The effect of moderate dose administration of dopamine on pulmonary vascular tone in the dog

by

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LIST OF ABBREVIATIONS

a	arterial
C-AMP	cyclic-adenosine monophosphate
CI	cardiac index
cm	centimeter
CO	cardiac output
CVP	central venous pressure
dl	decaliter
DIS	diastolic pressure (systemic)
ECG	electrocardiogram
F	French
GFR	glomerular filtration rate
Hg	mercury
Hgm	hemoglobin
HL	haldol
HR	heart rate
IV	intravenous
kg	kilogram
L	liter
LVDEP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVSWI	left ventricular stroke work index
M	meter
MAP	mean arterial pressure (systemic)

mcg	microgram
mg	milligram
min	minute
ml	milliliter
mm	millimeter
PAD	pulmonary arterial diastolic pressure
PAM	pulmonary arterial mean pressure
PAP	pulmonary artery pressure
PAS	pulmonary arterial systolic pressure
PB	phenoxybenzamine
PCW	pulmonary capillary wedge pressure
PL	propranolol
PO_2	partial pressure of oxygen
PVR	pulmonary vascular resistance
PVRI	pulmonary vascular resistance index
RPF	renal plasma flow
RVEDP	right ventricular end-diastolic pressure
RVSWI	right ventricular stroke work index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
SYS	systolic pressure (systemic)

INTRODUCTION

Dopamine (3,4-dihydroxyphenylethylamine) is an endogenous catecholamine. It is the predominate neurotransmitter in the mammalian extrapyramidal system, as well as the immediate precursor of norepinephrine in catecholamine synthesis (1,14). Dopamine is a mixed amine in that it acts on alpha and beta adrenergic receptors in the sympathetic nervous system and on dopaminergic receptors. The degree of receptor stimulation is dependent upon the concentration or dosage of dopamine administered as an exogenous preparation. Low to moderate doses of dopamine (1-20 mcg/kg/min) cause predominant beta and dopaminergic receptor stimulation. High doses (greater than 20 mcg/kg/min) cause predominant stimulation of alpha and beta receptors (1,6,14,32-34).

Low to moderate dose administration of dopamine results in predominant beta and dopaminergic stimulation with some alpha receptor stimulation. The beta stimulation results in positive inotropic response in the myocardium. The cardiac output (CO) is increased secondary to the increases in the force of myocardial contraction and stroke volume. In this dose range, dopamine has a negligible chronotropic action on the myocardium. Selective vasodilatation is apparent and may result in a slightly decreased systemic vascular resistance. The decreased resistance counters the increased

cardiac output with the systolic arterial blood pressure remaining essentially unaffected. Dopamine produces coronary vasodilatation, secondary to increased myocardial oxygen consumption. When compared to other catecholamines, dopamine is less arrhythmogenic. The renal and mesenteric vasculature are dilated during low and moderate dose dopamine administration. This action is a result of stimulation of dopaminergic receptors in these vascular beds. Renal blood flow is thereby increased. The increased renal flow, as well as a direct action on the renal tubules by dopamine, results in increased urinary and sodium excretion (1,6,14, 32-34).

High dose administration of dopamine is manifest by predominant alpha receptor stimulation resulting in significant vasoconstriction of all vascular beds. The CO remains elevated, the blood pressure is increased and urinary and sodium excretion are diminished (1,2,6,9-14,16-18,19, 24,27-29,31-36).

Because of the physiological response produced by dopamine, it becomes an attractive agent to use in the treatment of various shock states (1-4,6-13,16-18,20,23-25,27,31-33, 35,36).

One question which has not been well-documented to date, is the effect of dopamine on the pulmonary hemodynamics. Changes in pulmonary hemodynamics may result in changes in

the left ventricular end-diastolic pressure (LVEDP) and myocardial oxygen consumption. If dopamine acts to increase pulmonary vascular resistance (PVR), one would expect the LVEDP and myocardial oxygen consumption to be increased. On the other hand, if dopamine decreases PVR, one would expect the LVEDP and myocardial oxygen consumption to decrease. Since dopamine is used to treat clinical states where myocardial function is marginal, the effect of dopamine on pulmonary hemodynamics warrants examination.

Several investigators have examined the effect of dopamine on pulmonary hemodynamics utilizing several techniques. These investigations have produced conflicting data (13,17, 18,25,35). The purpose of this study is to obtain a clearer understanding of the effect administration of dopamine in the low and moderate dose ranges has on pulmonary hemodynamics. This evaluation was achieved by comparing various hemodynamic parameters obtained from whole animal preparations.

LITERATURE REVIEW

Over the last fifteen years, dopamine has been shown to be of major importance in catecholamine metabolism. In addition to acting as precursor to norepinephrine and epinephrine, dopamine has been found in greater concentrations than that of norepinephrine in some areas of the body (2,5). Dopamine has been shown to be a central neuromediator in the extrapyramidal system. Recent studies have shown concentrations of dopamine to exist in the pancreas, the carotid bodies and the lung. These studies have suggested certain physiological functions for dopamine within these areas of the body (2,5,10,17).

In addition to its known physiological actions, dopamine is known to have pharmacologic actions when administered as an exogenous preparation in pharmacologic doses. Dopamine has been shown to act directly on alpha, beta and dopaminergic receptors, and to cause the release of norepinephrine from sympathetic nerve terminals. These combined direct and indirect actions of dopamine result in its classification as a mixed amine (1,2,6,9,10,12,14,28).

Pharmacology of Dopamine

The degree of receptor stimulation is dependent upon the dose of dopamine administered. Low to moderate pharmacologic doses of dopamine (dose range of 1-20 mcg/kg/min, I.V. infusion) result in predominant $beta_1$ and dopaminergic receptor stimulation. High doses of dopamine (greater than 20 mcg/kg/min) result in predominant alpha and beta receptor stimulation (1,2,3,6,9,10,12,14,28,32-34).

Cardiac actions

Low and moderate doses of dopamine exert a positive inotropic action on the heart similar to that of the other sympathomimetic amines. The positive inotropic action on the heart results in an increase in coronary output secondary to increased stroke volume (1,6,9,10,12,14,32-34). The blockade of dopamine's cardiac action by propranolol confirms this action is mediated via $beta_1$ stimulation (1,6,9,10,12, 14). The positive chronotropic action of dopamine seen at high doses appears to be dependent on the positive inotropic action (10,11). No evidence has been found to suggest a specific dopaminergic receptor acting in the heart to produce either positive inotropic and/or chronotropic effects (1,10,11).

The arrhythmogenic properties of dopamine are significantly less than those of other sympathomimetic amines,

although a high dose level (greater than 20 mcg/kg/min) of dopamine can become arrhythmogenic. Catecholamine sensitizing agents, such as cyclopropane or halothane, do enhance dopamine's tendency to produce ventricular ectopy (6,10).

Dopamine infusions in moderate and high doses have been shown to increase coronary blood flow, probably via increased myocardial oxygen consumption (1,3,6,8,10). Studies by Goldberg have shown an unaltered oxygen and lactate extraction by the heart during low dose administration of dopamine (3,8,10-12).

Vascular actions

As with cardiac action, the action of dopamine on the vasculature is complex and dose dependent. Dopamine acts as a vasopressor at high doses and as a selective vasodilator at low and moderate doses. The vasopressor response, seen at high doses, appears to be mediated by alpha receptor stimulation. The vasopressor response is apparent in all vascular beds at doses greater than 20 mcg/kg/min (1,6,10-12,16,32-34). The selective vasodilatation, apparent at low and moderate doses, is in the renal and mesenteric vascular beds and has been shown to be mediated via dopaminergic receptors in these beds. This vasodilatation is overwhelmed by predominant alpha stimulation at high doses of dopamine (1,6,10-12,16,32-34).

