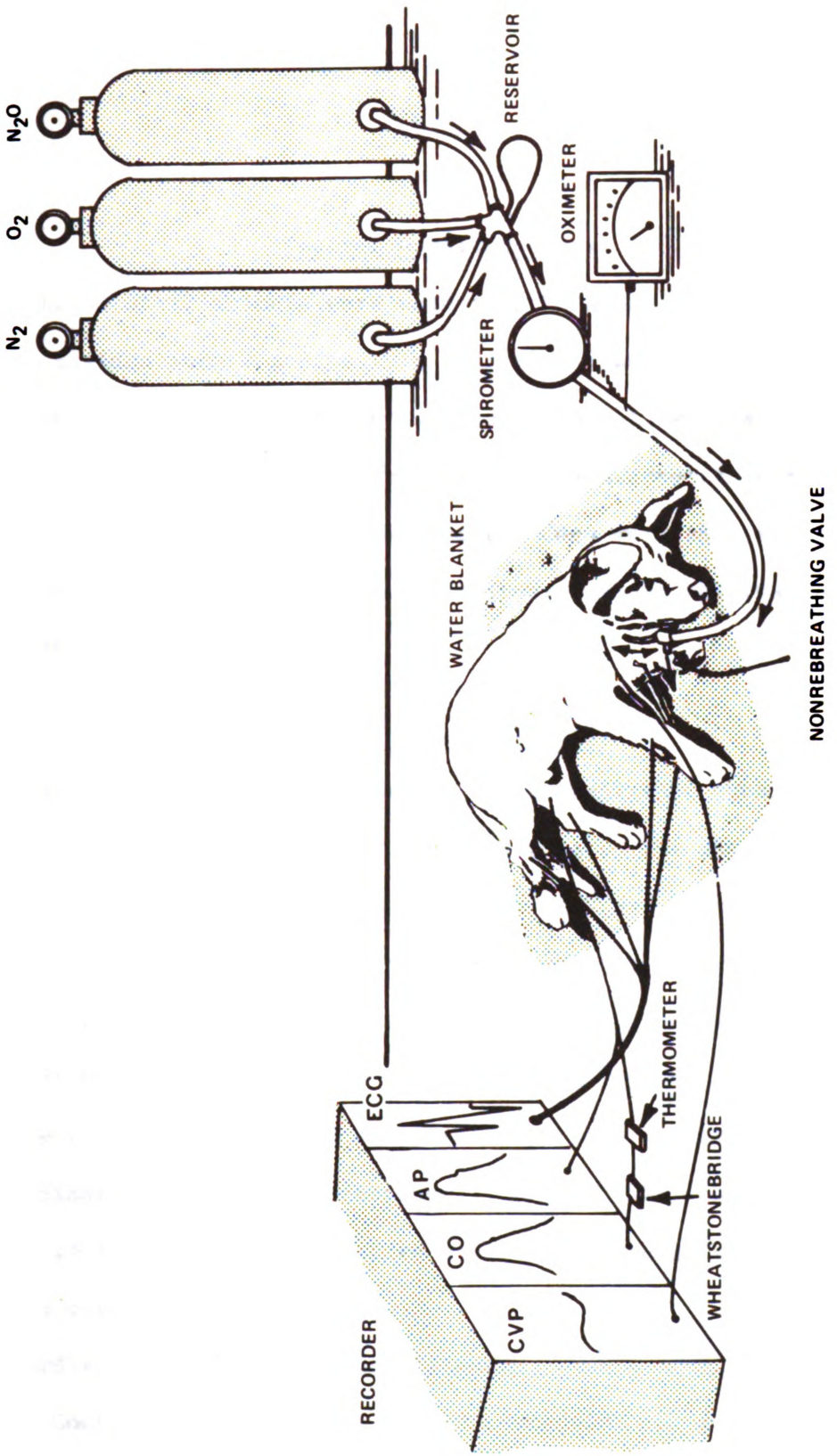

Figure 2. Illustration of the mechanical and electronic layout for data recording.

RESULTS

General Considerations

A total of 12 animals were used for the study, with 4 dogs equally divided into 3 groups. In addition, 3 were used to develop the technic and 1 died subsequent to an iatrogenic accident. One dog was studied each week. Catheters and tracheostomies were removed from all dogs following the study and the dogs were observed closely for 3 days. All animals survived the study without observable complications.

Group I: Innovar-Vet

Evaluation of Innovar-Vet alone was accomplished with 4 dogs whose average body weight was 11.4 kg (10.5-13.6 kg). The cardiovascular and respiratory data are presented in Tables 2 and 3, respectively. Cardiac output, mean arterial pressure, heart rate, stroke volume, total peripheral resistance, pHa, PaO_2 and $PaCO_2$, respiratory rate, tidal volume and minute volume are plotted in Figures 3 through 6.

The average duration of anesthesia was 42.5 minutes, at which time all 4 animals had a 2+ pain response. Three of the 4 dogs had at least a 1+ response for the entire study. The fourth had no pain response during the study.

Cardiac output was not significantly changed ($P>0.05$) during the study. Control value was 2.35 $\pm$ 0.27 L/min with the dogs breathing

Table 2. Cardiovascular data with Innovar-Vet

	CONTROLS			TIME (MINUTES)			
VARIABLE	AIR	O_2		10	20	30	40
CO (l/min)	2.41 ±.30	2.35 ±.27	INNOVAR–VET	2.38 ±.21	2.23 ±.24	2.44 ±.31	2.13 ±.27
SAP (mm Hg)	133 ± 3	130 ± 7		118 ± 6	109* ± 7	103* ± 4	106* ± 6
DAP (mm Hg)	83 ± 7	92 ± 9		71 ± 4	71 ± 8	65 ± 3	66 ± 2
MAP (mm Hg)	100 ± 6	105 ± 6		94 ± 7	91 ± 9	85 ± 4	88 ± 5
HR (beats/min)	87 ±13	93 ±17		69 ± 7	82 ± 8	85 ± 9	92 ± 5
CVP (mm Hg)	3 ± 1	3 ± 2		4 ± 2	3 ± 2	3 ± 2	2 ± 1
SV (ml)	28 ± 3	26 ± 2		35* ± 2	27 ± 2	29 ± 3	23 ± 2
TPR (pru)	42 ± 3	44 ± 3		39 ± 4	41 ± 4	36 ± 5	42 ± 4
PCV (%)	37 ± 3	37 ± 4		37 ± 4	37 ± 4	36 ± 4	35 ± 4

Represents mean values and standard errors (±) from 4 dogs given Innovar–Vet alone. Controls taken breathing room air and 33% oxygen. Experimental values taken at 10 minute intervals following injection. CO= Cardiac Output; SAP = Systolic Arterial Pressure; DAP = Diastolic Arterial Pressure; MAP = Mean Arterial Pressure; HR = Heart Rate; CVP = Central Venous Pressure; SV = Stroke Volume; TPR = Total Periperal Resistance; PCV = Packed Cell Volume. * Changes of $P < 0.05$ or greater from O_2 control.

Table 3. Respiratory data with Innovar-Vet

	CONTROLS			TIME (MINUTES)			
VARIABLE	AIR	O_2		10	20	30	40
pH_a	7.42 ± .03	7.40 ± .02	INNOVAR–VET	7.26* ± .01	7.32* ± .01	7.33* ± .01	7.34* ± .02
pH_v	7.38 ± .02	7.36 ± .01		7.25* ± .01	7.29* ± .01	7.30* ± .01	7.33* ± .01
P_aO_2 (mm Hg)	96 ± 8	114 ± 17		136 ± 16	132 ± 14	147 ± 14	143 ± 15
P_vO_2 (mm Hg)	49 ± 4	52 ± 6		63 ± 4	58 ± 11	61 ± 2	58 ± 8
P_aCO_2 (mm Hg)	26 ± 2	26 ± 2		35 ± 3	33 ± 3	30 ± 2	32 ± 3
BD (meq/l)	6 ± 2	9 ± 2		11 ± 1	8 ± 2	9 ± 1	8 ± 1
P_vCO_2 (mm Hg)	30 ± 1	29 ± 1		38 ± 3	35 ± 2	35 ± 3	35 ± 3
$\dot{V}$ (l/min)	5.53 ±1.89	7.15 ± 2.70		5.78 ± 3.44	8.33 ± 3.90	11.80 ± 3.99	13.81 ± 3.76
RR (resp./min)	69 ± 29	123 ± 34		76 ± 43	92 ± 42	129 ± 41	140 ± 35
V_T (ml)	87 ± 5	75 ± 5		78 ± 10	93 ± 7	90 ± 3	97 ± 3

Represents mean values and standard errors (±) from 4 dogs given Innovar-Vet alone. Controls taken breathing room air and 33% oxygen. Experimental values taken at 10 minute intervals following injection. pH_a = Arterial pH; pH_v = Venous pH; P_aO_2 = Arterial Oxygen Tension; P_vO_2 = Venous Oxygen Tension; P_aCO_2 = Arterial Carbon Dioxide Tension; BD = Base Deficit; P_vCO_2 = Venous Carbon Dioxide Tension; $\dot{V}$ = Minute Volume; RR = Respiratory Rate; V_T = Tidal Volume.

* Changes of $P < 0.05$ or greater from O_2 control.

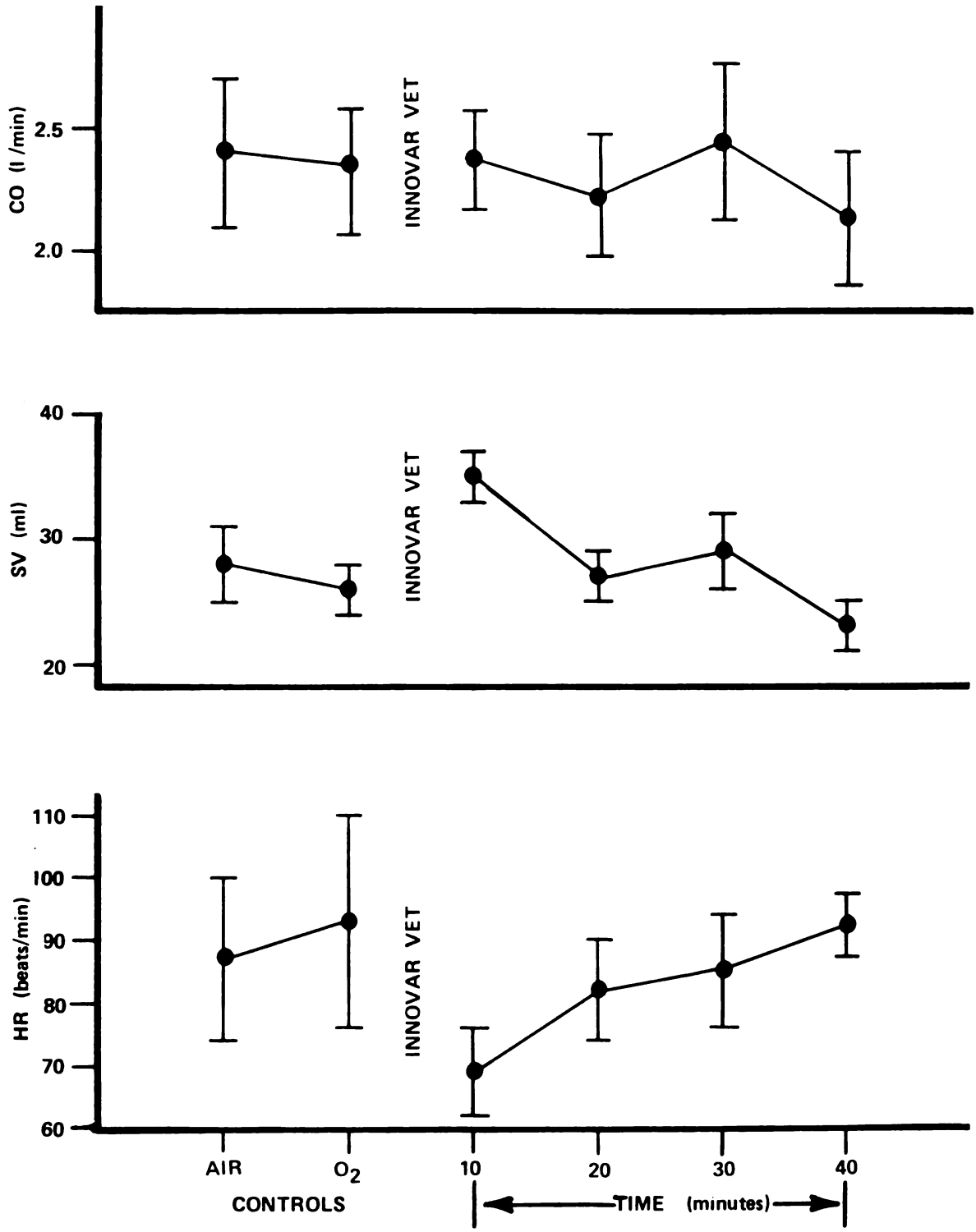

Figure 3. Cardiac output, stroke volume, and heart rate with Innovar-Vet. Mean values and standard errors plotted for 4 dogs given Innovar-Vet alone. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals. CO = Cardiac Output; SV = Stroke Volume; HR = Heart Rate

