ROLE OF THE CAROTID BODY CHEMORECEPTORS IN THE REFLEX REGULATION OF THE CARDIOVASCULAR SYSTEM

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PAUL EDWIN PARKER
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Paul Edwin Parker

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of the requirements for

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Major professor

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ABSTRACT

ROLE OF THE CAROTID BODY CHEMORECEPTORS
IN THE REFLEX REGULATION OF THE
CARDIOVASCULAR SYSTEM

By

Paul Edwin Parker

While the respiratory responses to carotid body chemoreceptor stimulation have been well defined, the cardiovascular responses have not been thoroughly investigated. The aim of this study was to determine the effects on canine forelimb, intestine, kidney and coronary vascular resistance of perfusing the isolated carotid bodies with hypoxic and/or hypercapnic blood.

Perfusion of the carotid bodies and sinuses was provided by a circuit containing an extracorporeal lung taken from another dog. To change the O_2 and CO_2 content of the blood perfusing the carotid bodies, the isolated lung was ventilated with various O_2 and CO_2 gas mixtures in N_2. Hypoxic-hypercapnia was produced by ventilation with a gas mixture containing 0% O_2 - 20% CO_2. Hypoxia alone was studied with 0% O_2 - 5% CO_2. Hypercapnia alone was achieved with a mixture containing 20% O_2 - 20% CO_2. The use of the carotid sinus perfusion circuit containing the isolated lung permitted

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rapid changes in carotid sinus blood gas content without detectable changes in systemic blood gas concentrations. The forelimb, intestine, kidney and coronary vascular beds were perfused at constant blood flow to determine active changes in vessel caliber.

The reflex responses to carotid chemoreceptor stimulation were studied before and following vegotomy. Systemic arterial pressure increased during hypoxic-hypercapnic chemoreceptor stimulation before vagotomy and increased after vagotomy during stimulation with hypoxia, hypoxic-hypercapnia and hypercapnia. Carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy increased vascular resistance in the kidney but caused no change in resistance in the forelimb, intestine or coronary vasculature. After vagotomy, hypoxic, hypoxic-hypercapnic and hypercapnic stimulation of the carotid bodies increased vascular resistance in the forelimb, intestine and kidney but not in the heart. The skin and muscle vascular beds of the forelimb appeared to contribute about equally to the increase in forelimb resistance. Preliminary studies of the changes in vascular resistance in the gracilis muscle and hindpaw (skin) vasculature indicated a rise in resistance during hypoxic-hypercapnic chemoreceptor stimulation following vagotomy.

Left ventricular contractile force decreased during chemoreceptor stimulation before and after vagotomy but a

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larger reduction in contractile force was observed following vagotomy. Heart rate was not consistently affected by carotid chemoreceptor stimulation either before or after vagotomy.

The increase in vascular resistance observed in the kidney before vagotomy and in the forelimb, intestine and kidney after vagotomy appeared to be a sympathoadrenal mediated response to carotid body chemoreceptor stimulation. These studies indicate that hypoxia and hypercapnia act on the carotid chemoreceptors to elicit changes in autonomic outflow to the vasculature similar to changes induced by lowering the pressure in the carotid sinuses.

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ROLE OF THE CAROTID BODY CHEMORECEPTORS IN THE REFLEX REGULATION OF THE CARDIOVASCULAR SYSTEM

By

Paul Edwin Parker

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Physiology

1972

G 802-94

DEDICATION

TO MY WIFE AND PARENTS

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ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Drs. F. J. Haddy, J. B. Scott and J. M. Dabney for their encouragement and invaluable assistance during the course of these investigations. The author is also indebted to the other members of his guidance committee, Drs. W. D. Collings, J. B. Hook and R. M. Daugherty, Jr. for their advice and consultation. The author's gratitude is also extended to Mr. B. T. Swindall, Mrs. J. Johnston and Mr. G. W. Gamble whose technical assistance made this project possible.

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INTRODUCTION

It is well-established that the arterial chemoreceptors reflexly affect the respiratory system and some data are available which suggest that they also affect the cardiovascular system (4). While the respiratory responses to carotid body stimulation have been well-defined (10,11), the cardiovascular responses have not been thoroughly investigated. The reasons for this study were threefold. First, few studies examining the reflex responses to carotid chemoreceptor stimulation employed selective stimulation of the carotid body. Most investigators reported the responses to systemic hypoxia. Second, of the few studies in which specific chemoreceptor stimulation was used, most were carried out employing pharmacologic rather than physiologic stimuli. Third, little attention has been paid to the role of hypercapnic carotid chemoreceptor stimulation.

The carotid body chemoreceptors are small, highly vascular bodies located near the bifurcation of the common carotid artery into the internal and external carotid branches. They are sensitive to changes in the P_{O_2}, P_{CO_2} and pH of the arterial blood (4). Afferent nerve fibers from the carotid sinus and carotid body are carried in the carotid sinus nerve

and join the glossopharyngeal nerve. The blood vessels supplying the carotid body have been shown to possess sympathetic motor innervation (12). Activation of this innervation causes vasoconstriction, locally regulating vascular resistance, thus altering the volume of arterial blood flowing past the chemoreceptors. A reduction in arterial blood oxygen tension and pH or an increase in carbon dioxide tension stimulates the chemoreceptors which increases the number of impulses in the afferent nerve fibers from the carotid bodies. It has been proposed that the increased activity in these afferent nerve fibers stimulates the medullary vasoconstrictor center resulting in an increased total peripheral resistance.

Bernthal (24,28,29) studied the reflex vasomotor responses in the canine forelimb and hindlimb evoked by selective carotid chemoreceptor stimulation. These studies indicated a predominately vasoconstrictor response in both forelimb and hindlimb. The report of increased hindlimb resistance to selective carotid stimulation was confirmed recently by Pelletier (21). A search of the literature revealed no reports of the reflex vascular responses of other vascular beds to selective carotid chemoreceptor stimulation.

Many investigators (40,41,42,43,44,48) reported studies on the change in heart rate evoked by chemoreceptor stimulation, however, the results of the studies have been extremely controversial. In animals breathing spontaneously stimulation of the carotid chemoreceptors elicited a consistent augmentation of

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ventilatory rate and depth but only slight increased or decreased heart rate (40,41,42). When respiration was maintained constant by artificial ventilation the heart rate usually diminished (43,48). In animals with controlled ventilation pharmacologic chemoreceptor stimulation elicited bradycardia (23,27,31).

An inotropic ventricular response to selective carotid chemoreceptor stimulation was reported recently by several investigators (43,48). Chemoreceptor stimulation before vagotomy decreases ventricular contractile force. De Geest et al. (48) reported that carotid chemoreceptor stimulation produced a slight positive inotropic effect following cervical vagotomy while Downing et al. (43) reported a negative inotropic effect.