The mesenteric vasodilatation is unaffected by alpha or beta blocking agents, antihistamines, or parasympathetic blocking agents. Dopaminergic blocking agents such as the buterophenons, apomorphine, phenothiazides, attenuate the vasodilatation of dopamine, suggesting a specific dopaminergic receptor in the renal and mesenteric vascular beds (10-12). The dopaminergic receptors also show specific structure activity relationships. Only one synthetic amine, epinine, has been found to have actions similar to dopamine. Apomorphine, while blocking the action of dopamine, appears to also have agonistic properties similar to dopamine (10,12). This evidence demonstrates the existence of a specific dopaminergic receptor in the renal and mesenteric vascular beds, which when stimulated, causes vasodilatation.

The vasopressor action of dopamine appears to be the result of more pronounced constriction of veins than of arteries (10). This vasopressor action is mediated by alpha receptor stimulation, as demonstrated by attenuation of the vasoconstriction by alpha blocking agents (such as phentolamine and phenoxybenzamine). The vasoconstriction is unaffected by beta and dopaminergic blocking agents (10-12). The vasopressor response is noted predominantly at higher doses of dopamine (greater than 20 mcg/kg/min) although some peripheral vasoconstriction occurs at low and moderate doses (6,10-12).

In addition to its direct action on dopaminergic receptors, dopamine causes alterations in the cardiovascular system through reflex and neurogenic actions. Doses of dopamine (greater than 20 mcg/kg/min) which increase CO as well as systemic vascular resistance (SVR), may cause reflex bradycardia and decreased vascular tone. This action, mediated through receptor stimulation, may help to reduce myocardial oxygen consumption (10).

The neurogenic changes in vascular tone produced by dopamine are produced by stimulation of lumbar autonomic ganglia. Histamine is released by this stimulation, and results in a vasodilatation similar to that produced by morphine (10,11).

A second dopaminergic receptor, different than the receptor seen in the renal and mesenteric vascular beds, has been hypothesized to exist in peripheral vascular beds. This receptor is suspected to produce vasodilatation by inhibiting sympathetic stimulation of these vascular beds, apparently by inhibiting the release of norepinephrine from sympathetic nerve terminals. The receptor appears to be located within the vessels themselves. The vasodilatation in the peripheral vascular beds is blocked by dopaminergic blocking agents (16,20).

Pulmonary vascular actions

To date, not a great deal of work has been done examining the effects of dopamine on the pulmonary vasculature and pulmonary hemodynamics. Dopamine has been shown to exist within the lung and is assumed to have some physiological action. This action is thought to be related to hypoxia and alterations in pulmonary hemodynamics. Since dopamine is used clinically as an exogenous preparation in pharmacologic doses, the majority of studies on the pulmonary vasculature and pulmonary hemodynamics have been in the pharmacologic dose range.

Waaler (35) in 1961 examined the action of dopamine on the pulmonary vasculature. In his preparation, a lobe from a canine lung was isolated, perfused and mechanically ventilated while monitoring the pulmonary vascular resistance (PVR), blood flow and pressure in the pulmonary and bronchial vasculature. A single constant volume reservoir was used to perfuse the pulmonary and bronchial vascular beds.

Waaler found that large doses of dopamine caused vasoconstriction in the pulmonary vasculature in the isolated, perfused lung-lobe preparations. The vasoconstrictions seen in the preparation were 1/20th to 1/30th of that seen during norepinephrine and epinephrine administration. Waaler (35) also observed that dopamine failed to produce vasoconstriction in the bronchial vascular bed, while norepinephrine and

epinephrine administration did produce bronchial vasoconstriction. Based on this apparent selectivity of action, Waaler (35) suggested that dopamine acts on a specific dopaminergic receptor, producing pulmonary vasoconstriction.

Harrison et al. (17) in 1969 also examined the effect of dopamine on the pulmonary vasculature. In their model, the pulmonary, left atrial pressure, aortic pressure and aortic blood flow were measured. Dopamine infusions were administered over ten minute periods at doses of 5, 15, 25 and 30 mcg/kg/min. The pulmonary vascular resistance was calculated based on the assumption that pulmonary blood flow equaled aortic blood flow at all times.

Harrison et al. (17) found that low and moderate doses of dopamine (5 and 16 mcg/kg/min) produced no significant rise in the pulmonary artery mean pressure (PAM). High doses (25 and 30 mcg/kg/min) produced a significant rise in the PAM. These changes in the PAM were directly reflected by changes seen in the left atrial pressure. Aortic pressure was unaffected by low and moderate dose infusion of dopamine, but rose significantly during high dose administration. The cardiac output increased at all dose levels. Heart rate (HR) and PVR were also unaffected by the various dosages administered. The systemic vascular resistance (SVR) fell slightly during the low and moderate dose administrations and increased during the 30 mcg/kg/min dopamine infusion.

The SVR was unaltered at the 25 mcg/kg/min dopamine infusion. Harrison et al. (17) concluded that dopamine acted to increase the tone of the pulmonary vessels without changing their caliber. He theorized the increase in the PAM was a result of the combination of increased cardiac output and the concurrent increase in pulmonary vessel tone.

In 1975, Holloway et al. (18) examined the effect of dopamine on the pulmonary vasculature of normal and pulmonary hypertensive patients. Heart rate, right ventricular end-diastolic pressure (RVEDP), pulmonary artery pressure (PAP) and aortic pressure were monitored. The systemic vascular resistance, pulmonary vascular resistance and cardiac index (CI) were calculated for all patients. Dopamine was administered at low to moderate doses (2 to 16 mcg/kg/min). During the dopamine administration the heart rate, cardiac index, pulmonary arterial and aortic pressures increased in all patients. The SVR decreased during the administration. The PVR and RVEDP were unaltered.

The administration of dopamine produced the predicted results of increasing cardiac output, diminishing SVR and increasing pulmonary artery pressure without affecting the PVR. In the study, Holloway showed the RVEDP to be unaffected by dopamine administration at low and moderate doses. Based on this information, he concluded that the increase in pulmonary artery pressure was secondary to increases in the

cardiac output and was not due to pulmonary vasoconstriction (18).

The effects of dopamine, isoproterenol and hypoxia on the pulmonary vasculature of isolated lung lobe preparations were studied by Mentzer et al. (25) in 1976. The lung lobes were perfused at a constant flow rate and the left atrial pressure was held constant. Dopamine was infused at 10-20 mcg/kg(body weight)/min. Pulmonary arterial flow and the pulmonary and left atrial pressures were monitored. Mentzer noted a 50% increase in pulmonary vascular resistance and pulmonary artery pressure during the dopamine infusions. The combination of dopamine and phentolamine (an alpha blocker), reportedly abolished the pulmonary vascular pressor action seen with dopamine alone. Beta receptor blockade by propranolol had no effect on dopamine's pulmonary pressor action. Mentzer concluded dopamine acts on alpha receptors in the pulmonary vasculature to produce pulmonary vasoconstriction and a secondary increase in PVR. Mentzer failed to note phentolamine is not a pure alpha blocker. One of its other actions is to cause pulmonary vasodiltation (1,14). The apparent pharmacologic blockade of dopamine's pulmonary pressor could actually have been countered by phentolamine's direct vasodilator action (14,25).