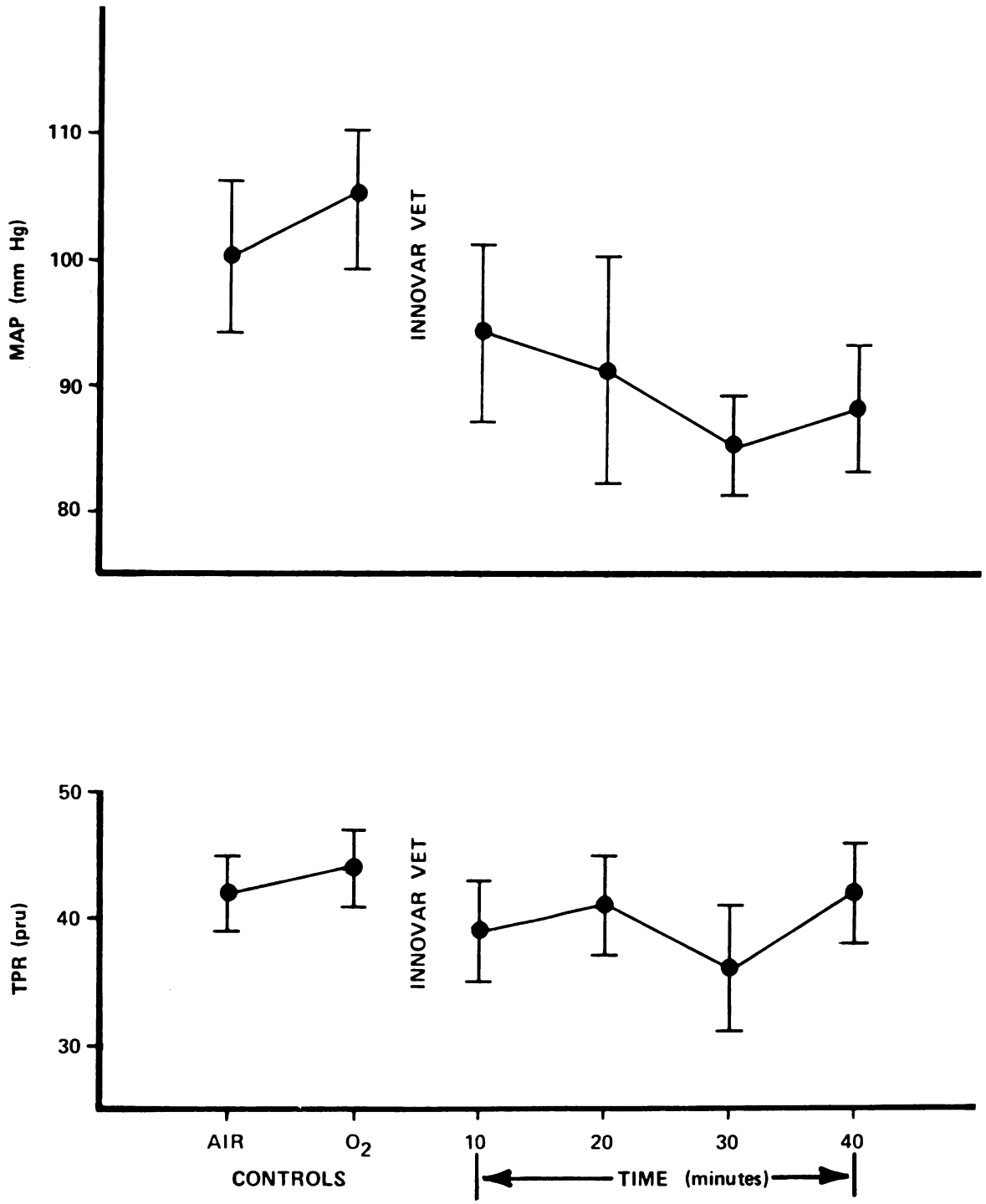

Figure 4. Mean arterial pressure and total peripheral resistance with Innovar-Vet. Mean values and standard errors plotted for 4 dogs given Innovar-Vet alone. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals. MAP = Mean Arterial Pressure; TPR = Total Periperal Resistance

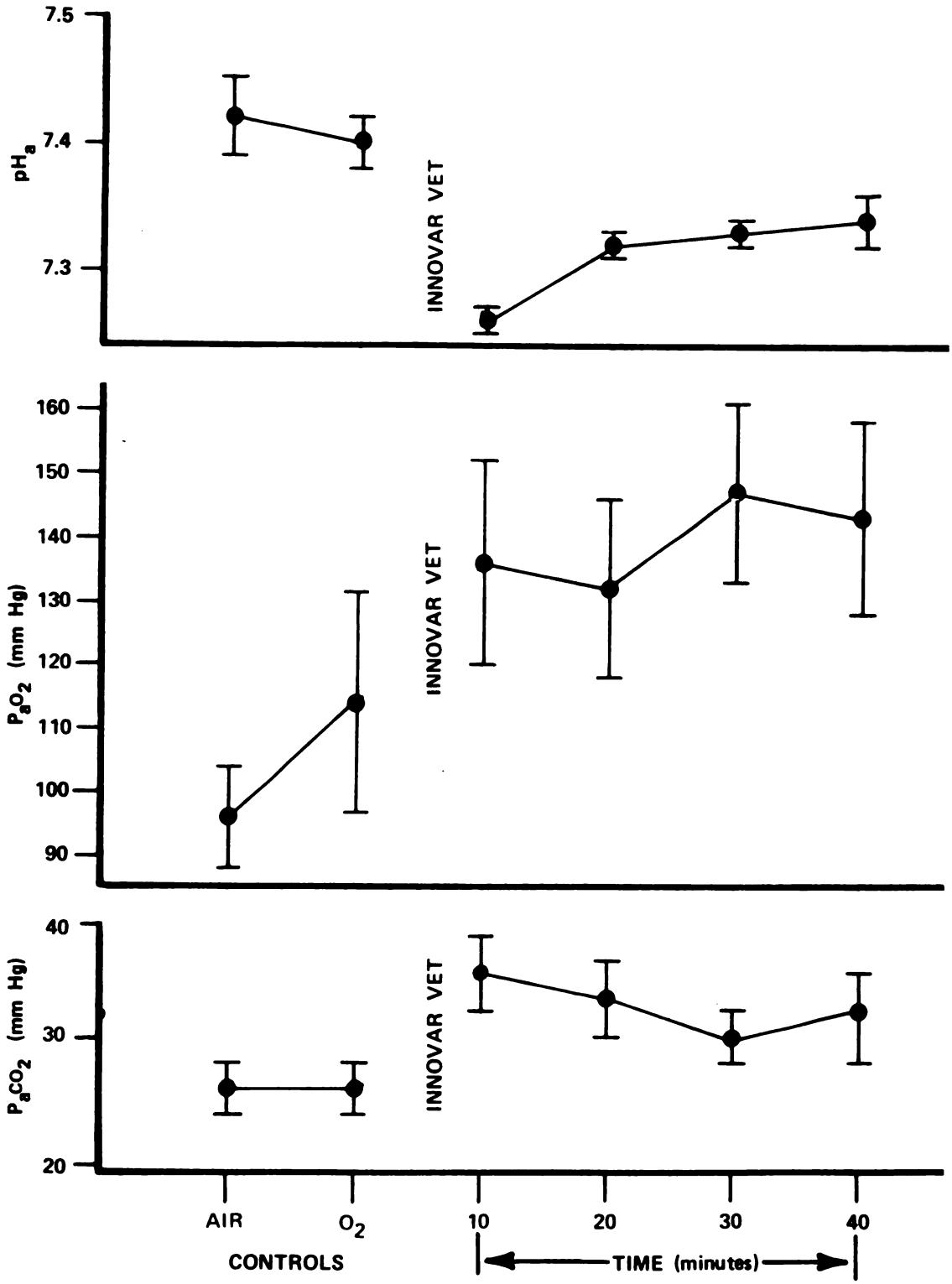

Figure 5. Arterial blood gases with Innovar-Vet. Mean values and standard errors plotted for 4 dogs given Innovar-Vet alone. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals. pH_a=Arterial pH; P_aO_2 = Arterial Oxygen Tension; P_aCO_2 = Arterial Carbon Dioxide Tension