A more thorough knowledge of the reflex cardiovascular effects of physiologic carotid body chemoreceptor stimulation is important for several reasons. Although it is doubtful whether the chemoreceptor reflexes exert any significant effect on the circulation at rest they certainly contribute to the maintenance of the cardiovascular system following hemorrhage (4). Once the mean arterial pressure has dropped to about 60 mm Hg, further reduction of the pressure does not evoke additional barostatic reflexes. However, inadequate local blood flow to the chemoreceptors due to the low levels of arterial pressure may produce anoxia at the chemoreceptors. The arterial chemoreceptors are also important clinically in

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cases of cardiopulmonary diseases and especially asthma since they are slowly adapting receptors (10).

The purpose of this study was to determine the reflex effects of selective, physiologic stimulation of the carotid body chemoreceptors on the forelimb, kidney, intestinal and coronary vasculature. This selective, physiologic chemoreceptor stimulation was accomplished by varying the gas content of autologous blood perfusing the isolated carotid sinuses and carotid bodies by means of an extracorpeal lung ventilated with various O_2 and CO_2 gas mixtures. The hypothesis tested in this study was: carotid body chemoreceptor stimulation with hypoxic, hypoxic-hypercapnic and hypercapnic blood before and following vagotomy evokes changes in vascular resistance in the forelimb, intestine, kidney and coronary vascular beds.

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Anatomy

The carotid body chemoreceptors are situated in the region of the bifurcation of the common carotid arteries into the internal and external carotid branches. In the dog the carotid bodies are located on the root of the occipital artery or on the common trunk of the occipital and ascending pharyngeal arteries. The veins draining the carotid bodies usually anastomose with the internal jugular vein (1). De Castro (2) examined the local circulation of the carotid body microscopically and suggested that most of the blood perfusing the body enters sinusoids while some may be channeled through arteriovenous anastomoses within the body. The blood flow in the isolated carotid body of the cat was found to average 40 mm^3 of blood/min if blood pressure was within the normal range (3). For a carotid body weighing 2 mg this value represents an equivalent blood flow of about 20 ml/g of carotid body tissue/min. As a result of the high volume rate of blood flow through the carotid body the amount of oxygen removed from the blood is small. In the cat, Daly *et al.* (3) found that at a blood flow rate of about 40 mm^3/min there was no significant arteriovenous oxygen difference

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Physiologic Stimuli

The carotid body chemoreceptors are stimulated by hypoxia, increased hydrogen ion concentration and by hypercapnia, possibly acting through changes in hydrogen ion concentration. This will be discussed subsequently. Von Euler et al. (4) demonstrated the relationship between carotid chemoreceptor response and arterial oxygen content in 1939. Hornbein et al. (8) quantified this relationship by observing the electrical activity of the carotid sinus nerve during hypoxic stimulation of the carotid body. These and other investigators (5,6) found the arterial oxygen-chemoreceptor response curve to be roughly hyperbolic. The rate of carotid chemoreceptor discharge increased about 1.5% for each mm Hg decrease in arterial P_{O_2} between 40 and 30 mm Hg P_{O_2} (8). The sensitivity of the chemoreceptors at high oxygen tensions was attenuated. However, an increase in chemoreceptor discharge still occurred when the arterial P_{O_2} was reduced from 500 to 150 mm Hg (8).

While some investigators (4) related excitation of the carotid chemoreceptors to arterial oxygen content the hypothesis was challenged by the observation that a greatly reduced oxygen content in a perfusate does not increase carotid body

activity as long as the O_2 tension of the perfusing fluid was adequately maintained (8). Duke et al. (9) observed that saturation of 70-80 percent of the blood hemoglobin with carbon monoxide produced no carotid chemoreceptor activation in cats. These findings supported Comroe and Schmidt's (11) proposal that the effective stimulus of the carotid body is a decrease in arterial P_{O_2} rather than a decrease in arterial oxygen content. This concept was challenged by the work of Landgren and Neil (7) who demonstrated that hemorrhagic hypotension greatly increased carotid body activity. Thus, if blood flow was markedly reduced as in hypotension the chemoreceptors could become hypoxic even though the arterial P_{O_2} and oxygen content were normal. However, these investigators did not monitor the blood P_{CO_2} during hemorrhagic hypotension. Comroe (10) defined the hypoxic stimulus to the carotid body as a decrease in the O_2 supply to the chemoreceptors below that necessary for their metabolic needs.

Perfusion of the carotid bodies with blood of varying P_{CO_2} produced a somewhat sigmoid shaped chemoreceptor response curve for the rate of chemoreceptor discharge when the P_{O_2} was held constant at normal values (8). Several investigators (12,13) observed the greatest gain in the CO_2 response curve occurring over the normal range of arterial P_{CO_2}, with a reduction in carotid body activity at arterial P_{CO_2} values above 150 mm Hg. At high oxygen tensions the carotid chemoreceptors response to CO_2 was greatly attenuated.

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Hornbein et al. (15) observed that in the presence of 100% O_2, a CO_2 tension of 150-300 mm Hg was required to yield significant carotid chemoreceptor excitation.

Although it is well-known that CO_2 and increased hydrogen ion concentration produce carotid body excitation, much controversy has arisen as to whether molecular CO_2 has a specific action on the chemoreceptors. Investigation of this point is complicated by the fact when the carotid body is exposed to CO_2 there is a simultaneous increase in H_2CO_3, H^+ and HCO_3^- formed catalytically by carbonic anhydrase. Joels and Neil (16), and Eyzaguirre and Koyano (17) have suggested that the chemoreceptor stimulating action of hypercapnia and increased hydrogen ion concentration are partly independent of each other. On the other hand, other investigators (15,18,19) have proposed that the effect of CO_2 is mediated by changes in intracellular hydrogen ion concentration rather than by the specific action of molecular CO_2. In recent work Travis (20), employing carbonic anhydrase inhibition to delay the hydration of CO_2, suggested that stimulation of the carotid body by CO_2 is predominately through the hydrogen ion.

Cardiovascular Reflexes

Selective chemoreceptor stimulation

It is now established that the carotid body chemoreceptors reflexly affect the cardiovascular system as well as

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respiration. Early investigations of the cardiovascular effects of arterial chemoreceptor excitation were carried out by ventilating animals with low O_2 or high CO_2 gases. This approach was inadequate since the responses it evoked were a complex combination of local effects on the tissues, effects due to direct stimulation of the central nervous system and effects due to arterial chemoreceptor stimulation.