Gooding et al. (13) in 1977, examined dopamine's effects

at pump controlled low and moderate cardiac outputs. Like Harrison et al. (17) they found that low and moderate levels of dopamine (8 and 16 mcg/kg/min) produced no significant changes in mean systemic arterial pressure (MAP), PAM and renal blood flow. By holding the cardiac output constant, Gooding et al. (13) were able to maintain the pulmonary artery pressure constant, thereby further supporting the hypothesis of Harrison et al., that increases in pulmonary artery pressures were due to increases in cardiac output while the pulmonary vascular bed maintains its basal tone.

Clinical uses

Dopamine's selective ability to produce a positive inotropic response in the myocardium, maintain arterial blood pressure, while not significantly changing systemic vascular resistance and to increase urinary and sodium excretion, make it the drug of choice in treating patients suffering from congestive heart failure and shock.

In congestive heart failure the principal goals are to improve left ventricular emptying and reduce the volume load on the cardiovascular system. Traditionally, this has been done by combining positive inotropic agents such as digitalis preparations or sympathomimetic amines and diuretics. Most digitalis preparations are slow acting and are of no immediate benefit in the management of the acute patient.

Isoproterenol has been used because of its inotropic action, but tends to be arrhythmogenic, as well as causing peripheral vasodilatation through $beta_2$ stimulation. The vasodilatation decreases the MAP and reduces blood flow in the renal and coronary vascular beds. Urinary output is diminished and increased myocardial ischemia have been noted during isoproterenol administration (6,10,11,25,27,31).

In acute pulmonary edema, dopamine may increase LVEDP and pulmonary vascular congestion and myocardial oxygen consumption. Nitroprusside (a nonspecific vasodilator) reduces both afterload (by decreasing aortic impedance) and preload (by reducing LVEDP and LVEDV) (1,14). When administered concurrently, dopamine and nitroprusside result in an increased cardiac output, increased urinary and sodium excretion, and decreased work load on the heart (via peripheral vasodilatation). The combination of these two agents results in an effective approach to the treatment of pulmonary edema (1,27,31).

The shock syndrome is manifest by cardiovascular collapse, redistributed blood flow and hypoperfusion of vital organs. A reflex sympatho-adrenal response compounds the problem by causing vasoconstriction and increased systemic vascular resistance with a further decrease in blood flow to vital organs (6,10,11,23,24,29). The supportive measures are

aimed at correcting blood volume, improving myocardial contractility and selectively altering the resistance in vascular beds (6,10,11,23,24,29).

In the past, shock therapy has centered about the use of sympathomimetic amines (isoproterenol, epinephrine and norepinephrine) with predominate alpha and $beta_1$ receptor stimulation. These agents increased the CO and elevated the MAP at the expense of an elevated SVR and hypoperfusion of renal and mesenteric vascular beds.

Alpha receptor blocking agents, such as phentolamine, have been used to attempt to counter the vasoconstriction seen in the renal and mesenteric vascular beds (6,10,11). These alpha blocking agents are not pure antagonists and produce hypotension by their direct action on the vasculature, thereby compounding the shock syndrome (6,10,11).

Dopamine in low to moderate doses acts predominantly on $beta_1$ and dopaminergic receptors in the heart and renal and mesenteric vascular beds. Its overall effect is to increase CO, decrease SVR (by vasodilatation of renal and mesenteric beds), increase renal blood flow and urinary and sodium excretion (6,10,11,23,24,29).

Moderate dose administration of dopamine (10-20 mcg/kg/min) produces the same response seen with the low dose administration, but with further increases in CO and pulse pressure. Urinary and sodium excretion are further increased

(probably secondary to increases in the CO) (23,24,29,36).

High dose administration of dopamine produces predominant alpha receptor stimulation, manifest by vasoconstriction in all vascular beds. The vasoconstriction is equivalent to that seen with norepinephrine administration. The renal vasculature is also constricted resulting in decreased urinary and sodium excretion. This high dose administration of dopamine is generally used only in profound shock (6,10,23,24,29,36).

Summary

The overall hemodynamic action of dopamine is dependent on the dose administered. The previous studies tend to suggest that dopamine produces increased pulmonary arterial pressures. As dopamine is used extensively in the clinical management of shock syndromes, its actual effect on the pulmonary vasculature warrant further study.

METHODS AND MATERIALS

Design

Twelve dogs, weighing 11.36-34.00 kg, were used in the study. Anesthesia was induced by intravenous administration of sodium thiopental (5.44 mg/kg) and maintained with methoxyflurane and oxygen. Methoxyflurane was used to minimize the cardiovascular effect of anesthesia. All animals were intubated and allowed to breathe spontaneously. Catheters were inserted into the descending aorta, inferior vena cava, a peripheral vein and a pulmonary artery.

Three catheters were connected to Bell and Howell Pressure Transducers type 4-327-0131 (0-400mm Hg) via non-distensible pressure lines. A catheter (60 cm, 7F) was inserted into the right femoral artery and advanced antereograde a premeasured distance to position the catheter tip in the thoracic aorta. This catheter was used to measure systemic arterial pressure and for arterial blood sampling. A second catheter (60 cm, 7F) was inserted into the right femoral vein and advanced anterograde a premeasured distance to place the catheter tip in the thoracic inferior vena cava for central venous pressure. A Swan-Ganz balloon-tipped catheter (Edwards model 93-115-7F) was advanced retrograde from the right external jugular vein to the pulmonary artery. This catheter was used to measure pulmonary artery

and capillary wedge pressures, and for sampling of mixed venous blood. The catheters and pressure lines were kept patent by either intermittent or constant low-flow flush with heparinized saline (10 units/ml). All pressures were recorded on a Beckman R611 Recorder.

The heart rate was monitored by a lead V_1 ECG, also recorded on the Beckman R611 Recorder.

A 18 gauge 2.5 inch plastic catheter was inserted into the left femoral vein for infusion of the drugs.

The twelve animals were divided into three equal-sized groups of four dogs each. Group one received an alpha blocking agent (phenoxybenzamine, 4 mg/kg, Smith, Kline & French). Group two received a beta blocking agent (propranolol, 1 mg/kg, Ayrest). Group three received a dopaminergic blocking agent (haldol, 0.1 mg/kg, McNeil).

Each animal was subjected to four treatments. During each treatment the arterial, central venous, pulmonary arterial and capillary wedge pressures were recorded. Arterial and mixed venous blood samples were obtained from the arterial and Swan-Ganz catheters. Oxygen consumption was determined from a spirometer.

The following experiment protocol was followed for each animal:

Treatment 1: An initial 15 minute control period during which baseline recordings of heart rate, arterial,

central venous and pulmonic pressures and oxygen consumption were recorded.

Treatment 2: Infusion of dopamine (Arnar-Stone) at 10.00-16.80 mcg/kg/min IV. After a five minute infusion, the hemodynamic measurements and oxygen consumption were recorded.

Treatment 3: After the parameters monitored returned to control values, the blocking agent used for each animal was administered IV. After a ten minute period, the hemodynamic parameters and oxygen consumption were recorded.

Treatment 4: After a twenty minute period was observed, dopamine was readministered at the dose administered during Treatment 2. After a five minute infusion, the hemodynamic parameters and oxygen consumption were recorded.

Hemodynamic Parameters

The heart rate, central venous, systolic, diastolic, and pulmonary wedge pressures were obtained directly from recordings. The oxygen consumption was determined directly from spirographic recordings. The mean arterial and pulmonic pressures, systemic and pulmonary vascular resistance indices, and the cardiac index were calculated from the recorded

parameters.