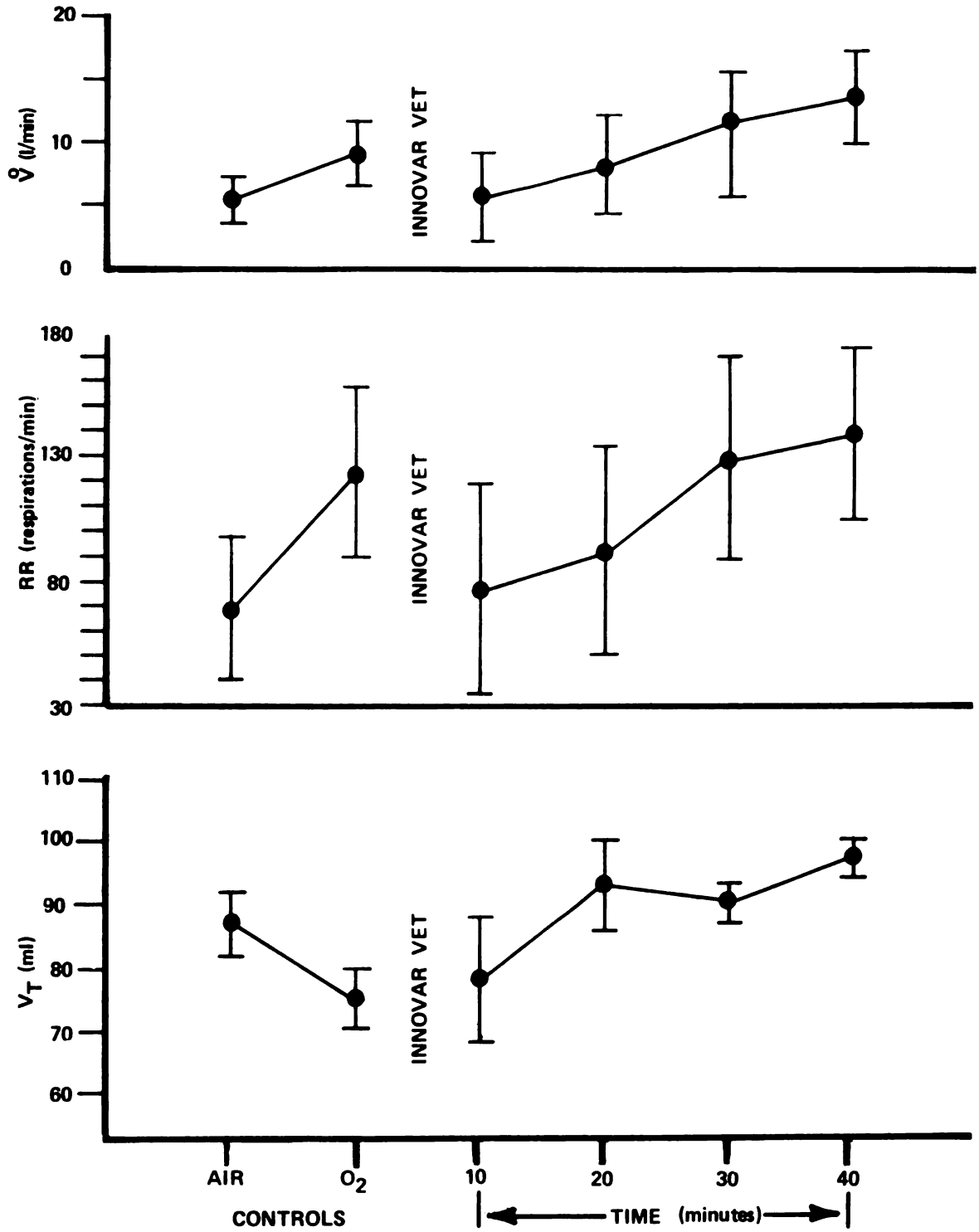

Figure 6. Minute volume, respiratory rate and tidal volume with Innovar-Vet. Mean values and standard errors plotted for 4 dogs given Innovar-Vet alone. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals. $\dot{V}$ = Minute Volume; RR = Respiratory Rate; V_T = Tidal Volume

33% oxygen. Thirty minutes postinjection cardiac output increased 4%[a] to 2.44 ± 0.31 L/min and 2.13 ± 0.27 L/min (9%) at 40 minutes. Heart rate decreased from a control of 93 ± 17 beats per minute to 69 ± 7 (25%) at 10 minutes and returned to control level at 40 minutes. However, these changes were not significant ($P>0.05$). Total peripheral vascular resistance and packed cell volume were not significantly changed. Stroke volume increased from a control value of 26 ± 2 ml to 35 ± 2 ml (35%) at 10 minutes postinjection; this change was statistically significant ($P<0.05$).

Systolic arterial pressure was significantly decreased ($P<0.05$). The change was not apparent until 20 minutes after injection and did not return to control values during the 40-minute recording period. Control was 130 ± 7 mm Hg and decreased to 103 ± 4 mm Hg (21%). Diastolic and mean pressures were not significantly affected.

Arterial and venous pH were significantly changed. Arterial pH decreased from a control of 7.40 ± .02 to 7.25 ± .01 ($P<0.01$) at the 10-minute interval. It then stabilized at 7.32 to 7.34 ($P<0.05$) for the remainder of the study. Venous pH followed a similar trend. The greatest depression occurred at the 10-minute interval (7.25 ± .01). The pH tended to rise during the remainder of the experiment but never reached control values. All venous pH changes were highly significant ($P<0.01$). The metabolic change was particularly evident at the 10-minute interval when base deficit increased from a control of 9 ± 2 mEq to 11 ± 1 (18%). The $PaCO_2$ increased from a control of 29 ± 1 mm Hg to 38 ± 3 mm Hg (31%) at the 10-minute interval and remained at 35 mm Hg for the duration of the study.

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[a]Percent change from control.

The response to auditory stimulation was variable. One dog had from 0 to 1+ response during the experiment, while another had 3+ most of the time. The range for the other 2 dogs at most time intervals was 1+ to 2+.

Nystagmus and muscle twitching were present in 3 of the 4 dogs. Apnea occurred in 2 dogs 1 to 3 minutes following injection, and slow respiration (5 respirations/min) with cyanosis present in a third animal. Respiration was spontaneous and not assisted, and all animals were breathing at a normal rate by 10 minutes postinjection. Panting began after 10 minutes in 2 dogs and continued for the remainder of the experiment. Borborygmus was present in 2 dogs, and defecation occurred in another. Premature ventricular contractions (1 per 4-5 normal contractions) occurred in 1 dog 5 minutes following injection.

Group II: Innovar-Vet with Nitrous Oxide

The combination of Innovar-Vet with 67% nitrous oxide and 33% oxygen was evaluated with 4 dogs averaging 10.1 kg (9.1 to 10.9). The cardiovascular and respiratory data are presented in Tables 4 and 5, respectively. Cardiac output, mean arterial pressure, heart rate, stroke volume, total peripheral resistance, arterial pH, PCO_2 and PO_2, respiratory rate, tidal volume, and minute volume are plotted in Figures 7 through 10.

The average duration of anesthesia was 70 minutes due to one animal remaining anesthetized for 110 minutes. Data were analyzed only through 50 minutes since 3 animals recovered at that interval (i.e., pain response of 2+ or more).

No cardiovascular variable was significantly changed ($P>0.05$) in this group. Control cardiac output was 2.05 $\pm$ .30 L/min with values

Table 4. Cardiovascular data with Innovar-Vet and nitrous oxide

	CONTROLS			TIME (MINUTES)				
VARIABLE	AIR	O_2		10	20	30	40	50
CO (l/min)	2.42 ± .33	2.05 ± .30	INNOVAR–VET & N_2O	2.33 ± .45	2.66 ± .24	2.63 ± .21	2.48 ± .34	2.82 ± .58
SAP (mm Hg)	114 ± 4	120 ± 1		117 ± 5	116 ± 7	122 ± 13	111 ± 6	117 ± 7
DAP (mm Hg)	83 ± 7	74 ± 6		67 ± 6	70 ± 7	84 ± 12	81 ± 5	84 ± 8
MAP (mm Hg)	94 ± 6	98 ± 5		84 ± 8	92 ± 10	103 ± 13	103 ± 9	104 ± 10
HR (beats/min)	98 ± 14	92 ± 24		69 ± 12	80 ± 11	86 ± 8	93 ± 10	108 ± 12
CVP (mm Hg)	2 ± 1	3 ± 1		5 ± 1	4 ± 2	3 ± 1	3 ± 1	2 ± 1
SV (ml)	30 ± 5	26 ± 5		33 ± 6	35 ± 5*	34 ± 4	27 ± 4	27 ± 5
TPR (pru)	40 ± 4	49 ± 6		44 ± 16	34 ± 4	37 ± 5	41 ± 3	39 ± 5
PCV (%)	36 ± 2	37 ± 2		36 ± 3	37 ± 2	37 ± 2	36 ± 2	37 ± 2

Represents mean values and standard errors (±) from 4 dogs given Innovar-Vet and nitrous oxide. Controls taken breathing room air and 33% oxygen. Experimental values taken at 10 minute intervals following injection.
CO = Cardiac Output; SAP = Systolic Arterial Pressure; DAP = Diastolic Arterial Pressure; MAP = Mean Arterial Pressure; HR = Heart Rate; CVP = Central Venous Pressure; SV = Stroke Volume; TPR = Total Periperal Resistance; PCV = Packed Cell Volume. * Changes of $P < 0.05$ or greater from O_2 control.

Table 5. Respiratory data with Innovar-Vet and nitrous oxide

	CONTROLS			TIME (MINUTES				
VARIABLE	AIR	O_2		10	20	30	40	50
pH_a	7.41 ±.02	7.37 ±.02		7.22* ±.01	7.26* ±.02	7.29* ±.01	7.30* ±.01	7.34 ±.04
pH_v	7.39 ±.03	7.34 ±.02		7.20* ±.02	7.25* ±.02	7.26* ±.02	7.28 ±.02	7.31 ±.03
P_aO_2 (mm Hg)	89 ± 7	141 ±17		133 ±23	139 ±16	151 ±22	161 ±18	142 ±16
P_vO_2 (mm Hg)	43 ± 3	52 ±13		69 ± 6	101 ±30	78 ± 5	91 ±20	76 ±10
P_aCO_2 (mm Hg)	29 ± 4	29 ± 4	INNOVAR–VET & N_2O	43 ± 8	37 ± 6	33 ± 4	32 ± 4	30 ± 4
BD (meq/l)	6 ± 3	10 ± 3		14 ± 4	13 ± 3	14 ± 3	10 ± 2	9 ± 3
P_vCO_2 (mm Hg)	32 ± 2	30 ± 3		45 ± 7	39 ± 4	36 ± 4	35 ± 4	32 ± 5
$\dot{V}$ (l/min)	6.12 ±1.70	4.33 ±.65		1.37 ±.20	4.31 ±2.27	3.67 ±1.56	4.31 ±.39	4.89 ±.82
RR (resp/min)	91 ±37	42 ± 6		10 ± 2	41 ±27	43 ± 24	42 ± 11	64 ± 22
V_T (ml)	79 ±13	104 ± 4		151 ±17	142 ±31	105 ±12	128 ±36	99 ± 26

Represents mean values and standard errors (±) from 4 dogs given Innovar-Vet and nitrous oxide. Controls taken breathing room air and 33% oxygen. Experimental values taken at 10 minute intervals following injection.
pH_a = Arterial pH; pH_v = Venous pH; P_aO_2 = Arterial Oxygen Tension; P_vO_2 = Venous Oxygen Tension; P_aCO_2 = Arterial Carbon Dioxide Tension; BD = Base Deficit; P_vCO_2 = Venous Carbon Dioxide Tension; $\dot{V}$ = Minute Volume; RR = Respiratory Rate; V_T = Tidal Volume
* Changes of $P < 0.05$ or greater from O_2 control.