Recently, Pelletier and Shepherd (21) subjected isolated perfused carotid sinuses of vagotomized dogs to hypoxic, hypoxic-hypercapnic and hypercapnic blood and observed increases in systemic pressure averaging 57, 51 and 24 mm Hg, respectively, for each stimulus. The mean P_{O_2} and pH values of the blood employed to stimulate the carotid chemoreceptors were as follows: hypoxic blood, 37 mm Hg, 7.30; hypoxic hypercapnic blood, 42 mm Hg, 7.07; hypercapnic blood, 96 mm Hg, 7.10.

The reflex cardiovascular effects of carotid body stimulation by pharmacologic agents was studied by Heymans et al. (4) in a bilaterally isolated carotid sinus preparation with one sinus denervated. An intracarotid injection of acidic sodium bicarbonate (pH=7.2) produced an increase in systemic arterial blood pressure while no effect was seen upon injection in the denervated side. Following the same procedure using alkaline solutions produced a transient decrease in systemic blood pressure. Many investigators (4,8,22,23,31) have employed the use of pharmacologic agents to stimulate the

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carotid chemoreceptors. Calvelo et al. (23) employed nicotine and cyanide to stimulate the bilaterally isolated carotid chemoreceptors in the dog. Their findings indicated that in non-vagotomized animals, injections of nicotine produced significant decreases in systemic arterial pressure. Injections of cyanide produced decreases in pressure in some experiments and increases in others. A subsequent study from the same laboratory (46) reported an increased systemic arterial pressure resulting from carotid chemoreceptor stimulation by both nicotine and cyanide in non-vagotomized dogs. A greater increase in systemic pressure was observed following carotid body stimulation in vagotomized dogs.

Bernthal et al. (24,28,29) studied the reflex vasomotor responses in canine forelimbs and hindlimbs evoked by chemoreceptor stimulation. Vasomotor activity was assessed in vagotomized dogs by observing changes in blood flow in the axillary artery by means of a thermo-electric method by Bronk. The preparation consisted of a bilaterally isolated, perfused carotid sinus circuit containing a reservoir to prevent reinfusion of the hypoxic blood perfusate. Perfusion of the sinuses with anoxic blood produced axillary vasoconstriction which became maximal in about 30 seconds. Reflex responses could not be elicited with blood equilibrated with more than 15% O_2. Similarly, Winder et al. (25) showed stagnant anoxia in the carotid body to evoke reflex vasoconstriction in forelimb vessels.

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While total limb vascular resistance appears to indicate a predominant vasoconstrictor response in forelimbs and hindlimbs, observations on the individual responses of the skeletal muscle and skin vascular beds are in need of further investigation. Calvelo et al. (23) observed the vasomotor responses in the gracilis muscle and paw of the hindlimb during carotid body stimulation with nicotine and cyanide. Intracarotid injections of either nicotine or cyanide caused increases in gracilis muscle perfusion pressure. Neither nicotine or cyanide caused significant changes in paw perfusion pressure. More consistent reductions in paw perfusion pressure were observed with pharmacologic chemoreceptor stimulation following phentolamine.

In a recent study by Pelletier and Shepherd (21) the response of the perfused hindlimb was observed during perfusion of the isolated carotid sinuses with hypoxic, hypoxic hypercapnic and hypercapnic blood. External iliac artery perfusion pressure increased 58 mm Hg during the hypoxic stimulus, 59 mm Hg during the hypoxic hypercapnic stimulus, and 31 mm Hg during the hypercapnic stimulus to the carotid chemoreceptors.

While a few studies have reported the effects of systemic hypoxia on the intestinal (24,47) and renal (32,33,34) vasculatures, no studies have been carried out in which responses of the intestine and kidney were observed during selective stimulation of the carotid chemoreceptors.

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Several investigators (23,27,31,46) reported that local injections of cyanide and nicotine into the carotid sinus circulation caused bradycardia. Other investigators (35,36, 37,38) observed reflex tachycardia to result from chemoreceptor stimulation by systemic anoxia. The experiments of several investigators (39,40,41,42,43) suggest that, in the dog, the tachycardia resulting from breathing low O_2 gas mixtures is not primarily a result of arterial chemoreceptor stimulation. Bernthal et al. (39) perfused the carotid sinuses with solutions of low O_2 content and observed a slight bradycardia during hypoxic stimulation which became more pronounced if the respiration was controlled by artificial ventilation. In experiments in animals with controlled ventilation where the isolated carotid sinuses were perfused with hypoxic blood, bradycardia, a reduced cardiac output and systemic vasoconstriction were observed (40,41,42,43). Allowing the animals to breathe spontaneously during carotid chemoreceptor perfusion with hypoxic blood produced variable responses with the heart rate remaining unchanged, increasing or decreasing (40, 41,42).

Although several investigators have determined the effects of chemoreceptor stimulation on the heart rate, there is little information concerning the effects of carotid chemoreceptor stimulation on the myocardium and coronary vascular resistance. In dogs having controlled respiration, Downing et al. (43) found that hypoxic stimulation of the isolated carotid sinuses

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produced a reduction of ventricular contractility. De Geest et al. (48) observed a similar negative inotropic effect of hypoxia in an isolated carotid sinus on a preparation which kept the left ventricle isovolumetric. After vagotomy a slight increase in ventricular performance was evoked, suggesting that the primary reflex cardiac effect of carotid chemoreceptor stimulation is to increase vagal tone. Stern and Rapaport (44) reported an increase in myocardial contractility and coronary vasodilation resulting from activation of the aortic chemoreceptors. Studies by Vatner et al. (45) have shown that direct stimulation of the carotid sinus nerve caused coronary vasodilation in conscious dogs which was attributed to a reduction of sympathetic tone. Recently, Hackett et al. (46) have demonstrated that stimulation of the isolated carotid bodies by nicotine and cyanide produced, reflexly, coronary vasodilation by activation of cholinergic fibers in the vagus.

Changes in systemic blood gas content

Early studies of the cardiovascular responses to chemoreceptor stimulation were performed by Heymans et al. (4). These investigators observed that acute hypoxia induced by nitrogen inhalation produced systemic hypertension only if the sinoaortic nerves were intact. If respiration was maintained constant by artificial ventilation the inhalation of the low O_2 gas mixture usually produced only a decrease in systemic pressure after section of the sinoaortic nerves (4,47).

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In the limb Litwin et al. (30) reported systemic anoxia induced by 5% O_2 caused vasoconstriction in the perfused hindlimb. Korner and Uther (26) reported a study employing a thermal conductivity method for estimating skin blood flow in unanesthetized rabbits which indicated that systemic hypoxia decreased cutaneous vascular tone and increased vascular tone in muscle.