Systemic and pulmonary vascular resistance indices

The systemic and pulmonary vascular resistance indices were calculated using the following equations (14):

Pulmonary vascular resistance index, $dynes \cdot sec \cdot cm^{-5} \cdot M^{-2}$ =

$$\frac{((PAM-PCW) \times 79.92)}{CI}$$

Systemic vascular resistance index, $dynes \cdot sec \cdot cm^{-5} \cdot M^{-2}$ =

$$\frac{((MAP-CVP) \times 79.92)}{CI}$$

These equations are derived from the equation:

$$\text{Resistance} = \frac{\text{pressure}}{\text{flow}} =$$

$$\frac{\text{mean pressure differential across the vascular bed}}{\text{blood flow}}$$

Conversion to the metric centimeter-gram-second (cgs) scale is accomplished by the following conversion:

By definition, 1 mm Hg = 1332 $dynes/cm^2$.

$$\text{Resistance} = \frac{\text{mean pressure differential, mm Hg} \times 1332 \frac{dynes}{cm^2}}{\text{blood flow, L/min} \times 1000 \text{ ml/L} \times \text{min/60 sec}}$$

Therefore,

$$\text{Resistance} = \frac{\text{mean pressure differential}}{\text{blood flow}}$$

$$\times 79.92 \ dynes \cdot sec \cdot cm^{-5}$$

By using the cardiac index instead of the cardiac output

for the blood flow, the vascular resistance index is obtained (19).

Mean systemic and pulmonary arterial pressures

The derived variables, MAP and PAM were calculated from the following equations (30):

MAP, mm Hg = DIS + (SYS - DIS)/3

PAM, mm Hg = PAD + (PAS - PAD)/3.

Cardiac index

CO was calculated by the Fick technique using the following equation (36).:

$$\text{Cardiac Output (CO), L/min} = \frac{\text{Oxygen consumption, L/min}}{\text{Arterial } O_2 \text{ content, L/L} - \text{Venous } O_2 \text{ content, L/L}}$$

Oxygen consumption was determined by allowing the animals to breathe room air for three minutes, then measuring the minute oxygen consumption with a spirometer. Arterial and mixed venous blood oxygen content were calculated from the following equation (7):

O_2 content, ml/decaliter = Hgm, g/dl x 1.39 x percent saturation Hgm + (pO_2, mm Hg x 0.0031).

Hemoglobin measurements were made by the cyanomethemoglobin

method. The arterial and mixed venous blood oxygen tensions were measured using a IL 513 blood gas analyzer (7,21). The CI was obtained by relating the CO to the body surface area using the following equation (30):

$$\text{Cardiac index, L/min-M}^2 = \frac{\text{Cardiac output, L/min}}{\text{Body surface area, M}^2}$$

The body surface area was derived from Table 3 in Link and Bertner's Handbook of Veterinary Procedures (22).

Data Analysis

The data for each of the parameters were assembled into a table, with forty-eight observations per parameter. The data were normalized by determining the variance of each parameter from the control value (obtained from treatment 1) for each animal. These values, expressed as percent of control, were then used to determine the mean percent of control for treatments 2, 3, and 4 for all groups and for each of the three groups.

The data for the treatments 2, 3, and 4 for each of the three groups were plotted for each treatment. Statistical analysis of variance procedures were performed on the data. Comparisons were made to determine significant differences between treatments 1, 2, 3 and 4 and between the three groups of animals for each treatment. A probability of 0.05 was used to determine the level of significance.

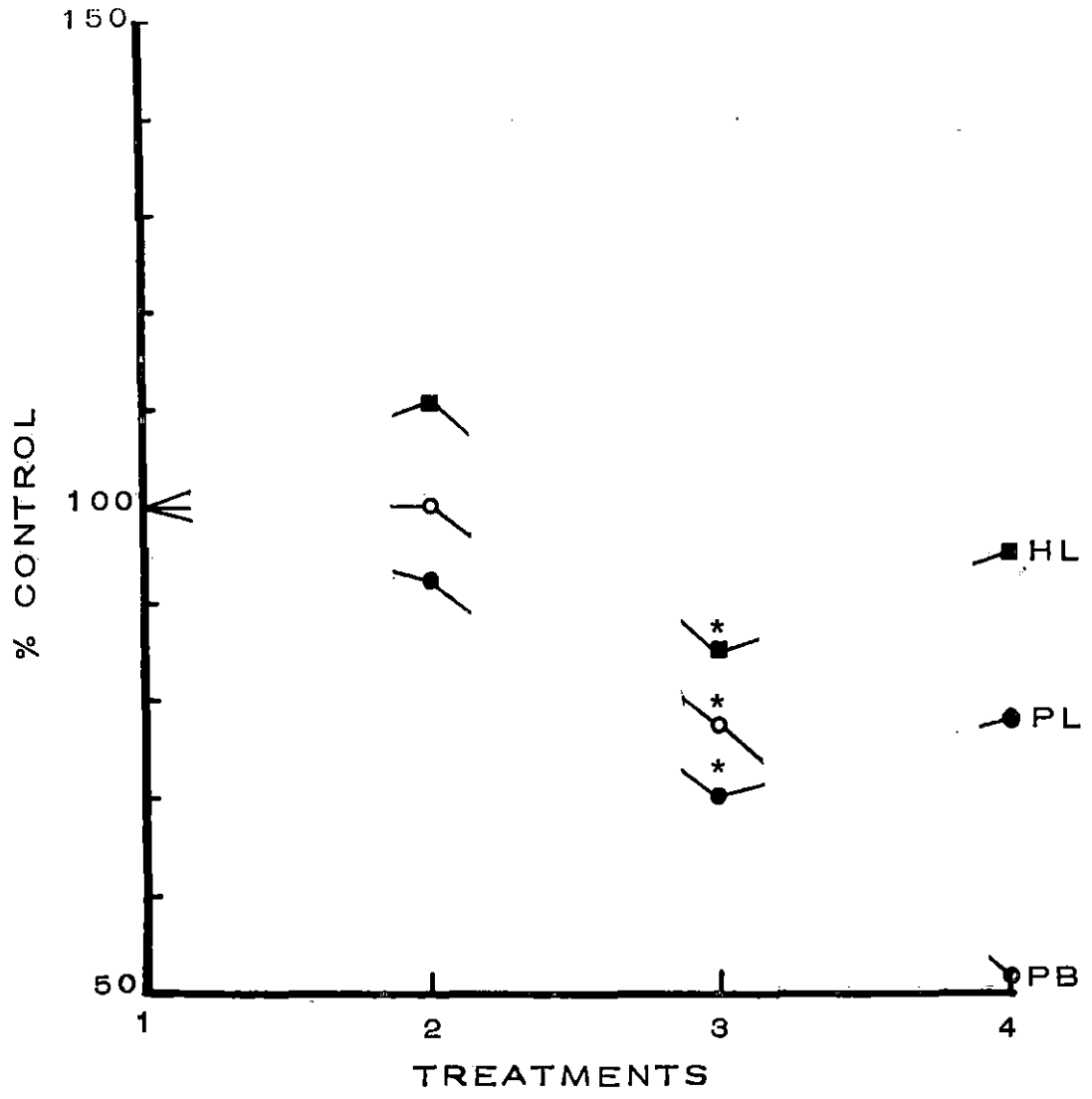
RESULTS AND DISCUSSION

Vascular Pressures

Figure 1 is a plot of the MAP. During treatment 2, the administration of dopamine, the MAP for group 1 (the phenoxybenzamine group) increased 0.23%, group 2 (the propranolol group) decreased 7.44%, and group 3 (the haldol group) increased 10.62%. None of the changes were significant. These changes are as predicted for moderate dose administration of dopamine and correlate well with those seen by Gooding et al. (13).