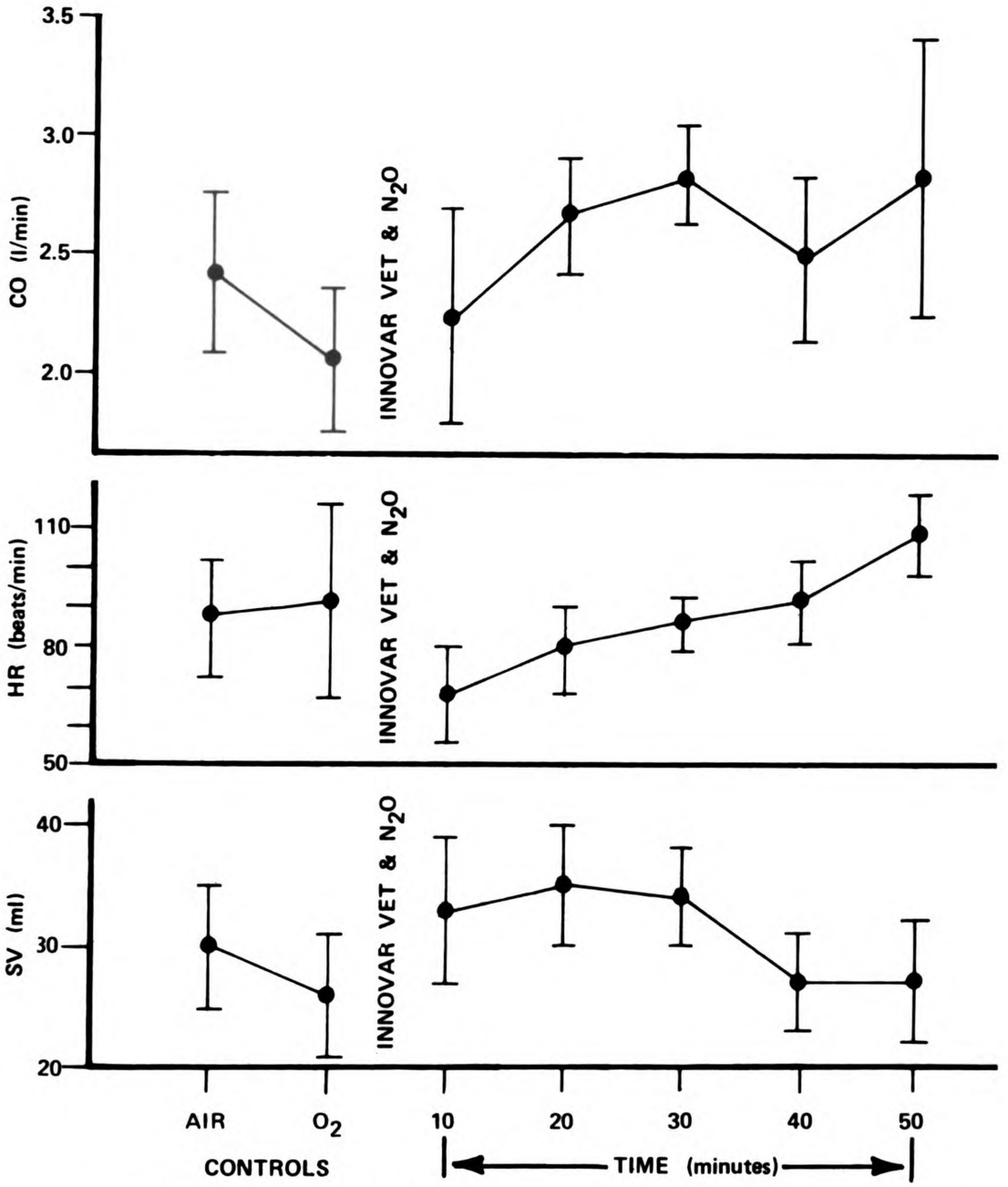

Figure 7. Cardiac output, stroke volume, and heart rate with Innovar-Vet and nitrous oxide. Mean values and standard errors plotted for 4 dogs given Innovar-Vet and nitrous oxide. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals.
CO = Cardiac Output; SV = Stroke Volume; HR = Heart Rate

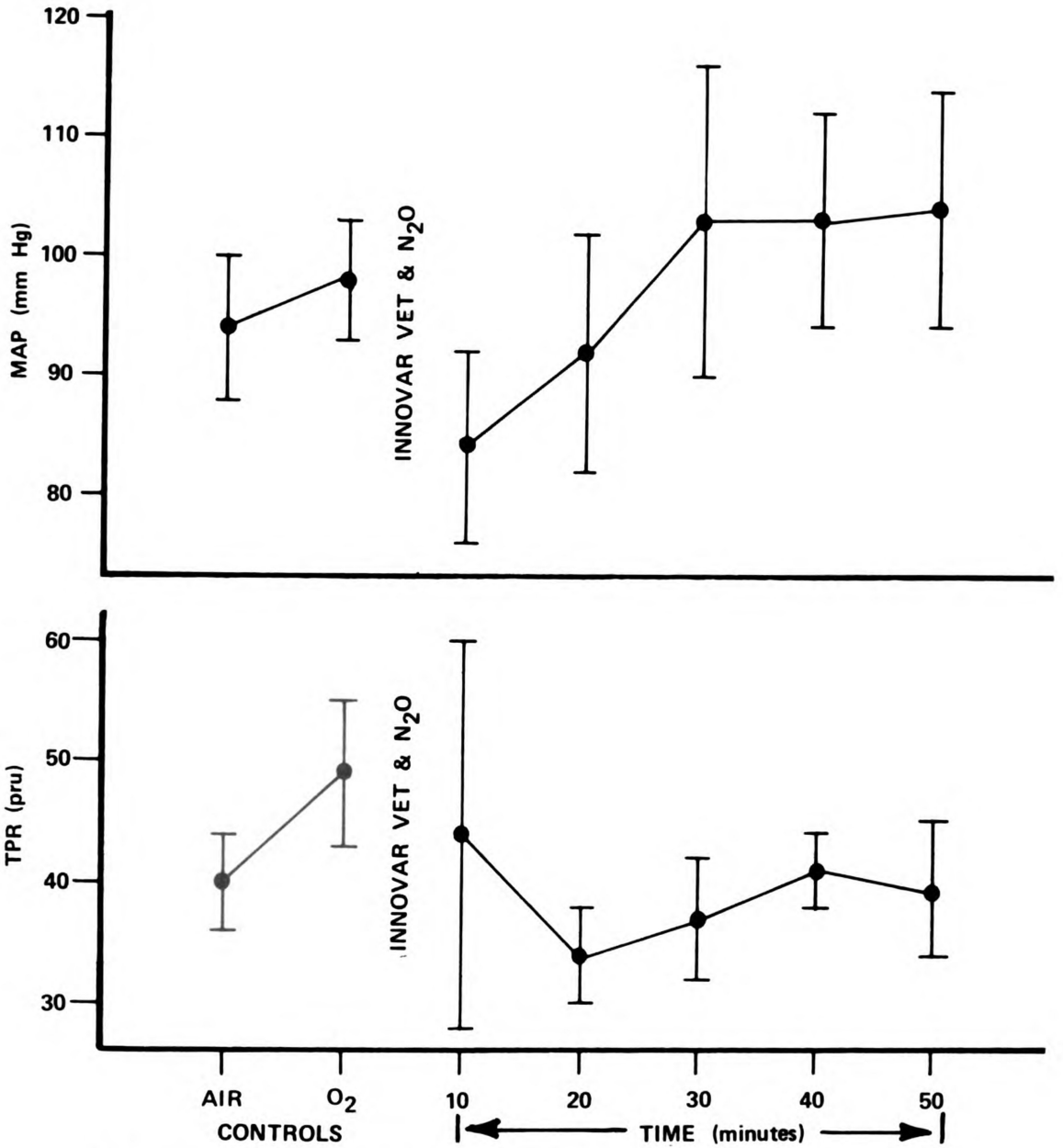

Figure 8. Mean arterial pressure and total peripheral resistance with Innovar-Vet and nitrous oxide. Mean values and standard errors plotted for 4 dogs given Innovar-Vet and nitrous oxide. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals. MAP = Mean Arterial Pressure; TPR = Total Peripheral Resistance

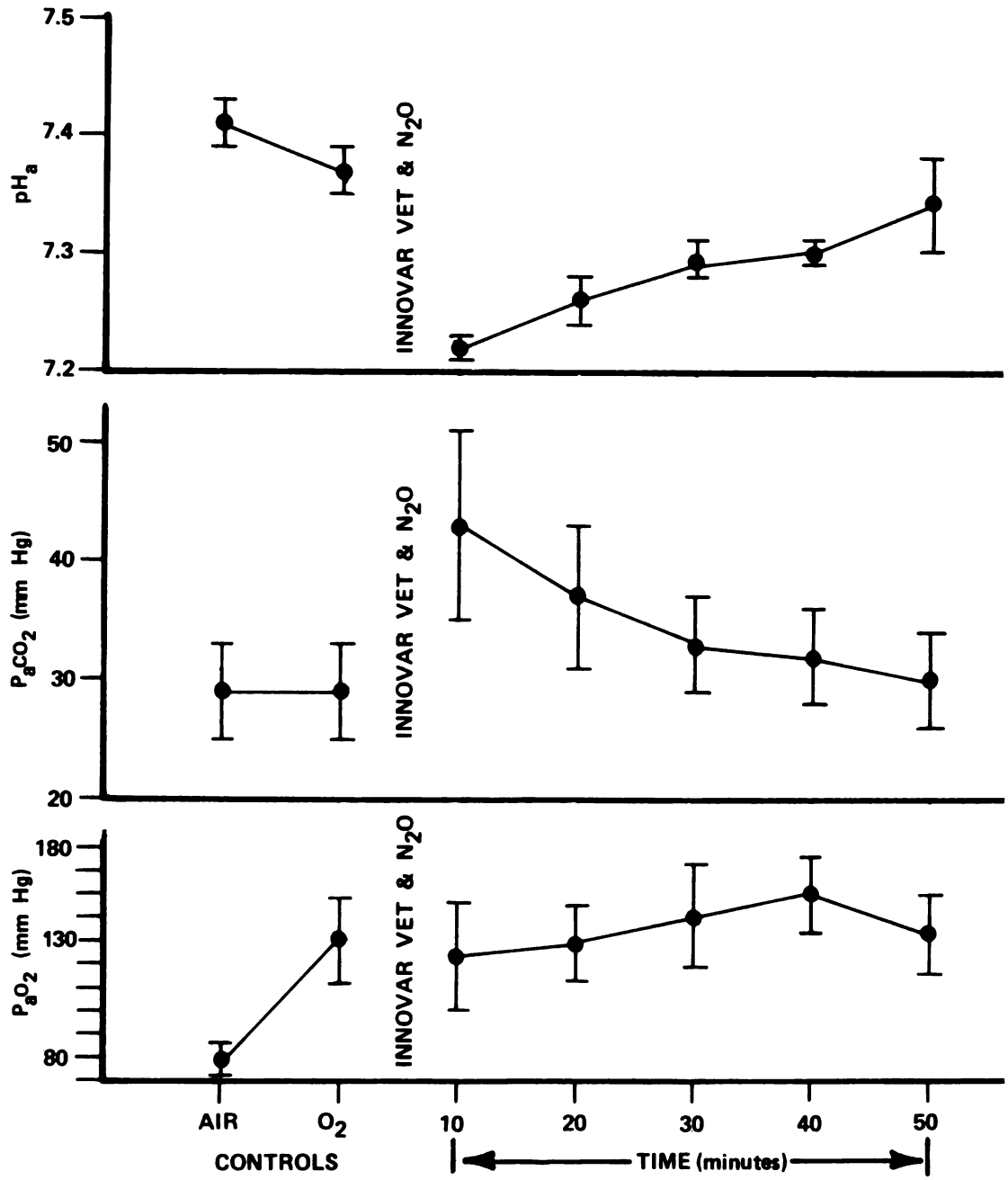

Figure 9. Arterial blood gases with Innovar-Vet and nitrous oxide. Mean values and standard errors plotted for 4 dogs given Innovar-Vet and nitrous oxide. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals. pH_a= Arterial pH; P_aO_2 = Arterial Oxygen Tension; P_aCO_2 = Arterial Carbon Dioxide Tension