Bernthal and Schwind (24) compared the reflex vasoconstrictor responses in the limb vasculature with those of the intestine during systemic hypoxia. The inhalation of 10% O_2 in nitrogen produced vasoconstruction in the intestinal vasculature which reduced the blood flow in the superior mesenteric artery by 65%. The same stimulus produced a decrease in mesenteric artery blood flow of 31% in a preparation where the aortic depressor nerves were cold blocked. The reflex response of the superior mesenteric artery to arterial hypoxia was also examined by Krasney (47) using an electromagnetic flowmeter. Under conditions of spontaneous respiration, ventilation with 6% O_2 - 94% N_2 evoked a marked increase in resistance in the superior mesenteric artery. When the animals were thoracotomized and artificially ventilated, arterial hypoxia produced a smaller increase in resistance in the superior mesenteric artery.

Studies which have attempted to examine the reflex response of the kidney to chemoreceptor stimulation have only been carried out using systemic hypoxia. Caldwell et al. (32)

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reported that moderate arterial hypoxia in man and the dog produced only minor reductions in renal blood flow and glomerular filtration rate. Franklin et al. (33) observed marked reductions in renal blood flow during systemic anoxia induced by asphyxia.

Korner (34) reported that exposing unanesthetized rabbits to 9.6% O_2 in N_2 or CO produced renal vasoconstriction. He observed that a greater reduction in arterial P_{O_2} was necessary to increase respiration. Denervation of the carotid sinus region and depressor nerves during hypoxia resulted in a decrease in renal vascular resistance, and subsequent exposures to hypoxia had little effect upon renal blood flow.

Although the literature reports various attempts by many investigators to elucidate the reflex responses to carotid chemoreceptor stimulation, few studies have been carried out in which the chemoreceptors were stimulated specifically. Of the few studies in which specific chemoreceptor stimulation was used, most were carried out employing pharmacologic rather than physiologic stimuli for the chemoreceptors. Little attention has been paid to the role of hypercapnia in reflex responses elicited by carotid chemoreceptor stimulation. In view of the inadequate knowledge in this area, the purpose of this investigation was to examine the reflex responses of the forelimb, hindlimb, kidney, intestine and coronary vasculature to selective physiologic stimulation of the carotid body chemoreceptors.

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METHODS

Mongrel dogs of either sex weighing 15-20 kg were anesthetized with sodium pentobarbital, 30 mg/kg, given intravenously. Respiration was maintained constant by a positive pressure respirator (Harvard Apparatus Co., model 607, Dover, Mass.). In the thoracotomized animals the lungs collapsed passively during expiration against a resistance of 2-2$\frac{1}{2}$ cm of water to prevent atelectasis. Following completion of the required surgery, the animals were treated with heparin sodium, 5 mg/kg, to prevent blood coagulation. All of the blood pressures monitored were continuously recorded by low volume displacement pressure transducers (Statham Laboratories, model P23Gb, Hato Rey, Puerto Rico) which provided imput into a direct writing oscillograph (Hewlett-Packard Co., model 7796A, Waltham, Mass.).

Perfusion of Carotid Bodies

The carotid sinuses and carotid bodies were surgically isolated bilaterally, taking care not to damage the carotid chemoreceptor innervation. The internal carotid, laryngeal, lingual, ascending pharyngeal, occipital and any other collateral arteries were ligated bilaterally. The internal

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carotid artery was ligated distal to the carotid sinus baroreceptor and the occipital and ascending pharyngeal arteries were ligated distal to the carotid body.

Perfusion of the isolated carotid sinuses and carotid bodies was provided by an extracorporeal circuit containing a lung removed from another dog (Figure 1). Prior to surgery heparin was administered to the animal donating the lung and the left lung was removed through an incision in the left fourth intercostal space. Blood from the left femoral artery of the experimental animal was pumped (Sigmamotor Inc., model T-6SH, Middleport, N. Y.) into the pulmonary artery of the isolated lung. The venous blood from this lung flowed through a cannula tied in the partially preserved left atrium and was delivered at a constant rate to the isolated carotid sinuses and bodies by a second blood pump (Sigmamotor Inc., model T-6SH). The outflowing blood from the carotid sinuses flowed past an oxygen electrode (Beckman Instruments, Inc., model 325814 oxygen macroelectrode, model 160 gas analyzer, Palo Alto, Calif.) and returned to the animal via the left jugular vein. The sinus perfusion pressure was maintained constant and approximately equal to that of aortic pressure during the control periods by adjusting a screw clamp on the sinus outflow cannula. The blood flow rate of the second pump in the extracorporeal lung perfusion circuit was fixed and the outflow resistance was adjusted such that the perfusion pressure was approximately equal to the aortic pressure. The pump flow

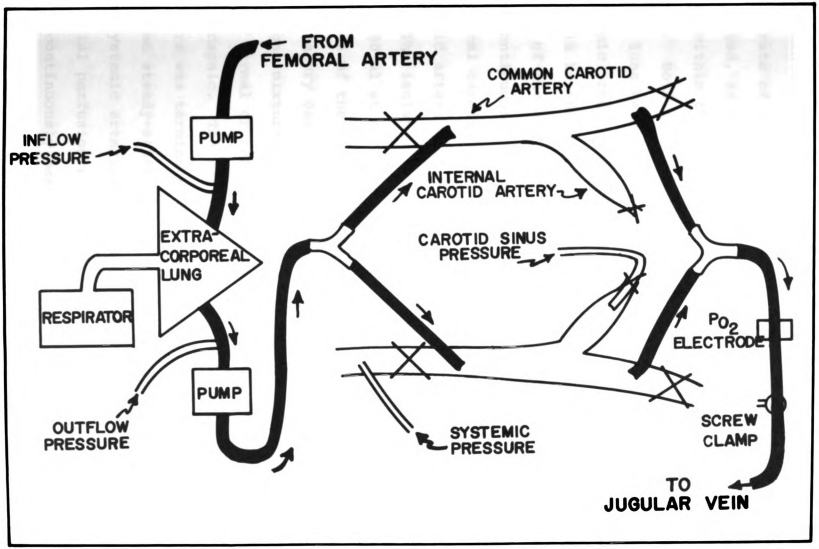

Figure 1. Carotid sinus perfusion circuit.

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was maintained at this rate throughout the experiment. The flow rate of the first pump in the perfusion circuit was adjusted, as necessary, to maintain the pulmonary vein pressure within the physiological range to prevent pulmonary edema. Both pulmonary artery and vein pressures of the isolated lung were measured throughout the experimental procedure. Systemic arterial pressure was continuously monitored from a cannula in the left common carotid that was advanced to the level of the aortic arch. Unilateral carotid sinus pressure was continuously measured from either a cannula in the left internal carotid artery or a cannula in the left external carotid artery advanced to the level of the carotid sinus.