During the administration of the blocking agents (treatment 3) all pressures were seen to decrease (23.25%, 22.71% and 25.77% for groups 1, 2, and 3 respectively). The three blocking agents act on the vasculature, either by a direct action on the vessels or through indirect effects mediated via the adrenergic system, to cause vasodilation and subsequent decrease in the systemic pressures (1, 14).

Dopamine administration with haldol or propranolol resulted in an increase in the MAP (8.07% and 10.40% for the haldol and propranolol groups respectively). This increase appears to be secondary to alpha adrenergic stimulation resulting in vasoconstriction. Dopamine administered with phenoxybenzamine resulted in a further decrease in the MAP (26.62%). Since the dopamine was unable to act on the alpha receptors bound by the phenoxybenzamine it was unable to



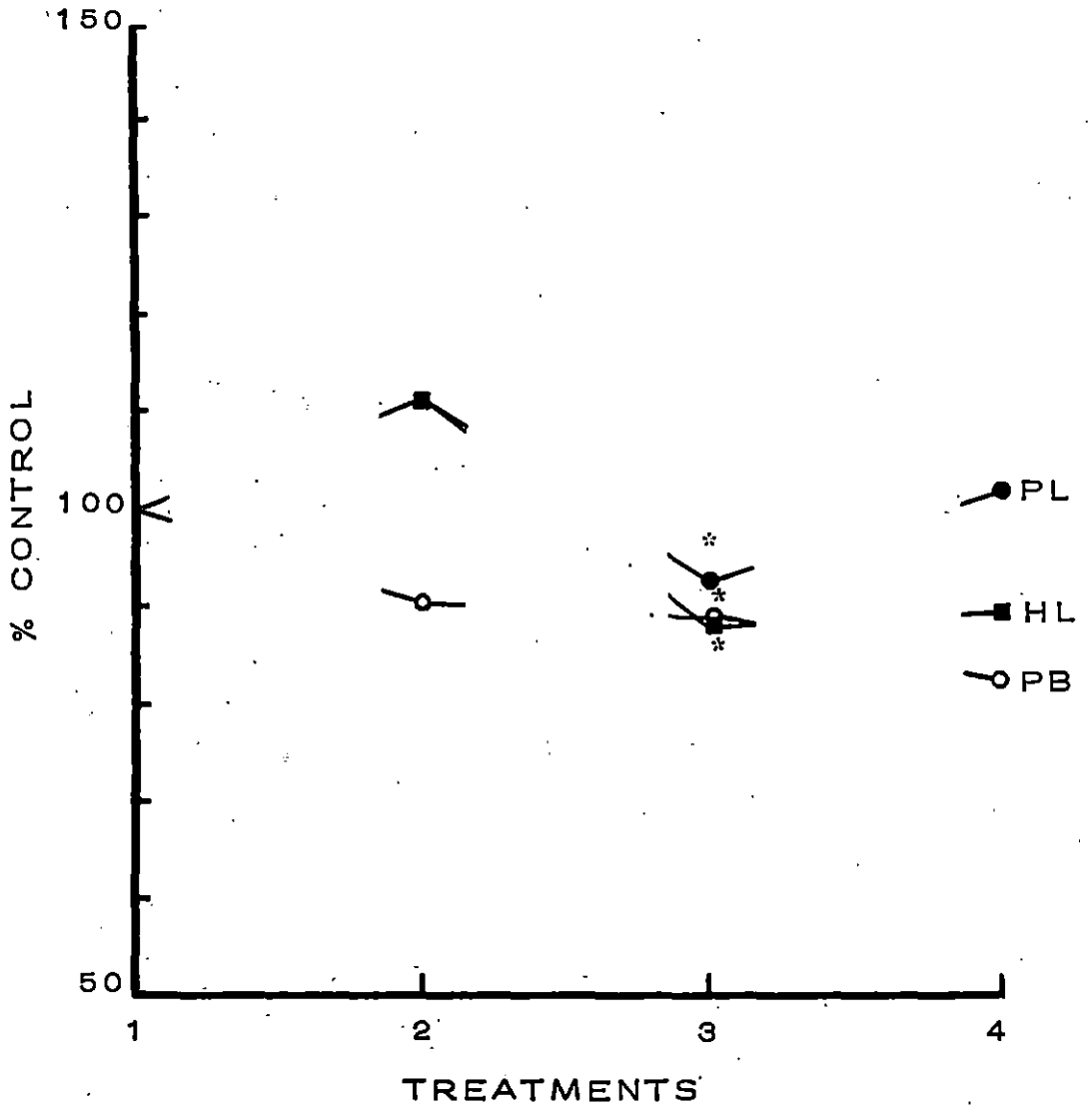
*Significant difference between treatment, p<.05.

Figure 1. Plot of the MAP (mean of 4 observations expressed as percentage of control) versus treatment

produce vasoconstriction. The further decrease in the MAP was probably due to renal and mesenteric vasodilatation secondary to dopaminergic receptor stimulation in these vascular beds. The systolic and diastolic pressures followed similar trends.

Statistical analysis indicates differences exist between treatments 2 and 3, but not between groups. One can question the validity of the analysis of variance for the comparison of the differences between groups on the basis of the limited number of values used in the analysis (degrees of freedom equal to 3). The trends do correlate well with expected results (1, 10-14).

Figure 2 is a plot of the PAM. Groups 2 and 3 (the propranolol and haldol groups) increased 11.41% and 11.25% respectively during the administration of dopamine. Group 1 (the phenoxybenzamine group) decreased 9.74% during the dopamine administration. A mean value of 104.31% was obtained for the PAM during the administration of dopamine (treatment 2) for all groups (see Table 3). This indicates the administration of dopamine produces a mild increase in the PAM, even though the phenoxybenzamine group value was seen to decrease. No statistically significant differences were noted the groups. Also all animals received similar doses of dopamine and therefore should have responded



*Significant difference between treatments, $p<.05$.

Figure 2. Plot of the PAM (mean of 4 observations expressed as percentage of control) versus treatment

similarly during treatment 2 (the administration of dopamine). Together these facts suggest the low PAM seen during the administration of dopamine for the phenoxybenzamine group was probably due to sampling error. The increase in the PAM seen during the administration of dopamine for the propanolol and haldol groups correlates well the increase seen by Mentzer et al. (25) during their dopamine administrations.

Groups 1, 2, and 3 decreased 0.03%, 19.41%, and 22.29% respectively, during the administration of the blocking agents. This decrease indicates the blocking agents produce vasodilatation in the pulmonary vasculature, similar to the effect seen in the systemic vasculature.

During treatment 4 (the administration of dopamine with blocking agents) the phenoxybenzamine group decreased 7.85% further, while the propranolol group increased 9.70% and the haldol group increased 0.71%. Again, a significant difference was seen to exist between treatments, but not between groups.

The decrease in the PAM during the administration of dopamine in the presence of alpha blockade produced by phenoxybenzamine is similar to the decrease seen by Mentzer et al. (25) during the administration of phentolamine. These changes indicate no pulmonary vasoconstriction occurred. The pressure decrease was probably secondary to

the decrease in the systemic pressures caused by the administration of dopamine in the presence of phenoxybenzamine. Administration of dopamine in the presence of propranolol induced beta blockade resulted in a slight increase in the PAM. This increase may have been due to stimulation of unblocked alpha receptors in the pulmonary vasculature. The increase could also have been the result of dopaminergic receptor stimulation in the pulmonary vascular bed while the $beta_2$ receptors were blocked, resulting in pulmonary vasoconstriction. Administration of dopamine in the presence of haldol also resulted in an increase in the PAM and thus eliminates the possibility that dopamine acted on dopaminergic receptors in the pulmonary vasculature to cause vasoconstriction. Similar changes were seen in the PAS and PAD.