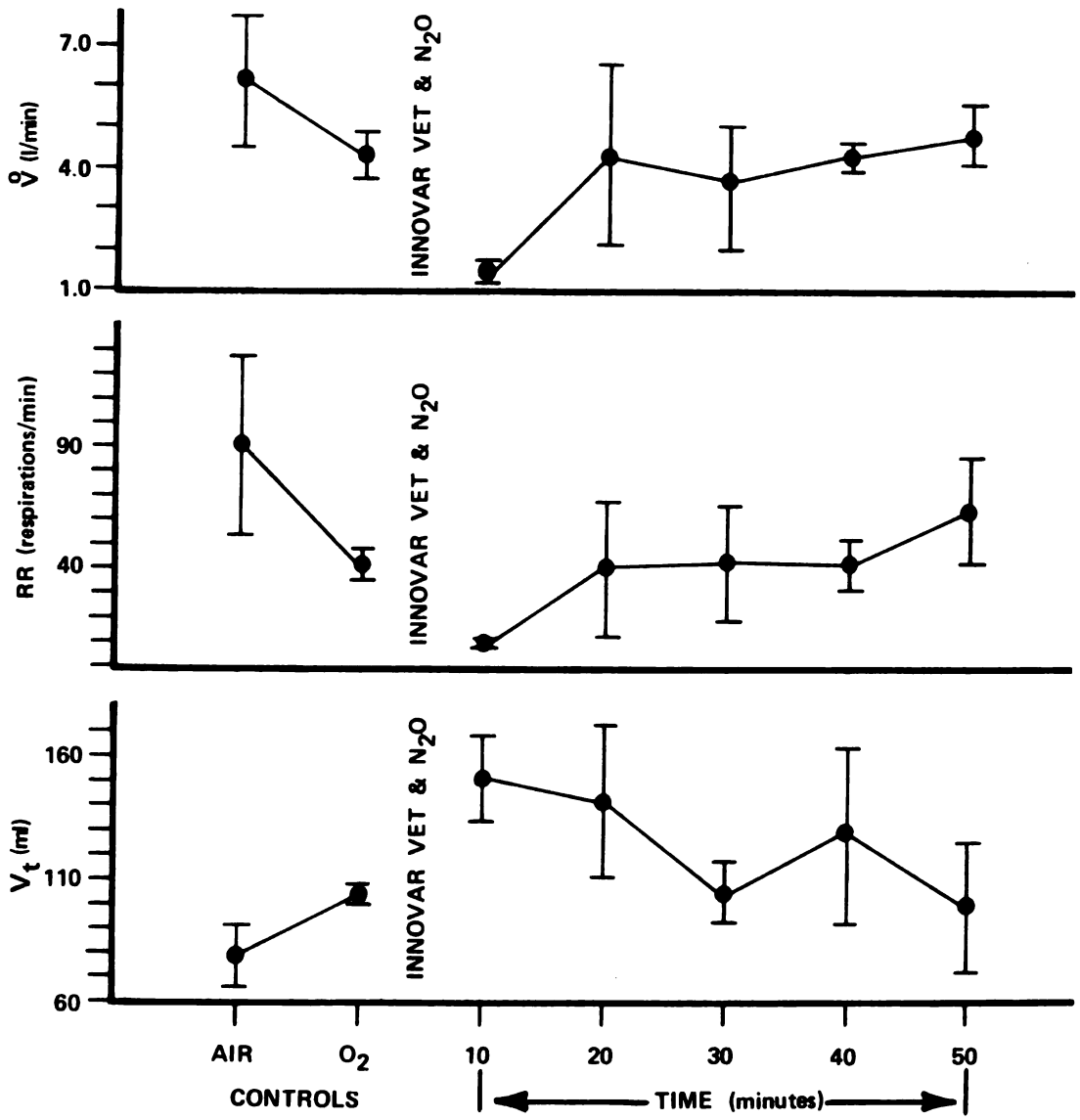

Figure 10. Minute volume, respiratory rate, and tidal volume with Innovar-Vet and nitrous oxide . Mean values and standard errors plotted for 4 dogs given Innovar-Vet and nitrous oxide. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals. $\dot{V}$ = Minute Volume; RR = Respiratory Rate; V_T = Tidal Volume

postinduction ranging from 2.23 ± .45 L/min at 10 minutes to 2.82 ± .58 L/min at 50 minutes (maximum of 37% increase from control). Mean arterial pressure was 98 ± 5 mm Hg at control and ranged from 84 ± 8 mm Hg at 10 min to 104 ± 10 mm Hg at 40 min (maximum at 14% change from control). The slight hypotension was most prominent at the 10-minute interval and returned to above control levels by 30 minutes. Heart rate decreased 25% initially from 92 ± 24 beats/min to 69 ± 12 at 10 minutes and returned to 80 ± 11 by 20 minutes. Stroke volume increased during the experiment and total peripheral resistance decreased 31% from 49 ± 6 units to 34 ± 4 at 20 minutes. Total peripheral resistance was 44 ± 16 at 10 minutes due to 1 dog having an extremely low cardiac output (1.07 L/min).

Bradycardia occurred in 2 of the 4 dogs for 2 to 3 minutes following induction. Numerous premature ventricular contractions (30-40% of total) occurred in 1 dog at the 10-minute interval.

Arterial pH decreased from control of 7.37 ± .02 to 7.22 ± .01 at 10 minutes, 7.26 ± .02 at 20 minutes, and 7.29 ± .01 at 30 minutes. All these changes were highly significant ($P<.01$). It was 7.30 ± .01 at 40 minutes ($P<0.05$) and had returned to 7.34 ± .04 at 50 minutes. The venous pH followed a similar trend with the most severe decrease ($P<0.01$) occurring at the 10-minute interval.

Ten minutes following the injection of Innovar-Vet, $PaCO_2$ increased 48% to 43 ± 8 mm Hg and returned to near control (29 ± 4 mm Hg) at the 50-minute interval. Base deficit returned to control levels at 40 minutes postinduction. Administration of 33% oxygen caused a significant increase in PaO_2 ($P<0.05$) in both the control and experimental time intervals.

Increasing the inspired concentration of oxygen caused a decrease in minute volume and respiratory rate. Administration of Innovar-Vet and nitrous oxide caused a further decrease. The respiratory rate decreased 54% from 91 $\pm$ 37 respirations/min breathing room air to 42 $\pm$ 6 respirations/min breathing 33% oxygen. Ten minutes postinduction the rate was 10 $\pm$ 2 respirations per minute. Respiratory rate returned to control levels after 20 minutes. Decreased respiratory rate was accompanied by increased tidal volume.

Analgesia was better in this group. Zero to 1+ pain response was present in all 4 dogs up to the 50-minute interval, at which time 3 of the 4 dogs recovered, despite a 67% N_2O breathing mixture. Response to auditory stimuli was greatly reduced. No animal exhibited more than a 1+ response at any time interval of the experiment breathing N_2O.

Nystagmus was present in 2 of the 4 animals during the experiment. Apnea occurred in 2 dogs following the injection of Innovar-Vet and persisted for 3 minutes. This was accompanied by transient cyanosis. Panting did not occur in any animal and only 1 had evidence of muscle tremors. Muscle relaxation, judged subjectively, was good in all 4 animals.

Group III: Innovar-Vet with Nitrous Oxide and Atropine

Innovar-Vet with nitrous oxide anesthesia and atropine premedication was studied in 4 dogs averaging 11.3 (10.9 to 11.8) kg. Cardiovascular and respiratory data are presented in Tables 6 and 7, respectively. Cardiac output, mean arterial pressure, heart rate, stroke volume, total vascular resistance, arterial pH, PO_2 and PCO_2, respiratory rate, tidal volume, and minute volume are plotted in

Table 6. Cardiovascular data with atropine, Innovar-Vet, and nitrous oxide

	CONTROLS			CONTROLS		TIME (MINUTES)					
VARIABLE	AIR	O_2		O_2		10	20	30	40	50	60
CO (1/min)	2.13 ± .16	1.82 ± .12	ATROPINE	3.32 * ± .81	INNOVAR-VET & N_2O	3.33 * ± .39	3.28 * ± .43	3.11 * ± .28	2.95 * ± .53	2.82 * ± .32	2.79 * ± .35
SAP (mm Hg)	125 ± 7	118 ± 10		119 ± 5		140* ± 4**	129 ± 1	126 ± 6	128 ± 4	121 ± 4	127 ± 3
DAP (mm Hg)	79 ± 6	67 ± 3		103* ± 3		115* ± 7	99* ± 3	95* ± 5	103* ± 3	98* ± 6	100* ± 4
MAP (mm Hg)	102 ± 6	96 ± 4		113* ± 4		126* ± 5**	115* ± 2	111* ± 1	116* ± 3	112* ± 4	114* ± 2
HR (beats/min)	73 ± 6	61 ± 7		205* ± 10		168* ± 12**	153* ± 9**	140* ± 8**	138* ± 9**	133* ± 6**	133* ± 3**
CVP (mm Hg)	4 ± 1	4 ± 1		2 ± 1		2 ± 1	1 ± 1	1 ± 1	1 ± 1	2 ± 2	1 ± 1
SV (ml)	30 ± 3	31 ± 3		17* ± 4		21* ± 3	22* ± 3	23* ± 2	22* ± 4	22* ± 3	21* ± 3
TPR (pru)	47 ± 4	52 ± 3		39 ± 7		40 ± 5	37 ± 4	36 ± 3	44 ± 8	42 ± 5	42 ± 4
PCV (%)	42 ± 4	44 ± 5		43 ± 4		42 ± 1	43 ± 1	42 ± 2	41 ± 1	41 ± 1	39 ± 1

Represents mean values and standard errors (±) from 4 dogs given premedication of atropine followed by Innovar-Vet and nitrous oxide. Controls taken breathing room air and 33% oxygen. Experimental values taken at 10 minute intervals following injection. CO = Cardiac Output; SAP = Systolic Arterial Pressure; DAP = Diastolic Arterial Pressure; MAP = Mean Arterial Pressure; HR = Heart Rate; CVP = Central Venous Pressure; SV = Stroke Volume; TPR = Total Peripheral Resistance; PCV = Packed Cell Volume.

* Changes of $P<0.05$ or greater from O_2 control before atropine.

** Changes of $P<0.05$ or greater from O_2 control after atropine.

Table 7. Respiratory data with atropine, Innovar-Vet and nitrous oxide

	CONTROLS			CONTROLS		TIME (MINUTES)					
VARIABLE	AIR	O_2	ATROPINE	O_2	INNOVAR–VET & N_2O	10	20	30	40	50	60
pH_a	7.42 ± .01	7.39 ± .01		7.36 ± .01		7.23 *,** ± .01	7.32 * ± .03	7.31 * ± .02	7.30 * ± .03	7.30 * ± .03	7.34 ± .04
pH_v	7.39 ± .02	7.36 ± .01		7.30 ± .04		7.24 * ± .02	7.31 ± .03	7.30 ± .02	7.30 * ± .02	7.28 * ± .02	7.33 ± .02
P_aO_2 (mm Hg)	79 ± 7	154 ± 12		153 ± 12		173 ± 23	164 ± 20	165 ± 20	159 ± 23	164 ± 18	170 ± 18
P_vO_2 (mm Hg)	40 ± 5	51 ± 5		59 ± 9		82 ± 12	77 ± 12	81 ± 16	80 ± 16	83 ± 16	81 ± 17
P_aCO_2 (mm Hg)	33 ± 3	30 ± 3		32 ± 2		43 ± 5	34 ± 6	36 ± 6	37 ± 6	35 ± 7	29 ± 3
BD (meq/l)	3 ± 2	5 ± 2		7 ± 1		10 ± 2	8 ± 2	8 ± 2	9 ± 2	9 ± 2	9 ± 3
P_vCO_2 (mm Hg)	38 ± 2	37 ± 4		35 ± 3		45 ± 4	37 ± 6	37 ± 5	38 ± 6	39 ± 6	35 ± 4
$\dot{V}$ (l/min)	4.15 ± .92	3.52 ± .68		16.08 ± 11.02		8.20 ± 5.59	17.19 ± 4.35	14.13 ± 4.28	16.07 ± 5.10	12.12 ± 5.71	10.33 ± 5.23
RR (resp/min)	60 ± 20	43 ± 16		94 ± 38		46 ± 22	136 ± 22	141 ± 38	148 ± 48	91 ± 43	57 ± 21
V_T (ml)	82 ± 13	93 ± 11		130 ± 39		159 ± 37	126 ± 29	111 ± 33	127 ± 33	143 ± 30	163 ± 23

Represents mean values and standard errors (±) from 4 dogs given premedication of atropine followed by Innovar-Vet and nitrous oxide. Controls taken breathing room air and 33% oxygen. Experimental values taken at 10 minute intervals following injection. pH_a = Arterial pH; pH_v = Venous pH; P_aO_2 = Arterial Oxygen Tension; P_vO_2 = Venous Oxygen Tension; P_aCO_2 = Arterial Carbon Dioxide Tension; BD = Base Deficit; P_vCO_2 = Venous Carbon Dioxide Tension; $\dot{V}$ = Minute Volume; RR = Respiratory Rate; V_T = Tidal Volume

* Changes of $P < 0.05$ or greater from O_2 control before atropine.