The isolated lung was ventilated with a stroke volume of 300-400 ml at a rate of 16/min which insured rapid equilibration of the blood perfusing the isolated lung with the ventilatory gas mixture. The isolated lung was ventilated with gas mixtures designed to maintain the gas content of the blood normal or render it hypoxic, hypoxic-hypercapnic or hypercapnic. The ventilatory period for a particular gas mixture was terminated when the monitored pressures had reached steady-state values, which usually took 3 to 4 minutes. The systemic arterial pressure, carotid sinus pressure and arterial perfusion pressure of the vascular bed under study were continuously measured throughout the experiment. The pH of the blood perfusing the carotid sinuses was measured just prior to termination of the ventilatory period. The blood

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samples for pH determinations were drawn anaerobically from the extracorporeal lung circuit between the lung and the pulmonary outflow pump.

To change the oxygen and carbon dioxide content of the blood perfusing the carotid bodies the isolated lung was ventilated with various O_2 and CO_2 gas mixtures in N_2. The control gas mixture contained either 20% O_2 - 5% CO_2 or 20% O_2 - $2\frac{1}{2}$% CO_2. The control gas mixture containing 20% O_2 - 5% CO_2 was employed during the study on the forelimb vascular beds while the control mixture containing 20% O_2 - $2\frac{1}{2}$% CO_2 was used in subsequent studies. Combined hypoxia and hypercapnia were produced in the blood perfusing the carotid bodies by ventilation of the isolated lung with a gas mixture containing 0% O_2 - 20% CO_2. Hypoxic blood was produced by ventilation with a gas mixture containing 0% O_2 - 5% CO_2. Hypercapnic blood was achieved by ventilation with a mixture containing 20% O_2 - 20% CO_2.

In an additional study on the coronary vasculature graded changes in P_{O_2} and pH of the perfusing blood were accomplished by employing additional gas mixtures. In this group of animals different levels of hypoxia were produced by ventilating the extracorporeal lung with gas mixtures containing 5% O_2 - $2\frac{1}{2}$% CO_2 and 10% O_2 - $2\frac{1}{2}$% CO_2. Hypoxic-hypercapnia was produced by ventilation with 10% O_2 - 10% CO_2 while hypercapnia alone was achieved by ventilation with 20% O_2 - 10% CO_2.

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All gas mixtures employed in the above studies were certified standard grade.

The use of the extracorporeal lung circuit permitted rapid changes in local blood gas content without detectable changes in systemic blood gas content. Samplings of systemic arterial blood during ventilation of this isolated lung preparation with various hypoxic and hypercapnic gas mixtures showed no alteration of systemic blood P_{O_2}, P_{CO_2} of pH (64).

As a check for chemoreceptor stimulation, the changes in respiratory movements produced by hypoxic-hypercapnic chemoreceptor stimulation before vagotomy were monitored by pneumograph or by observation. Increased respiratory movements during stimulation suggested that the surgical procedures employed for isolation and perfusion of the carotid sinuses and bodies had not greatly affected the innervation of the chemoreceptors.

Forelimb

To study the reflex effects of carotid body stimulation on forelimb vascular resistance the innervated, collateral free forelimb of 13 dogs was perfused through the brachial artery at constant flow. The skin of the right forelimb of the dog was circumferentially sectioned 3-5 cm above the elbow. The brachial artery, the brachial and cephalic veins and the forelimb nerves were isolated and the remaining muscles and

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connective tissue sectioned by electro-cautery. Following the administration of heparin, a blood pump (Sigmamotor Inc., model T-6SH) was interposed between the right femoral artery and the right brachial artery. Forelimb perfusion pressure was measured just proximal to the point of cannulation of the brachial artery. Blood entered the limb only through the brachial artery and returned from the limb through the brachial and cephalic veins. The forelimb nerves (median, ulnar, radial and musculocutaneous) were left intact and were coated with an inert silicone solution to prevent drying. The brachial and cephalic veins were partially transected 3-5 cm above the elbow and the distal end of each vessel was cannulated with a short section of polyethylene tubing (P.E. 320). The outflow from both veins was directed into a reservoir maintained at constant volume with a variable speed pump (Sigmamotor Inc., T-6SH) which continuously returned blood to the animal via a cannulated jugular vein. Blood flow was determined by timed collections of the brachial and cephalic venous outflows just prior to the termination of a ventilatory period. In the dog forelimb the median cubital vein represents the major anastomotic channel between the brachial and cephalic veins. This vessel was ligated in all experiments so that the brachial venous flow was predominately from muscle whereas cephalic flow was predominately from skin. Although this approach does not accomplish complete functional isolation of skin and muscle blood flows, the degree of

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separation is sufficient to permit comparison of resistance changes in the two parallel coupled beds (68).

The experimental protocol was to ventilate the extracorporeal lung with the control gas mixture (20% O_2 - 5% CO_2). When the monitored pressures had stabilized, brachial and cephalic vein outflows were measured and a blood sample for pH determination was drawn anaerobically from the carotid sinus perfusion circuit. After the initial control period the extracorporeal lung was ventilated randomly with the hypoxic (0% O_2 - 5% CO_2), combined hypoxic-hypercapnic (0% O_2 - 20% CO_2) and hypercapnic (20% O_2 - 20% CO_2) gas mixtures. When the monitored pressures had stabilized during chemoreceptor stimulation the outflows were again measured, blood was drawn for determination of pH and the extracorporeal lung was returned to the control gas mixture. Following stabilization during the control period, the blood flow measurements and blood samplings were repeated. At this point the animals were bilaterally vagotomized at the cervical level. Upon stabilization, the carotid chemoreceptors were again randomly stimulated with hypoxic, hypoxic-hypercapnic and hypercapnic blood according to the procedure described above.

Intestine

To study the reflex effects of carotid body chemoreceptor stimulation on intestinal vascular resistance, an isolated

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segment of ileum was perfused through a mesenteric artery at constant flow in 9 animals. A section of ileum 15-20 cm in length was exteriorized through a midline incision. Taking care to minimize damage to extrinsic nerves, the single large artery to this section of ileum was dissected free, the collaterals ligated and the mesentery cut on both sides of the section so that all arterial flow to the section was carried by this single artery. Blood flow to the isolated section was provided by cannulating the distal end of the artery, interposing a blood pump (Sigmamotor Inc., model TM10, Middleport, N. Y.) between the right femoral artery and the artery to the segment. Perfusion pressure of the isolated section was measured through a 22 gauge needle tipped cannula inserted into the output tubing of the pump. The veins from the ileal section were left intact. Occlusive ligatures of heavy cord were placed at each end of the ileal section under study. An open tipped cannula was inserted into the saline filled lumen of the section to Monitor intraluminal pressure. After all operative procedures were completed the section of intestine was moistened with saline and covered with a sheet of cellophane to prevent drying. A heat lamp was used to maintain the segment at near body temperature.