As with the systemic pressure the lack of significant differences between groups is probably due to the small sample size.

Vascular Resistances

The systemic and pulmonic vascular resistance indices are plotted in Figures 3 and 4. The administration of dopamine (treatment 2) resulted in the expected changes in the SVRI (11.90%, 13.05%, and 39.74% for the phenoxybenzamine,

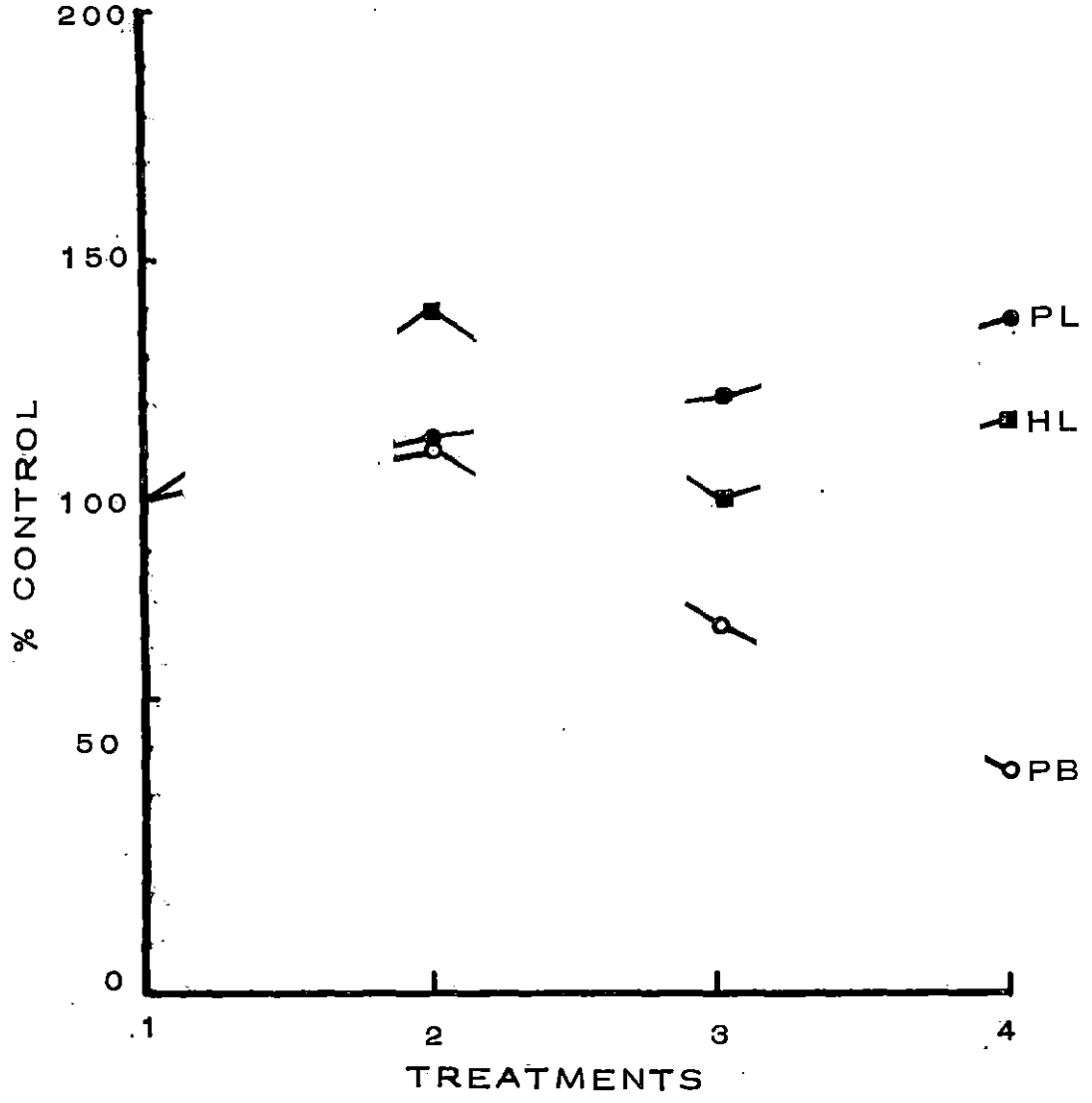


Figure 3. Plot of the SVRI (mean of 4 observations expressed on percent of control) versus treatment

propranolol and haldol groups, respectively).

During the administration of propranolol the SVRI increased 9.58% further. The SVRI decrease 36.63% during the administration of phenoxybenzamine and 37.80% during the administration of haldol. The phenoxybenzamine and haldol administrations produced the expected decrease in the SVRI, mediated by the vasodilatory action of the agents. The increase in the SVRI during the administration of propranolol was probably due to alpha receptor antagonism in the presence of beta blockade.

The SVRI increased during the administration of dopamine in the propranolol and haldol groups. The propranolol groups increased 15.97% and the haldol group increased 15.16%. These increases are as expected in that the action of dopamine to produce mild vasoconstriction via alpha adrenergic stimulation is unblocked by either blocking agent (1,10-12,14). The phenoxybenzamine group decreased 28.90% during the administration of dopamine in the presence of phenoxybenzamine. This decrease is also as expected since the vasoconstrictor action of dopamine is blocked by the phenoxybenzamine while the vasodilatory effect on the renal and mesenteric vasculature is unaltered. The result is systemic vasodilatation and a decrease in the SVRI. The trends in the SVRI correlate well with the trends seen in the MAP. No

statistically significant differences were seen between groups or treatments (see Table 5).

The PVRI is plotted in Figure 4. During the administration of dopamine the PVRI increased 38.08%, 46.81%, and 50.48% for the phenoxybenzamine, propranolol, and haldol groups respectively. As with the SVRI, the increase suggests dopamine produced pulmonary vasoconstriction, by direct action on the pulmonary vasculature. The increase in the PVRI correlates well with the increase seen by Mentzer et al. (25) during the administration of dopamine.

The PVRI decreased during the administration of the blocking agents. The phenoxybenzamine group decreased 28.55%, the propranolol group decreased 24.56%, and the haldol group decreased 16.67%. The decrease in the PVRI was probably secondary to both a direct action on the pulmonary vasculature and systemic changes.

During the administration of dopamine in the presence of the blocking agents propranolol and haldol the PVRI increased. The propranolol group increased 35.68% and the haldol group increased 59.41%. Since the PVRI increased during the administration of dopamine in the presence of propranolol the action of dopamine on the pulmonary vasculature is not blocked by beta blocking agents. Therefore, the increase in the PVRI caused by dopamine is not mediated