** Changes of $P < 0.05$ or greater from O_2 control after atropine.

Figures 11 through 14. The average duration of anesthesia was 80 minutes, but data were analyzed only through 60 minutes since 2 animals were responsive at that time.

The cardiac output increased 82% from a control of 1.82 ± .12 L/min to 3.32 ± .81 L/min ($P<0.05$) 15 minutes after the administration of atropine. The high cardiac output was maintained over the 60-minute period and was not affected by the Innovar-Vet and nitrous oxide. The increase in cardiac output was due to an increase in heart rate. Control heart rate was 61 ± 7 bpm, which was increased 236% by atropine to 205 ± 10 bpm. This highly significant change ($P<0.01$) was evident for the entire study. When Innovar-Vet and nitrous oxide were administered, heart rate decreased slightly to 168 ± 12 bpm and steadily decreased to 133 ± 3 bpm at the 60-minute interval. The increase in heart rate was accompanied by a change in stroke volume which decreased 45% from a control value of 31 ± 3 ml to 17 ± 4 ml 15 minutes following atropine ($P<0.05$). This increased 32% to 21 ± 3 ml 10 minutes after the administration of the anesthetic agents.

Mean arterial pressure increased 18% from a control of 96 ± 4 mm Hg to 113 ± 4 mm Hg after atropine. This increased an additional 31% to 126 ± 5 mm Hg following Innovar-Vet and nitrous oxide and maintained at 111 to 116 mm Hg for the remainder of the experiment. All these changes were highly significant ($P<0.01$).

Systolic pressure was significantly affected only at the 10-minute interval. The control values were 118 ± 10 mm Hg before atropine, 119 ± 5 mm Hg 15 min after atropine and then increased by 19% to 140 ± 4 mm Hg at the 10-minute interval ($P<0.01$). Diastolic pressure followed the same trend as mean pressure. Control was 67 ± 3 mm Hg and increased 54% to 103 ± 3 mm Hg after atropine. Values during

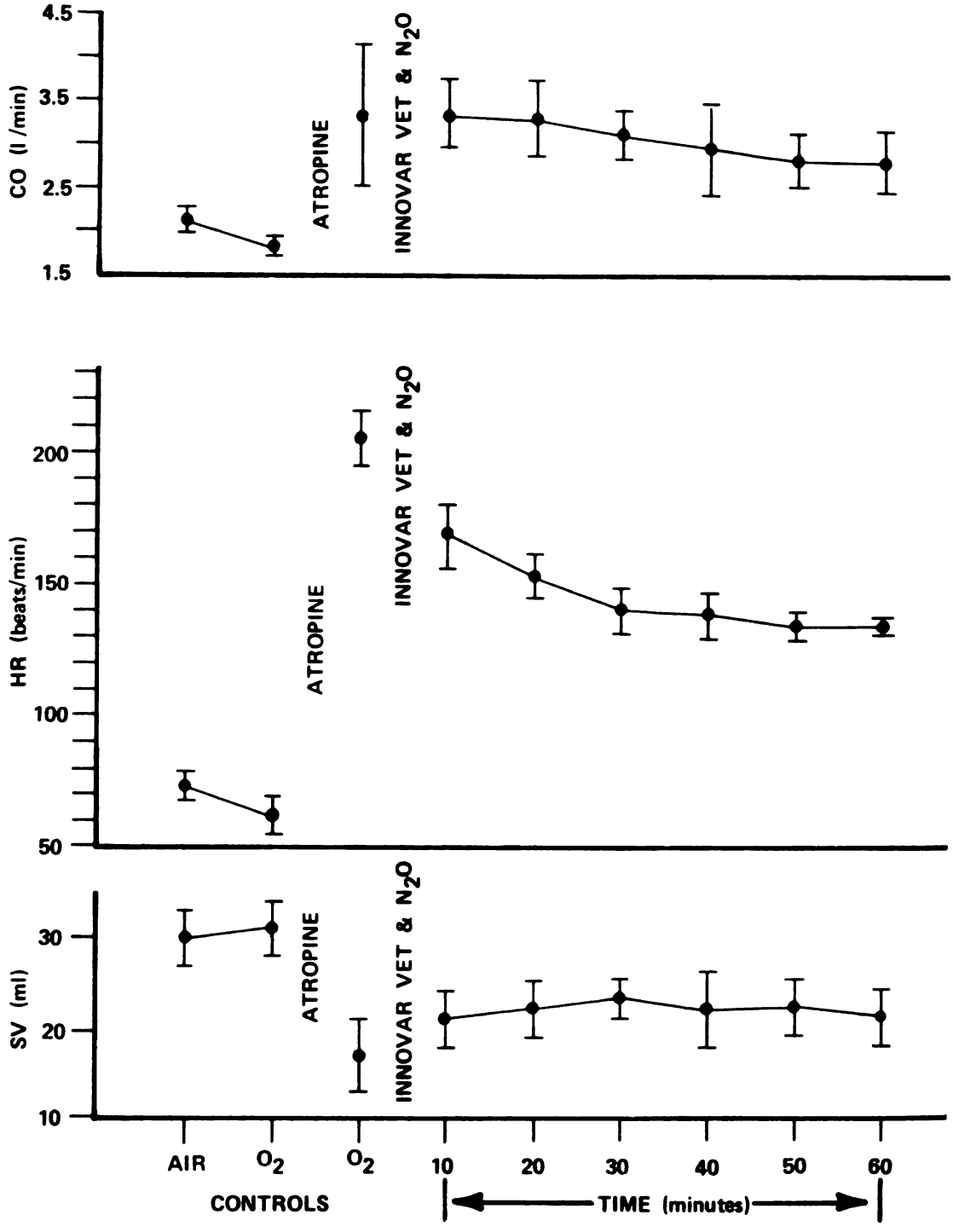

Figure 11. Cardiac output, stroke volume, and heart rate with atropine, Innovar-Vet, and nitrous oxide. Mean values and standard errors plotted for 4 dogs given Innovar-Vet and nitrous oxide with atropine premedication. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals.
CO = Cardiac Output; SV = Stroke Volume; HR = Heart Rate

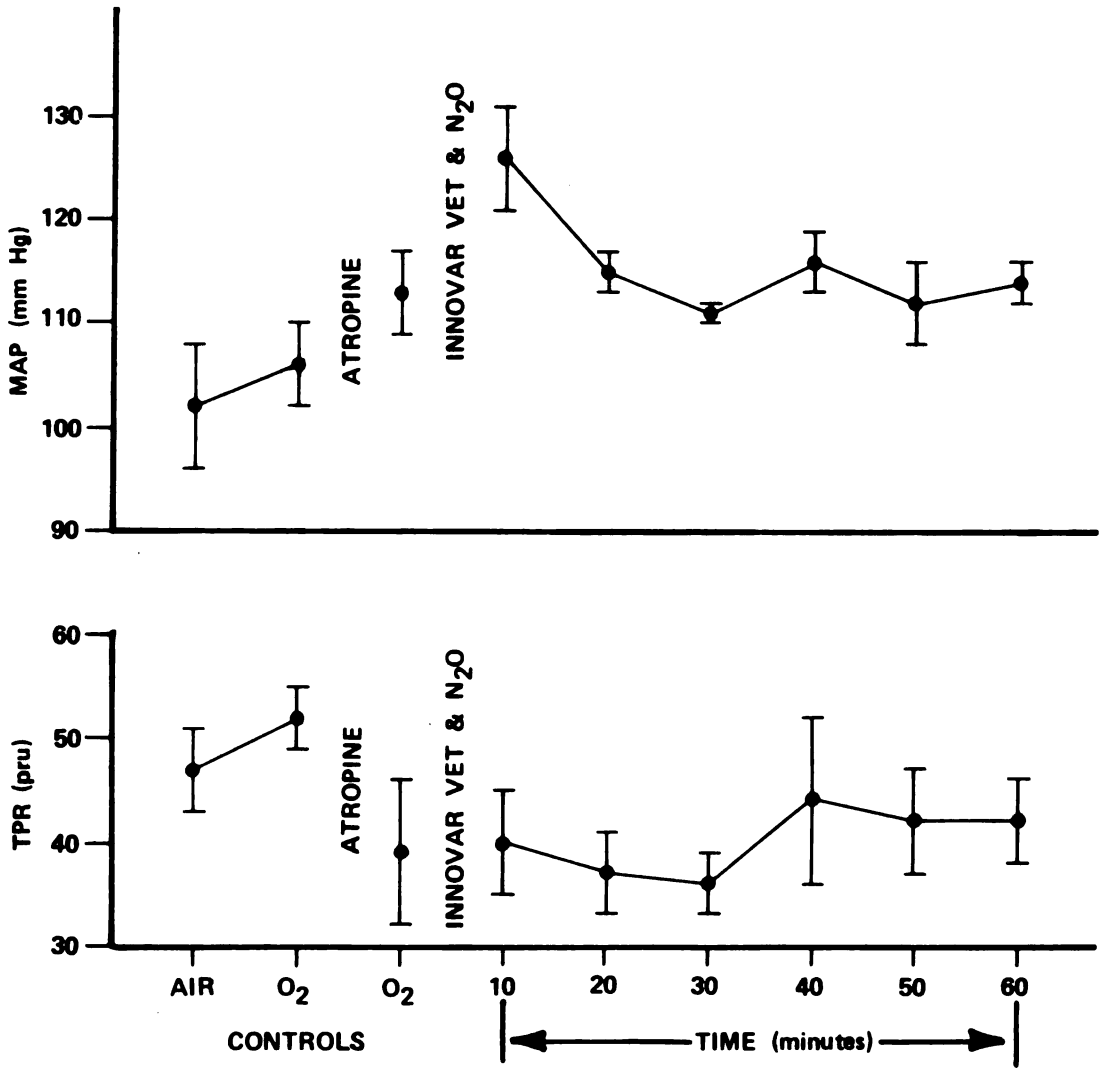

Figure 12. Mean arterial pressures and total peripheral resistance with atropine, Innovar-Vet, and nitrous oxide. Mean values and standard errors plotted for 4 dogs given Innovar-Vet and nitrous oxide with atropine premedication. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals.
MAP = Mean Arterial Pressure; TPR = Total Peripheral Resistance