In four animals the superior mesenteric artery was perfused at constant blood flow. The superior mesenteric artery was exposed through a midline abdominal incision. The artery was carefully dissected free and cannulated distally with a

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stainless steel cannula. Blood flow to the cannulated superior mesenteric artery was maintained constant by a pump (Sigmamotor Inc., model T-6SH). The venous outflow from the intestine was undisturbed. Following completion of all operative procedures the intestine was moistened with saline and covered with cellophane to prevent drying. A heat lamp was used to maintain the area at near body temperature.

Except for minor differences the experimental protocol followed in this study was the same as that for the forelimb. The exceptions in this study were: 1) the control gas mixture employed contained 20% O_2 - $2\frac{1}{2}$% CO_2, 2) only the combined hypoxic-hypercapnic (0% O_2 - 20% CO_2) gas mixture was administered before vagotomy, and 3) there were no measurements of venous outflow.

Kidney

To study the reflex effects of carotid body stimulation on renal vascular resistance the left kidney was perfused at constant blood flow in 10 animals. The left kidney was exposed retroperitoneally through a flank incision and retracted medially to visualize the renal artery. Following the administration of heparin the renal artery was cannulated and a blood pump (Sigmamotor Inc., model T-6SH) was interposed between the right femoral artery and the left renal artery. The perfusion rate of the renal artery was initially set so as

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The experimental protocol followed in this study was the same as that for the intestine. Following an initial control period the extracorporeal lung was ventilated with the hypoxic-hypercapnic gas mixture and then returned to the control gas. The animals were then vagotomized and the procedure repeated after a control period by randomly ventilating the isolated lung with the hypoxic, hypoxic-hypercapnic and hypercapnic gases.

To study the reflex effects of carotid sinus hypotension on renal vascular resistance the kidney preparation employed above was used. Carotid sinus pressure was reduced by decreasing the outflow resistance of the sinus perfusion circuit.

Heart

To study the reflex effects of carotid body stimulation on coronary vascular resistance the left common coronary artery was perfused at constant blood flow in 10 dogs. The heart was exposed through the left third intercostal space and a suture was passed around the left common coronary artery at the junction of the artery with the aorta. The animal was heparinized and the input tubing to the pump (Sigmamotor Inc., model T-6SH) inserted into the right femoral artery and filled

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with blood. A curved metal cannula of about the same diameter as the internal diameter of the left common coronary artery was attached to the output tubing of the pump and inserted into the left subclavian artery. While the pump was delivering blood, the cannula tip was manipulated down the ascending aorta into the mouth of the left common coronary artery and tied in place. The perfusion rate of the coronary artery was initially set so as to produce a perfusion pressure as close to aortic and carotid sinus pressure as possible while maintaining the viability of the heart. The perfusion pressure of the coronary artery was measured with a 22 gauge needle tipped cannula inserted into the output tubing of the pump. Left ventricular contractile force was measured with a 120 ohm strain gauge arch (James L. Butterfield, P. O. Box 412, Charleston, S. C.) sutured to the surface of the left ventricle. Contractile force was assessed by measuring (in mm) the pen deflection on the recorded tracing during the control and experimental periods. The data were reported as the percent change in contractile force during the experimental maneuvers.

The experimental protocol followed in the heart studies was the same as that for the intestine and kidney. A second series of heart studies was carried out in 6 animals in which the only deviations from the previously described protocol were that gas mixtures containing 10% O_2 - 10% CO_2 (hypoxic-hypercapnia), 20% O_2 - 10% CO_2 (hypercapnia) and 10% O_2 - $2\frac{1}{2}$% CO_2 or 5% O_2 - $2\frac{1}{2}$% CO_2 (hypoxia) were substituted for the

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Gracilis--Hindpaw

To further delineate the reflex effects of carotid body stimulation on resistance to blood flow through skin and skeletal muscle an isolated skin, skeletal muscle preparation was employed. The right gracilis muscle was exposed and dissected free from connective tissue. All blood vessels communicating with the gracilis except the major artery and vein were ligated. Heavy cord occlusive ligatures were placed at each end of the muscle to eliminate collateral blood flow. The obturator nerve remained intact. The gracilis muscle was perfused at constant flow by interposing a blood pump (Sigmamotor Inc., model TM10) between the right femoral artery and the gracilis artery. The perfusion rate of the gracilis was initially set so as to produce a perfusion pressure approximately equal to systemic and carotid sinus pressure.

The skin of the right hindpaw was circumferentially sectioned 3-5 cm above the tarsus. The right cranial tibial artery, right superficial branch of the cranial tibial artery, plantar and dorsal branches of the saphenous vein and hindpaw nerves were isolated and the remaining connective tissue and muscles sectioned by electro-cautery. The tibia and fibula were cut and the ends of the marrow cavities packed with bone

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wax. Blood entered the paw only through the cranial tibial artery and superficial branch of the cranial tibial artery. The hindpaw nerves (tibial, saphenous, superficial and deep fibular) were left intact and coated with an inert silicone spray to prevent drying. The tibial arteries were perfused at constant flow by a second blood pump (Sigmamotor Inc., model TM10) which delivered blood from the right femoral artery to a Y-cannula which allowed simultaneous perfusion of the tibial arteries. The perfusion pressure of the gracilis and tibial arteries were measured via a 22 gauge needle tipped cannula inserted into the output tubing of the perfusion pumps. This preparation permitted almost complete separation of skin and muscle blood flow (68).

Reflex effects of chemoreceptor stimulation in skin were studied in 3 animals. In these animals the skin of the right hindpaw was circumferentially sectioned 3-5 cm above the tarsus. The right cranial tibial artery and the superficial branch of the cranial tibial artery were isolated and perfused by means of the perfusion circuit described above. In these experiments the collateral flow to the paw was not disturbed.

Finally, in 2 animals the skin of the paw remained intact and the right cranial tibial artery was isolated through a small longitudinal incision in the skin. The cranial tibial artery was then perfused by means of a blood pump (Sigmamotor Inc., Model TM10) which diverted blood from the right femoral artery.

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The experimental protocol followed in the hindlimb studies was identical for each of the 3 series of experiments. The protocol differed from that employed in the forelimb, intestine and kidney studies in that only the control (20% O_2 - 2½% CO_2) and hypoxic-hypercapnic (0% O_2 - 20% CO_2) gas mixtures were used to ventilate the extracorporeal lung before the following vagotomy.

Analysis of Samples and Treatment of Data

The pH determinations from blood samples were measured with an expanded scale microelectrode pH meter (Radiometer Inc., model 22, Copenhagen, Denmark). Statistical evaluations were made using the Student t-test modified for paired replicates. P values less than 0.05 were considered significant (69).