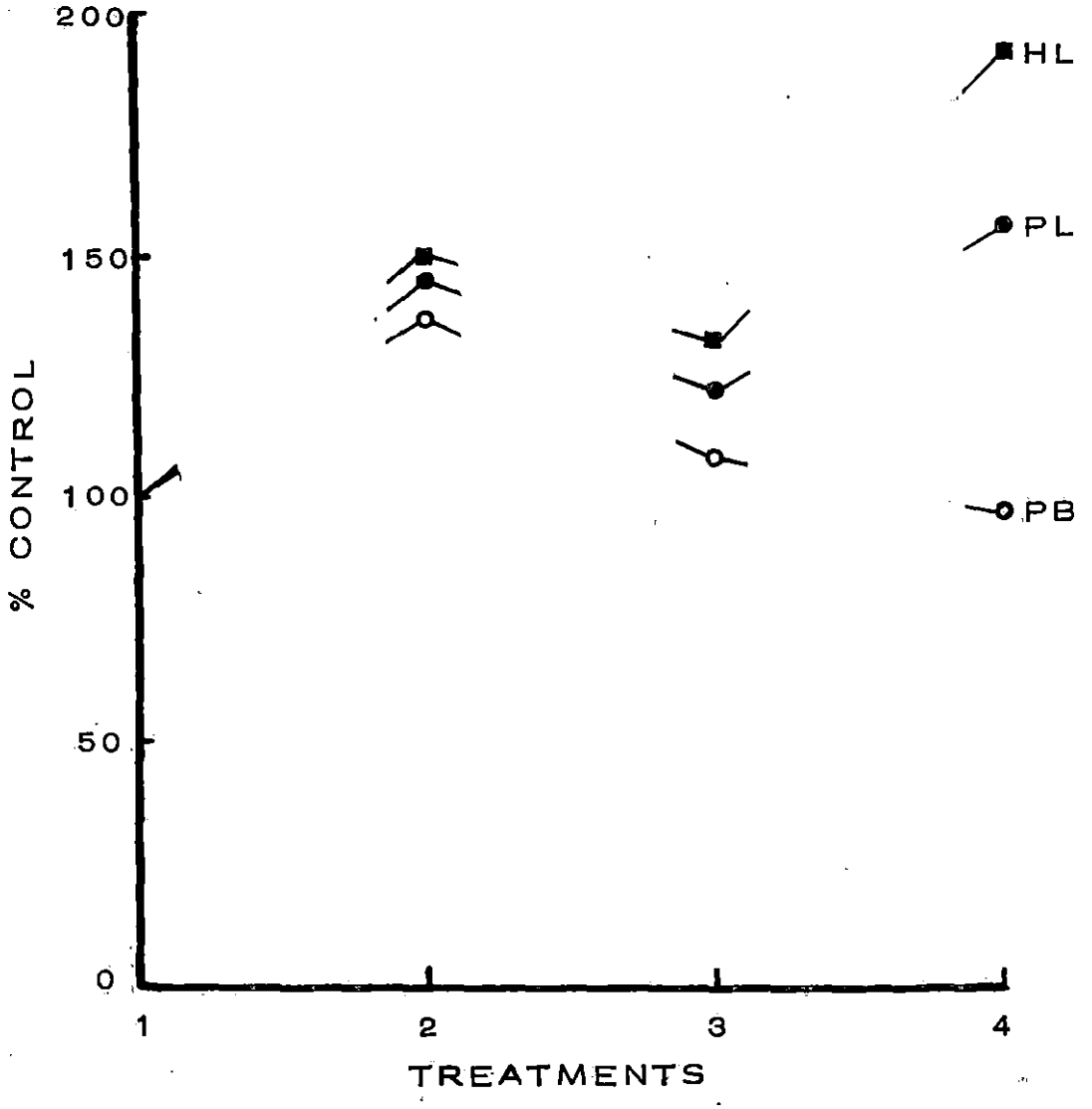


Figure 4. Plot of PVRI (mean of 4 observations expressed as percent of control) versus treatment

by beta adrenergic stimulation. The increase in the PVRI caused by the administration of dopamine in the presence of haldol indicates the action of dopamine on the PVRI is not mediated by dopaminergic receptors in the pulmonary vasculature. This is further supported by the similar responses seen in the SVRI during the administration of dopamine in the presence of the blocking agents.

The PVRI decreased 11.37% during the administration of dopamine in the presence of phenoxybenzamine. The decrease, similar to the decrease in the SVRI, suggests dopamine acts on alpha receptors in the pulmonary vasculature to cause vasoconstriction. Mentzer et al. (25) saw similar attenuation of dopamine's action on the PVRI during alpha blockade.

Again, no significant differences were seen between either treatments or groups (see Table 5).

Conclusion

This study was designed to compare changes in the pulmonary and systemic vasculatures produced by moderate dose administration of dopamine. Based on the data presented, the administration of dopamine appears to increase the parameters MAP, PAM, SVRI, and PVRI. These increases correlate well with those seen by Gooding et al. (13) and Mentzer et al. (25). The increases in the MAP and SVRI are very

similar to the increases in the PAM and PVRI during dopamine administration.

The administration of the blocking agents resulted in the predicted decrease in the MAP, PAM, and PVRI. During the propranolol administration the SVRI increased slightly. An explanation of this variance is offered above in the Vascular Resistance section. Again, the trends seen in the PAM and PVRI corresponded with the trends seen in the MAP and SVRI (except for the SVRI during the propranolol administration.

Administration of dopamine in the presence of the three blocking agents indicates systemic and pulmonary vasoconstriction is mediated by alpha receptors. The PAM and PVRI increased during the administration of dopamine and decreased during the administration of dopamine in the presence of alpha blockade. This response is identical to that seen in the systemic parameters MAP and SVRI, indicating dopamine works in a similar manner in both the systemic and pulmonic vasculatures. The attenuation of dopamine's action on the PAM and PVRI during alpha blockade produced by phenoxybenzamine is also similar to that seen by Mentzer et al. (25) during dopamine administration in the presence of alpha blockade produced by phentolamine. In addition, dopamine's effects on the PAM and PVRI are not significantly attenuated by either beta or dopaminergic blockade. Together, these

facts strongly support the hypothesis that moderate dose administration of dopamine acts on alpha receptors in the pulmonary vasculature to produce pulmonary vasoconstriction.

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APPENDIX

Table 1. Display of data derived from the twelve animals (for each animal the parameters shown are for each of the four treatments)

OBS	GROUP	DOG	TREATMENT	SYS	DYS	PAS	PAD	PCW	MAP	PAM
1	1.PHENO	1	1	177	153	27	18	12	161.0	21.00
2	1.PHENO	1	2	165	142	25	16	9	149.7	19.00
3	1.PHENO	1	3	165	118	21	16	8	133.7	17.70
4	1.PHENO	1	4	60	36	23	16	9	44.0	18.30
5	1.PHENO	2	1	165	125	27	14	11	138.3	
6	1.PHENO	2	2	195	130	25	13	7	151.7	16.70
7	1.PHENO	2	3	106	35	27	14	9	58.7	18.70
8	1.PHENO	2	4	118	30	23	13	7	59.3	16.20
9	1.PHENO	3	1	150	118	29	21	16	128.7	23.70
10	1.PHENO	3	2	160	118	27	20	9	132.0	22.30
11	1.PHENO	3	3	124	82	23	14	7	96.0	17.00
12	1.PHENO	3	4	124	71	20	14	7	88.7	16.00
13	1.PHENO	4	1	107	86	14	8	6	93.0	10.00
14	1.PHENO	4	2	107	80	12	7	5	89.0	8.67
15	1.PHENO	4	3	127	87	13	9	6	100.3	10.33
16	1.PHENO	4	4	94	40	12	7	5	58.0	8.67
17	2.PROPL	1	1	107	80	18	10	8	89.0	12.70
18	2.PROPL	1	2	114	67	17	8	6	82.7	11.00
19	2.PROPL	1	3	100	67	15	9	8	78.0	11.00
20	2.PROPL	1	4	107	73	16	8	6	84.3	10.70
21	2.PROPL	2	1	81	54	14	7	7	63.0	9.30
22	2.PROPL	2	2	100	47	16	9	8	64.7	11.30
23	2.PROPL	2	3	75	30	12	6	6	45.0	8.00
24	2.PROPL	2	4	80	47	13	7	7	58.0	9.00
25	2.PROPL	3	1	165	115	13	7	5	131.7	9.00