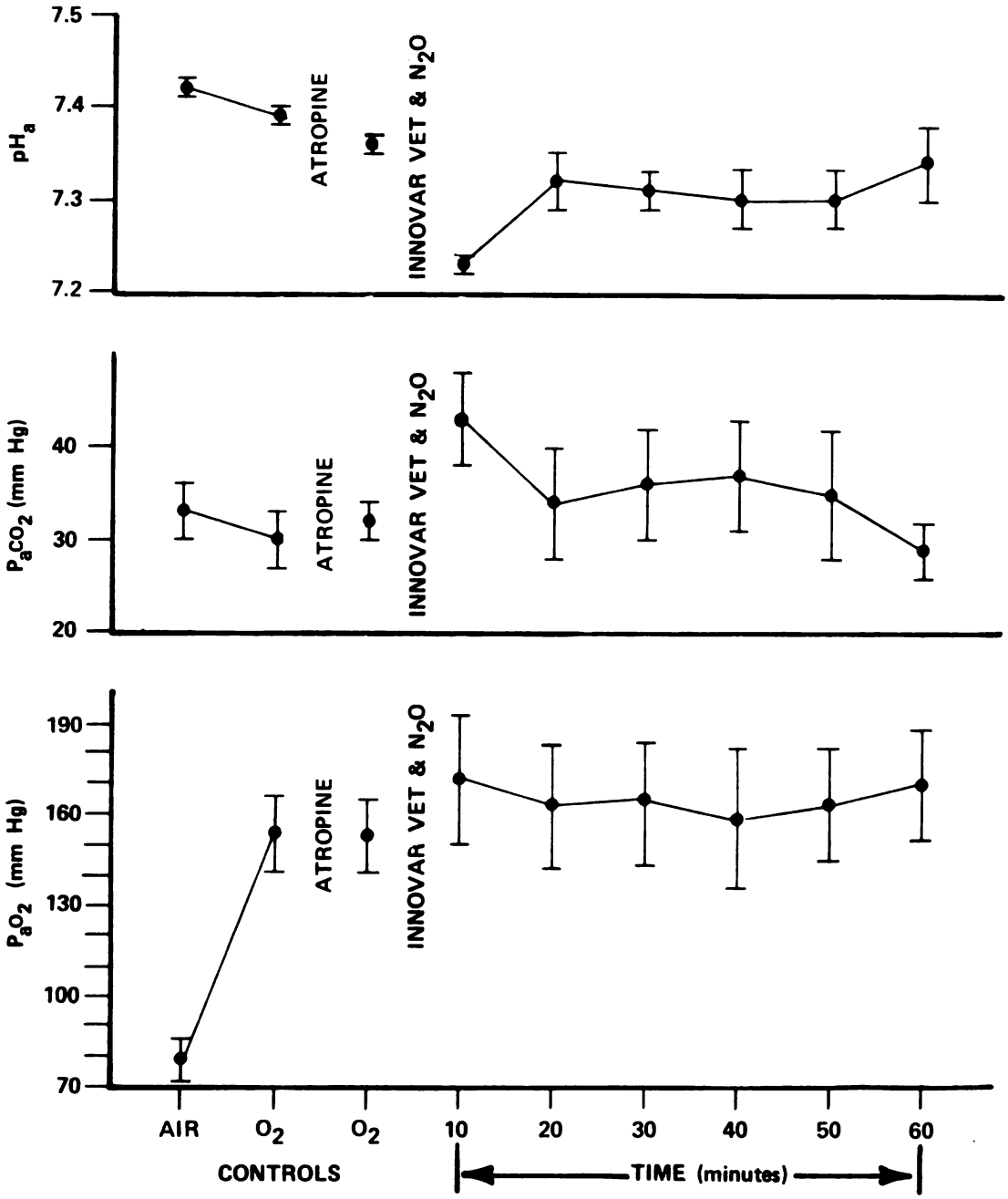

Figure 13. Arterial blood gases with atropine, Innovar-Vet. and nitrous oxide. Mean values and standard errors plotted for 4 dogs given Innovar-Vet and nitrous oxide with atropine premedication. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals. pH_a = Arterial pH; P_aO_2 = Arterial Oxygen Tension; P_aCO_2 = Arterial Carbon Dioxide Tension

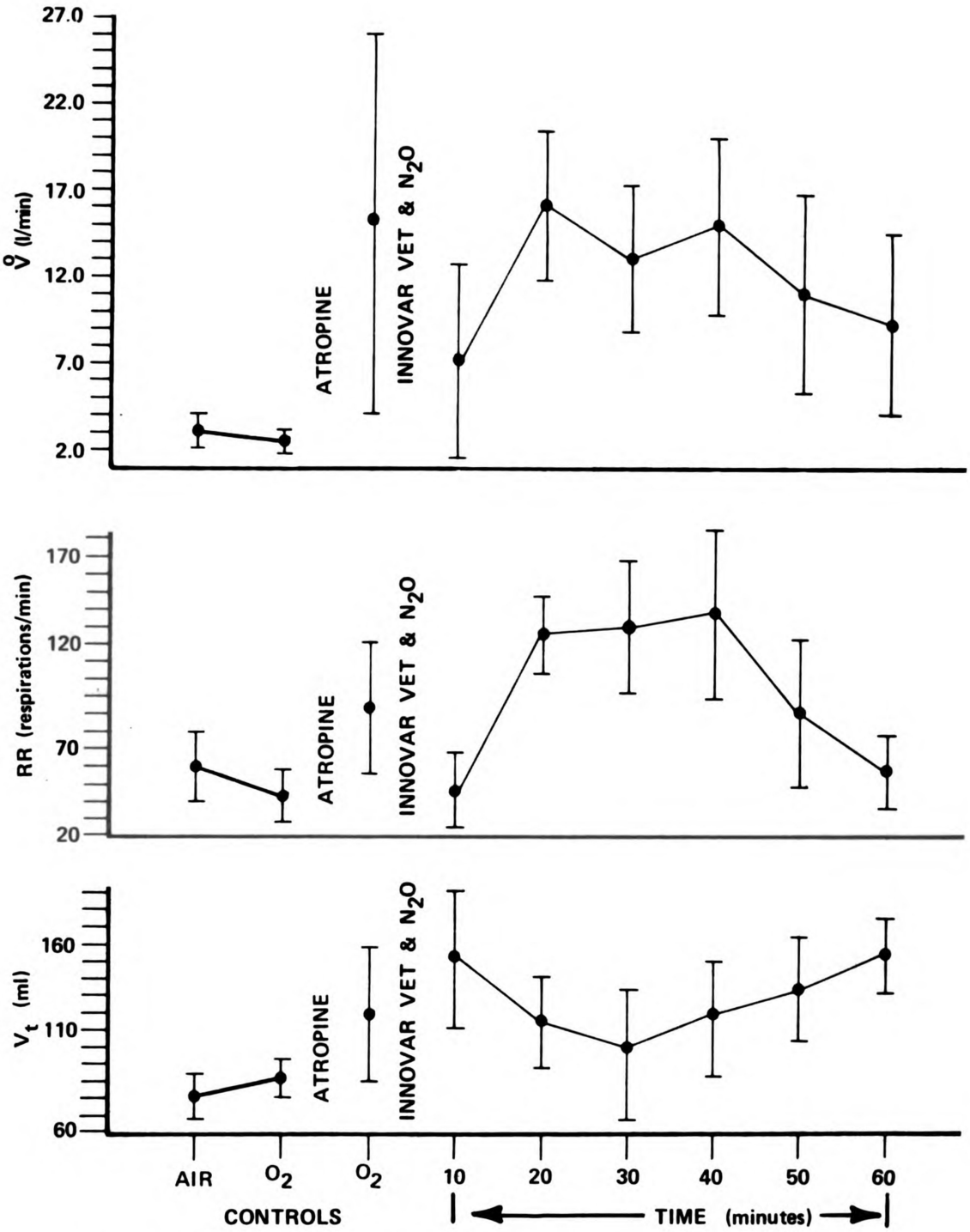

Figure 14. Minute volume, respiratory rate, and tidal volume with atropine, Innovar-Vet and nitrous oxide. Mean values and standard errors plotted for 4 dogs given Innovar-Vet and nitrous oxide with atropine premedication. Controls taken breathing room air and 33% oxygen. Experimental values plotted at 10 minute intervals.
$\dot{V}$ = Minute Volume; RR = Respiratory Rate; V_T = Tidal Volume

anesthesia ranged from 95 to 115 mm Hg. These changes were also highly significant ($P<0.01$).

Although not a significant change, total peripheral resistance decreased by 25% following atropine from 52 $\pm$ 3 units to 39 $\pm$ 7 units. Administration of the anesthetic agents had no further effect.

Atropine had no significant effect on arterial pH. However, administration of Innovar-Vet and nitrous oxide caused a decrease from 7.36 $\pm$ .01 to 7.23 $\pm$ .01 at the 10-minute interval ($P<0.01$). By 20 minutes it had returned to 7.32 $\pm$ .03 ($P<0.05$) and gradually returned to control values at 60 minutes.

The $PaCO_2$ increased by 34% from an atropine control of 32 $\pm$ 2 mm Hg to 43 $\pm$ 5 mm Hg at the 10-minute interval. By 20 minutes, it had returned to 34 $\pm$ 6 mm Hg. The base deficit after atropine was 7 $\pm$ 1 mEq/L and increased to 10 $\pm$ 2 mEq/L 10 minutes after the anesthetics were administered. This stabilized at 8 to 9 mEq/L for the remainder of the experiment. None of these changes were significant. The administration of 33% oxygen caused a highly significant increase ($P<0.01$) in PaO_2 from 79 $\pm$ 7 mm Hg to over 150 mm Hg.

Atropine caused a nonsignificant increase in minute volume from a control of 3.52 $\pm$ .68 L/min to 16.08 $\pm$ 11.02 L/min. This high minute volume remained for the entire experiment. This increase was attributed to nonsignificant increases in both respiratory rate and tidal volume.

Apnea occurred in 2 of the 4 dogs, which lasted for 2 to 3 minutes. Two dogs began panting at the 10-minute interval and continued for the entire experiment. Muscle tremors involving the head and neck occurred in 2 dogs near the end of the experiment. Muscle relaxation was good and flatulence was evident in 3 of the dogs.

Slight (1+) response to auditory stimuli was present in 1 dog for the entire trial. Complete analgesia (0 pain response) was evident in 3 of the 4 animals.

DISCUSSION AND CONCLUSIONS

The results of this experiment did not completely agree with those reported by other investigators as cited in the literature. Some of the differences may be related to the influence of other anesthetic agents used concomitantly with droperidol-fentanyl in some animal studies. Also, drug doses used experimentally varied greatly from those used clinically. Bolus intravenous injection (i.e., given in less than 1 minute) used in some of the experiments may depress the cardiovascular system much more than a slow injection. Effects of drugs in human beings cannot always be equated to changes observed in animals. Experimentally, healthy animals have been used, while clinically this anesthetic has been used principally for the poor-risk patient. Finally, very few laboratory investigations utilized consistent control data.

There is considerable discrepancy in the literature concerning the adrenergic blocking effects of Innovar and, more specifically, the effects of droperidol. Some of this may have resulted from an alpha blocking contaminant in the original drug mixture. Edmonds-Seal and Prys-Roberts (1970) stated that alpha-adrenergic blockade has been over-emphasized and this effect was inconsistent with other well documented studies. The antiarrhythmic effects of the droperidol may indicate some type of beta blocking as well. When all aspects are considered, droperidol-fentanyl cannot be classified as a typical adrenergic blocking agent.

The increased excretion of epinephrine as found by Giesecke *et al.* (1967) may help explain the observed cardiovascular stability even in the presence of alpha adrenergic blockage which may be produced by droperidol. Possible explanations for this increased excretion of epinephrine may be due to stimulation of the adrenal medulla by a central mechanism or an increase in excretion secondary to the alpha blocking effect of droperidol. This alpha block may also account for the increase in contractile force which was reported following the administration of droperidol. The ionotropic effect may have been caused by the increased epinephrine levels.

Fentanyl has been shown to increase vagal stimulation of the heart. The resulting bradycardia can be effectively counteracted by anticholinergic drugs. The hypotensive effects of fentanyl were due to a negative ionotropic effect which was indicated by Goldberg *et al.* (1969) in isolated myocardial preparations. This resulted in a decrease in the active state of the myocardium. Clinically, this may be obscured by sympathoadrenal stimulation.

The dogs used for this study were a very homogeneous group which helped reduce variable factors. All 12 were purebred Beagle half-brothers of the same age and near the same weight. Their genetic background was computerized to detect and eliminate any animals whose parents exhibited defective traits. They were all acclimated to their surroundings for 2 months before the experiment began.

Since data were to be gathered on the conscious unmedicated dog, it was necessary that they be conditioned for this procedure. In order to minimize excitement and provide a stable control period, each dog was trained to lie on a table in lateral recumbency. No dog was used until it would do this for long periods of time without apprehension.