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RESULTS

Forelimb

The average responses of the forelimb, systemic blood pressure and heart rate to perfusion of the isolated carotid sinus regions with hypoxic, hypoxic-hypercapnic and hypercapnic blood before vagotomy are shown in Table 1. The only significant response observed was an increase in systemic arterial pressure during ventilation of the extracorporeal lung with 0% O_2 - 20% CO_2.

The average responses of the forelimb to perfusion of the carotid sinuses with hypoxic, hypoxic-hypercapnic and hypercapnic blood following vagotomy are shown in Table 2. Significant increases in systemic arterial and brachial artery perfusion pressure occurred during ventilation with each experimental gas. Systemic arterial pressure increased to a greater extent (31%) during hypoxic-hypercapnia than during hypoxia alone (14%) or hypercapnia alone (15%). Brachial artery perfusion pressure also increased to a greater extent (18%) during hypoxic-hypercapnia than during hypoxia alone (9%) or hypercapnia alone (11%). There were no significant changes in brachail or cephalic vein outflows indicating that the changes in resistance were comparable in both

Table 1. Average forelimb responses to carotid chemoreceptor stimulation with hypoxic-hypercapnic, hypoxic and hypercapnic blood before vagotomy. P_S = systemic arterial pressure. P_{CS} = carotid sinus pressure. P_{BA} = brachial artery pressure. HR = heart rate. (C) = control. Mean brachial artery blood flow = 86 ml/min.

Table 1. Average forelimb responses to carotid chemoreceptor stimulation with hypoxic-hypercapnic, hypoxic and hypercapnic blood before vagotomy. P_S = systemic arterial pressure. P_{CS} = carotid sinus pressure. P_{BA} = brachial artery pressure. HR = heart rate. (C) = control. Mean brachial artery blood flow = 86 ml/min.

VENTILATORY MIXTURE (ISOLATED LUNG)	P_{CS}	P_S	Mean Diff. ± SE.	P_{BA}	Mean Diff. ± SE.	HR	Mean Diff. ± SE.
20% O_2 - 5% CO_2 (C)	127	133	18* ± 5.3	119	5 ± 2.6	175	-1 ± 2.6
0% O_2 - 20% CO_2	121	151		124		174	
20% O_2 - 5% CO_2 (C)	126	132	3 ± 4.5	119	4 ± 2.4	176	-3 ± 3.0
0% O_2 - 5% CO_2	122	135		123		173	
20% O_2 - 5% CO_2 (C)	127	128	9 ± 3.4	124	7 ± 2.1	175	0 ± 1.2
20% O_2 - 20% CO_2	121	137		131		175	

*P <0.05 (Student's t-test for paired observations), n = 10.

continued

Table 1a. Average forelimb response to carotid chemoreceptor stimulation with hypoxic-hypercapnic, hypoxic and hypercapnic blood before vagotomy. F_{BV} = brachial vein flow. F_{CV} = cephalic vein flow. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean brachial artery blood flow = 86 ml/min.

Table 1a. Average forelimb responses to carotid chemoreceptor stimulation with hypoxic-hypercapnic, hypoxic and hypercapnic blood before vagotomy. F_{BV} = brachial vein flow. F_{CV} = cephalic vein flow. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean brachial artery blood flow = 86 ml/min.

VENTILATORY MIXTURE (ISOLATED LUNG)	F_{BV}	Mean Diff. ± SE.	F_{CV}	Mean Diff. ± SE.	P_{O_2}	pH
20% O_2 - 5% CO_2 (C)	51	0 ± 0.5	49	0 ± 0.8	116	7.28
0% O_2 - 20% CO_2	51		49		19	
20% O_2 - 5% CO_2 (C)	50	1 ± 1.2	50	0 ± 0.7	113	7.29
O_2 - 5% CO_2	51		50		14	7.31
20% O_2 - 5% CO_2 (C)	49	1 ± 0.7	51	0 ± 1.0	109	7.29
20% O_2 - 20% CO_2	50		51		130	6.95

*$P < 0.05$ (Student's t-test for paired observations), n = 10.

Table 2. Average forelimb responses to carotid chemoreceptor stimulation with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. P_S = systemic arterial pressure. P_{CS} = carotid sinus pressure. P_{BA} = brachial artery pressure. HR = heart rate. (C) = control. Mean brachial artery blood flow = 95 ml/min.

Table 2. Average forelimb responses to carotid chemoreceptor stimulation with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. P_S = systemic arterial pressure. P_{CS} = carotid sinus pressure. P_{BA} = brachial artery pressure. HR = heart rate. (C) = control. Mean brachial artery blood flow = 95 ml/min.

VENTILATORY MIXTURE (ISOLATED LUNG)	P_{CS}	P_S	Mean Diff. ± SE.	P_{BA}	Mean Diff. ± SE.	HR	Mean Diff. ± SE.
20% O_2 - 5% CO_2 (C)	118	119	37*± 6.1	119	21*± 6.7	156	0 ± 2.8
0% O_2 - 20% CO_2	117	156		140		156	
20% O_2 - 5% CO_2 (C)	115	111	16*± 4.6	124	11*± 4.7	159	-2 ± 2.1
0% O_2 - 5% CO_2	114	127		135		157	
20% O_2 - 5% CO_2 (C)	114	100	15*± 6.1	127	14*± 3.3	157	7*± 2.4
20% O_2 - 20% CO_2	112	115		141		164	

*$P < 0.05$ (Student's t-test for paired observations), n = 13.

continued

Table 2a. Average forelimb responses to carotid chemoreceptor stimulation with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. F_{BV} = brachial vein flow. F_{CV} = cephalic vein flow. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean brachial artery blood flow = 95 ml/min.

Table 2a. Average forelimb responses to carotid chemoreceptor stimulation with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. F_{BV} = brachial vein flow. F_{CV} = cephalic vein flow. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean brachial artery blood flow - 95 ml/min.

VENTILATORY MIXTURE (ISOLATED LUNG)	F_{BV}	Mean Diff. ± SE.	F_{CV}	Mean Diff. ± SE.	P_{O_2}	pH
20% O_2 - 5% CO_2 (C)	46	0 ± 1.0	56	3 ± 1.1	115	7.28
0% O_2 - 20% CO_2	46		59		19	6.92
20% O_2 - 5% CO_2 (C)	44	0 ± 0.6	57	1 ± 0.3	110	7.25
0% O_2 - 5% CO_2	44		58		14	7.27
20% O_2 - 5% CO_2 (C)	43	0 ± 0.4	58	-1 ± 0.6	110	7.27
20% O_2 - 20% CO_2	43		57		129	6.91

*$P < 0.05$ (Student's t-test for paired observations), n = 13.

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skin and muscle. The only change in heart rate was an increase during chemoreceptor stimulation with hypercapnic blood.