26	2.PROPL	3	2	150	85	14	8	6	106.7	10.00
27	2.PROPL	3	3	135	100	13	7	5	111.7	9.00
28	2.PROPL	3	4	135	90	14	9	6	105.0	10.70
29	2.PROPL	4	1	130	90	12	7	6	103.3	8.70
30	2.PROPL	4	2	130	80	19	7	7	96.7	11.00
31	2.PROPL	4	3	60	25	13	6	6	36.7	8.30
32	2.PROPL	4	4	70	35	12	8	6	46.7	9.30
33	3.HALDL	1	1	90	70	16	13	12	76.7	14.00
34	3.HALDL	1	2	110	75	16	13	13	86.7	14.00
35	3.HALDL	1	3	50	35	15	13	12	40.0	13.60
36	3.HALDL	1	4	75	50	16	13	11	58.3	14.00
37	3.HALDL	2	1	95	70	12	4	4	78.3	6.70
38	3.HALDL	2	2	100	75	12	6	4	83.3	8.00
39	3.HALDL	2	3	75	45	9	4	2	55.0	5.60
40	3.HALDL	2	4	70	40	9	4	2	50.0	5.60
41	3.HALDL	3	1	67	40	12	6	6	49.0	8.00
42	3.HALDL	3	2	87	47	14	6	5	60.3	8.70
43	3.HALDL	3	3	87	60	11	4	3	69.0	6.30
44	3.HALDL	3	4	100	74	11	4	2	82.7	6.30
45	3.HALDL	4	1	127	94	15	5	4	105.00	8.30
46	3.HALDL	4	2	127	94	17	6	5	105.0	9.70
47	3.HALDL	4	3	106	67	14	5	4	80.0	8.00
48	3.HALDL	4	4	94	67	14	5	5	76.0	8.00

Table 2. Display of data from Table 1 after normalization (the normalization was performed by taking the value of each parameter and expressing it as a percent of the control value (treatment 1) for each animal, treatments 2, 3, and 4 were normalized in this manner for the twelve animals)

Group	Dog	Treatment	MAP	PAM	SVRI	PVRI
1.PHENO	1	2	92.981	90.476	51.914	62.192
1.PHENO	1	3	83.043	84.286	28.584	37.218
1.PHENO	1	4	27.329	87.143	32.354	97.711
1.PHENO	2	2	109.689	89.785	51.378	56.683
1.PHENO	2	3	42.444	100.538	37.691	112.098
1.PHENO	2	4	42.878	87.097	28.092	80.555
1.PHENO	3	2	102.564	94.093	173.179	269.270
1.PHENO	3	3	74.592	71.730	82.654	136.440
1.PHENO	3	4	68.920	67.511	99.207	160.648
1.PHENO	4	2	95.699	86.700	171.129	164.174
1.PHENO	4	3	107.849	103.300	152.180	152.424
1.PHENO	4	4	62.366	86.700	35.831	53.739
2.PROPL	1	2	92.921	86.614	282.816	343.597
2.PROPL	1	3	87.640	86.614	287.771	221.439
2.PROPL	1	4	94.719	84.252	267.664	263.309
2.PROPL	2	2	102.698	121.505	67.055	96.287
2.PROPL	2	3	71.429	86.022	147.802	187.005
2.PROPL	2	4	92.063	96.774	223.654	228.589
2.PROPL	3	2	81.017	111.111	53.869	67.635
2.PROPL	3	3	84.814	100.000	45.554	53.859
2.PROPL	3	4	79.727	118.889	37.168	56.515
2.PROPL	4	2	93.611	126.437	48.489	79.728
2.PROPL	4	3	35.528	95.402	9.428	26.714
2.PROPL	4	4	45.208	106.897	25.951	83.333
3.HALDL	1	2	113.038	100.000	88.037	39.756
3.HALDL	1	3	52.151	97.143	47.957	84.053
3.HALDL	1	4	76.010	100.000	73.070	154.264
3.HALDL	2	2	106.386	119.403	220.481	306.838
3.HALDL	2	3	70.243	83.502	90.674	173.219
3.HALDL	2	4	63.857	82.582	189.332	397.721
3.HALDL	3	2	123.061	108.750	63.452	94.444
3.HALDL	3	3	140.816	78.750	109.405	129.521

Table 2 (Continued)

Group	Dog	Treatment	MAP	PAM	SVRI	PVRI
3.HALDL	3	4	168.776	78.750	120.851	155.229
3.HALDL	4	2	100.000	116.867	187.021	160.809
3.HALDL	4	3	76.190	96.386	159.758	147.256
3.HALDL	4	4	72.381	96.386	85.150	64.506

Table 3. Display of data used for the statistical analysis of variance procedure used in the comparison of the difference between treatments 2, 3, and 4. The values for each parameter (expressed as percent of control) for each animal were summed for each treatment. This sum was then divided by the number of observations for each treatment (12 observations per treatment) to obtain a mean value

Treatment	MAP	PAM	SVRI	PVRI
2	101.138856	104.311822	121.568415	145.125414
3	77.228355	90.312648	99.954916	121.767457
4	74.519482	91.164951	100.694370	149.676508

Table 4. Display of data used for the statistical analysis of variance procedure used in the comparison of the difference between groups 1, 2, and 3 for the treatments 2, 3, and 4. (The values for each parameter (expressed as percent of control) for each animal were summed for groups 1, 2, and 3 for each treatment. This sum was then divided by the number of observations per treatment for each group (4 observations per treatment) to obtain a mean value for the parameters)

Group	Treatment	MAP	PAM	SVRI	PVRI
1.PHENO	2	100.233369	90.263491	111.900226	138.080049
1.PHENO	3	76.982244	89.963327	75.277521	109.535991
1.PHENO	4	50.373139	82.112545	46.371174	98.163161
2.PROPL	2	92.562017	111.416861	113.057302	146.811810
2.PROPL	3	69.852645	92.009494	122.638694	122.254167
2.PROPL	4	77.929344	101.702901	138.609114	157.936579
3.HALDL	2	110.621183	111.255114	139.747716	150.404383
3.HALDL	3	84.850174	88.965122	101.948533	133.512211
3.HALDL	4	95.255963	89.679408	117.102823	192.929783

Table 5. Display of F values obtained from the statistical analysis of variance procedures performed on the data in Tables 3 and 4

Parameter	MAP	PAM	SVRI	PVRI
F for difference between treatment	6.82*	8.40*	0.95	0.74
F for difference between groups	1.10	2.95	0.45	0.27

*$p<.05$.

Table 6. Mean values and standard deviations for the MAP, PAM, SVRI and PVRI data points plotted in Figures 1, 2, 3 and 4

Parameter	Group	Treatments 2 Mean[a]	2 SD[b]	3 Mean	3 SD	4 Mean	4 SD
MAP	Pheno	100.233	7.483	76.982	27.007	50.373	18.929
	Propl	92.562	8.893	68.853	23.950	77.929	22.770
	Haldl	110.621	9.855	84.850	38.686	95.256	49.277
PAM	Pheno	90.268	3.035	89.894	14.769	82.110	9.735
	Propl	111.417	17.726	92.009	6.839	101.703	14.723
	Haldl	111.255	8.770	89.328	9.173	95.256	49.277
SVRI	Pheno	111.900	69.581	75.277	56.455	46.371	35.654
	Propl	113.057	113.440	122.639	124.714	138.609	124.993
	Haldl	139.748	75.824	101.949	46.332	117.103	52.251
PVRI	Pheno	138.087	100.452	109.536	50.983	98.163	45.417
	Propl	146.812	131.715	122.254	96.326	157.937	103.194
	Haldl	150.484	115.407	133.512	37.539	192.930	143.002

[a]Mean of 4 values for each group, expressed as percent of control, from Table 2.

[b]Standard deviation.