If a dog was particularly nervous on the day of the experiment, he was either given time to sufficiently quiet down or the procedure was postponed to another day.

The instrumentation used was particularly successful. A total of 19 variables were measured with a minimum of physiological disturbance. The chest was not opened for instrumentation as is commonly done; therefore, intrathoracic dynamics were not altered. The only significant physiological change was due to the tracheostomy. Since a large volume of the dog's normal anatomical dead space was bypassed, the control PCO_2 readings were lower than those reported for normal dogs.

All dogs began the experiments with increased base deficits (5 to 10 mEq/L). This was due to the dogs compensating for the mild respiratory alkalosis with a mild metabolic acidosis. This combination resulted in control pHs being within the normal range.

Since Groups II and III were to be evaluated experimentally breathing 67% nitrous oxide and 33% oxygen, it was decided that control and experimental measurements would be taken with all the dogs breathing 33% oxygen. Therefore, control measurements were taken with all dogs breathing 67% nitrogen and 33% oxygen. In addition, the entire Group I experiment was run using this breathing mixture. Thus inspired O_2 content was equal in the control and study periods. As a result, the only significant change detected between the air controls and the oxygen controls in the 3 groups was the increase in arterial and venous PO_2.

Innovar-Vet

The duration of anesthesia with Innovar-Vet alone was very constant. No dog recovered in less than 40 minutes and none stayed

anesthetized for more than 50 minutes. This is more constant than has been reported by Krahwinkel *et al.* (1972) for intramuscular Innovar-Vet, but is consistent with that reported by Krahwinkel and Sawyer (1972) for intravenous administration. It was decided that evidence of recovery would be when the dog showed a 2+ pain response (lift head) to toe clamping.

Innovar-Vet alone caused statistically significant cardiovascular changes only in systolic pressure. Cardiac output was very stable and did not change from control. This is consistent with the observations of Abel and Waldhausen (1968) in chronic instrumentated dogs. Systolic arterial pressure decreased significantly and was probably due to alpha block by the droperidol fraction as indicated by Yelnosky *et al.* (1964). Although the diastolic and mean pressures both decreased, these changes were not statistically significant due to the small sample size. Although the heart rate decreased from 93 $\pm$ 17 to 69 $\pm$ 7, this was not statistically significant. However, on a larger sample size it may have been and could be attributed to the effect of the fentanyl component. Yelnosky and Gardocki (1964) showed that this bradycardia would occur in vagotomized dogs, but Dobkin *et al.* (1970) were able to block the induced bradycardia with atropine.

When heart rate decreased, stroke volume increased which maintained cardiac output constant. This was apparently due to increased filling time evoking a Starling response as illustrated by Burton (1965). Peripheral vascular resistance was not significantly changed in this group.

A transient acidosis was induced with Innovar-Vet. This was due to a combination of respiratory and metabolic acidosis. The respiratory depression immediately following administration of Innovar-Vet resulted

in increased PCO_2 and decreased PO_2. These values had returned to near normal by 10 minutes postinjection when the first measurement was made. Schotz and Ziegler (1967) reported a similar respiratory and metabolic acidosis in spontaneously breathing human patients, but they theorized this to be due only to respiratory depression with hypercarbia and hypoxemia. However, Dobkin *et al.* (1964) were not able to detect any plasma bicarbonate change in human patients being ventilated. In poor-risk patients, sodium bicarbonate should be administered and respiration controlled or assisted to counteract this acidosis.

Respiration was definitely depressed by Innovar-Vet. This was evidenced by apnea and cyanosis immediately following injection. Since measurements were not recorded for analysis until 10 minutes after injection, the peak respiratory depression was observed but not recorded. This peak depression occurred 1 to 2 minutes after injection and persisted for approximately 5 minutes. By the time the 10-minute measurements were taken, respiration was improved but had not reached control values.

Most dogs responded to auditory stimulation. This constitutes a profound problem with this anesthetic since operating rooms are usually noisy. This finding is consistent with the reports of Soma and Shields (1964).

Other evidences of central nervous system stimulation were nystagmus and muscle twitching. These are most likely due to an effect of fentanyl on the brain as reported by Soma (1971). Panting, which occurred in 2 of the 4 dogs, has been noted by Krahwinkel *et al.* (1972), and has been theorized to be due to the effect of fentanyl on the thermoregulatory centers of the brain.

Innovar-Vet with Nitrous Oxide

Anesthetic duration was increased with nitrous oxide by 10 minutes compared to Innovar-Vet alone. This can be accounted for by the analgesic properties of nitrous oxide. One dog had a prolonged effect from this combination, resulting in 110 minutes of anesthesia. He appeared to be conscious for the final 60 minutes, but did not respond to the pain stimuli.

The cardiovascular system was less affected with the combination of Innovar-Vet and nitrous oxide than with Innovar-Vet alone. This was evidenced by the fact that no cardiovascular variable was significantly affected. This is contrary to Dobkin *et al.* (1964), who found slight hypotensive and bradycardia effects in dogs given the same mixture.

Cardiac output was increased with nitrous oxide, although the change was not significant. Control was 2.05 $\pm$ 0.30 L/min and, at 30 minutes, output had increased to 2.83 $\pm$ 0.21 L/min. There was no change in arterial pressure at any time. Since hypotension was present in Group I and not in Group II, there is the possibility of a pressor effect caused by nitrous oxide, as was reported in man by Eisele and Smith (1972). These findings are contradictory to Dobkin and Byles (1966), who reported that Innovar-Vet and nitrous oxide caused a decrease in arterial pressure and in heart rate in dogs. Total peripheral resistance was not significantly decreased when all 4 dogs in this group are analyzed. However, if the one dog with a very high resistance (92 units) is removed, the change is highly significant ($P<0.025$).

Increased cardiac output and lack of hypotension suggests that nitrous oxide may be vasoactive. Moran *et al.* (1972) found a similar increase in cardiac output in dogs.

Similar to the results found in Group I, the only respiratory variables with significant changes were those of arterial and venous pH. The change had metabolic and respiratory factors similar to Group I. These highly significant changes ($P<0.01$) persisted longer, suggesting that the respiration was depressed for a longer period than in Group I. Both PCO_2 and base deficit were increased and changes were greater than in Group I.

Increasing the inspired oxygen concentration from room air to 33% produced a slight decrease in minute volume. This was concurrent with an increase in PO_2. Comroe (1965) reported the same effect in conscious man when breathing mixtures when changed from room air to oxygen.

Respiration was depressed by Innovar-Vet and nitrous oxide as evidenced by a decrease in minute volume. This was due to a decrease in respiratory rate (from 42 to 10), but by 20 minutes returned to control values. However, when the rate decreased, tidal volume increased (from 104 ml to 151 ml). This is in partial agreement with Teutenberg *et al.* (1967), who reported a decrease in rate and depth in human patients given this mixture. Those values returned to normal in 15 minutes.

The combination of Innovar-Vet and nitrous oxide provided better analgesia than Innovar-Vet alone, as evidenced by the analgesic scores. Nitrous oxide alone will not provide anesthesia but is a good analgesic at 67%. It also provided good muscle relaxation and muscle tremors were eliminated.

The response to auditory stimuli was greatly reduced from Innovar-Vet alone. Also, panting was not present in any of the dogs of this group but was present in 2 of 4 in Group I.

Innovar-Vet with Nitrous Oxide and Atropine

The anesthetic duration on this group was 10 minutes longer than for the group without atropine. The extended anesthetic duration may have been due to individual animal differences or a direct effect of atropine. These effects were not distinguished in this study.

Atropine caused an 82% increase in cardiac output. The change was due to a 200% increase in heart rate from control values accompanied by a 75% decrease in stroke volume. The increase in cardiac output is consistent with the findings in man by Berry *et al.* (1958). Diastolic pressure was also significantly increased by atropine, but systolic was not. This resulted in an increase in mean arterial pressure. Eger (1962) reported from studies with human patients that atropine caused an increase in cardiac output without a change in stroke volume and that any tendency towards arterial hypertension was offset by a decrease in peripheral resistance.

Atropine also seemed to have a stimulatory effect on respiration as minute volume increased, but no changes were noted in blood gas values. Due to a very large standard error of the mean, this change in minute volume was not significant.

Cardiac output did not change with the subsequent administration of the anesthetic drugs. However, mean and systolic pressure were transiently increased. The change was significant at 10 minutes but had returned to control levels by 20 minutes. The mechanism of this pressor effect is difficult to explain, since total peripheral resistance was unchanged when compared to the preanesthetic control.

Acidosis occurred with this group as in Groups I and II, but was of shorter duration. This was possibly due to the higher cardiac output providing better perfusion and returning the pH to normal levels sooner.

Respiration was definitely depressed by this combination of drugs for approximately 5 minutes. By the 10-minute sampling period, respiration had returned to near control, but the PCO_2 and base deficit were elevated. Therefore, as in Groups I and II, the true picture of respiratory depression is not apparent in the results.

Analgesia and auditory responses were similar to those of Group II. Muscle relaxation was also comparable to Group II. Two dogs panted from this group, compared to none in Group II. This may be due to the respiratory effects of the atropine as cited by Eger (1962).

This combination of Innovar-Vet and nitrous oxide appears to be a safe anesthetic. The cardiovascular system is minimally affected, whereas most general anesthetics depress both the cardiovascular and respiratory systems. Respiration should be assisted during the first 5 to 10 minutes since this was the period of profound respiratory depression. In addition, in poor-risk clinical cases, it would be advisable to administer sodium bicarbonate to counteract the metabolic acidosis. Innovar-Vet should be administered slowly and to effect over several minutes with the dose not to exceed 1 ml/25 lb (11.4 kg).

Atropine should be used as a preanesthetic to prevent the initial bradycardia and premature ventricular contractions. This transient bradycardia is not present in all animals but should be prevented.

SUMMARY

The cardiopulmonary effects of droperidol-fentanyl, nitrous oxide, and atropine were evaluated and analyzed in 12 adult male Beagles. The cardiovascular variables measured were: cardiac output, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, central venous pressure, heart rate, stroke volume, total peripheral resistance, and packed cell volume. Respiratory measurements included arterial and venous pH, PO_2 and PCO_2, base deficit minute volume, respiratory rate, and tidal volume. In addition, analgesia, response to auditory stimuli, and muscle relaxation were subjectively evaluated. All dogs were surgically instrumented with a catheter in the aorta for measuring cardiac output by thermal dilution. Arterial and venous catheters were inserted and a chronic tracheostomy was performed. EAch dog served as its own control and data obtained from the unanesthetized, unmedicated animals were compared with data recorded following administration of the test drugs.

The dogs were randomly divided into 3 groups of 4 dogs each. Group I was given intravenous droperidol-fentanyl alone; Group II was given droperidol-fentanyl with 67% nitrous oxide, and Group III was given atropine sulfate as premedication followed by droperidol-fentanyl and 67% nitrous oxide.

Respiration was depressed in all 3 groups for 3 to 5 minutes following injection of the droperidol-fentanyl. This resulted in a respiratory and metabolic acidosis in all animals.

In addition, droperidol-fentanyl alone caused a decrease in systolic pressure and a slight decrease in heart rate. These dogs were sensitive to auditory stimulation. No cardiovascular changes were noted when nitrous oxide was added in the Group II animals. Analgesia and muscle relaxation were improved over the Group I animals. The premedication of atropine sulfate in Group III resulted in increased cardiac output, heart rate, and diastolic pressure. The subsequent administration of droperidol-fentanyl-nitrous oxide caused a transient increase in mean and systolic pressure. This latter anesthetic regime along with assisted or controlled respiration provides an excellent anesthetic state with minimal cardiopulmonary depression.

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