A representative response of the systemic arterial pressure and forelimb perfusion pressure to the hypoxic-hypercapnic gas mixture is presented in Figure 2. This figure was taken from an experimental recording following vagotomy. During the control period the extracorporeal lung was ventilated with the control gas mixture (20% O_2 - 5% CO_2). Upon switching the ventilatory gas to 0% O_2 - 20% CO_2 the O_2 tension of the blood perfusing the carotid sinus perfusion circuit fell rapidly from 105 to 20 mm Hg. The pH of the blood perfusing the sinuses decreased from 7.28 to 6.91. This was accompanied by a marked increase in systemic arterial and brachial artery perfusion pressure. Outflows from the brachial and cephalic veins were not altered during chemoreceptor stimulation indicating no differential effect on the skin or muscle vascular beds. Carotid sinus perfusion pressure remained relatively constant with any changes being immediately compensated by adjusting the variable resistance clamp on the sinus outflow cannula. Upon returning to ventilation with the control gas, systemic arterial and brachial artery perfusion pressure rapidly returned to control levels.

A typical response to the hypoxic gas mixture following vagotomy is shown in Figure 3. Upon switching from the control gas mixture to 0% O_2 - 5% CO_2 a rapid fall in the O_2

Figure 2. Representative forelimb vascular response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood in a vagotomized dog.

P_{O2} = O_2 tension of carotid sinus blood.

P_{CS} = carotid sinus pressure.

pH = pH of sinus blood.

P_S = systemic arterial pressure.

BV = brachial vein flow.

CV = cephalic vein flow.

P_{BA} = brachial artery pressure.

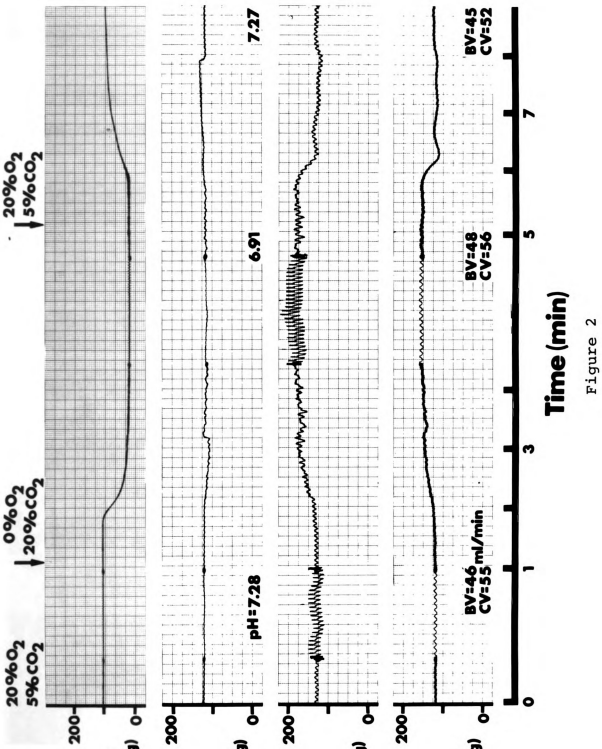
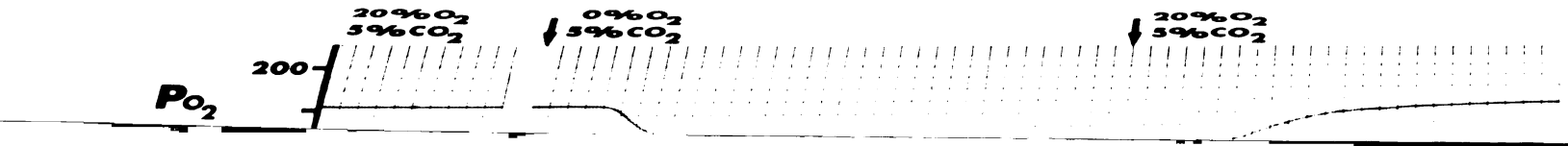
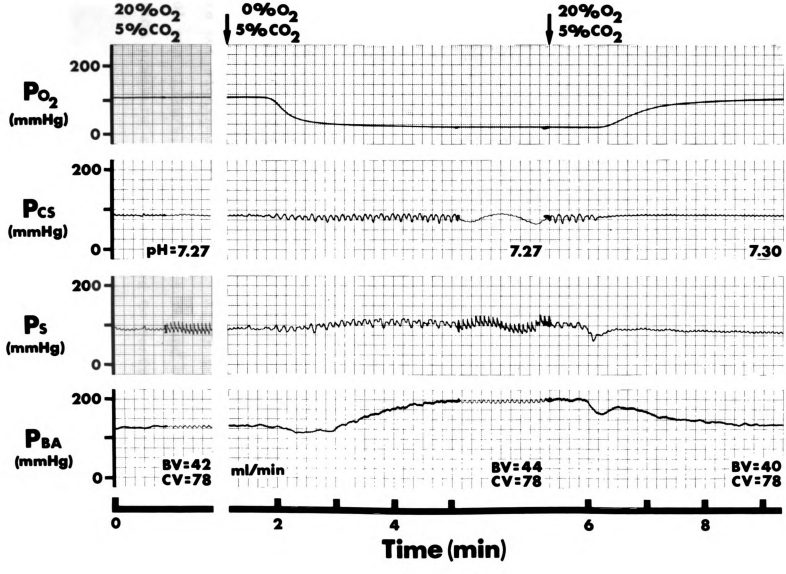

20%O2
5%CO2
0%O2
20%CO2
20%O2
5%CO2
PO2 (mmHg)
200
0
PCS (mmHg)
pH=7.28
6.91
7.27
PS (mmHg)
PBA (mmHg)
BV=46
CV=55 ml/min
BV=48
CV=56
BV=45
CV=52
0
1
3
5
7
Time (min)

Figure 2

Figure 3. Representative forelimb vascular response to carotid chemoreceptor stimulation with hypoxic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.
P_{CS} = carotid sinus pressure.
pH = pH of sinus blood.
P_S = systemic arterial pressure.
BV = brachial vein flow.
CV = cephalic vein flow.
P_{BA} = brachial artery pressure.




20%O2
5%CO2
0%O2
5%CO2
20%O2
5%CO2
200
PO2
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pH=7.27
7.27
7.30
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PS
(mmHg)
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200
PBA
(mmHg)
0
BV=42
CV=78
ml/min
BV=44
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BV=40
CV=78
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Figure 3

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tension of the carotid sinus blood occurred. The pH of the sinus blood was uneffected by this gas mixture. At a constant carotid sinus pressure, systemic arterial and brachial artery perfusion pressure increased markedly. Brachial and cephalic vein outflows were not significantly altered, indicating no shift in flow between skin and skeletal muscle. Upon ventilation with the control gas, systemic pressure, brachial artery perfusion pressure, and P_{O_2} of the sinus blood rapidly returned to control levels.

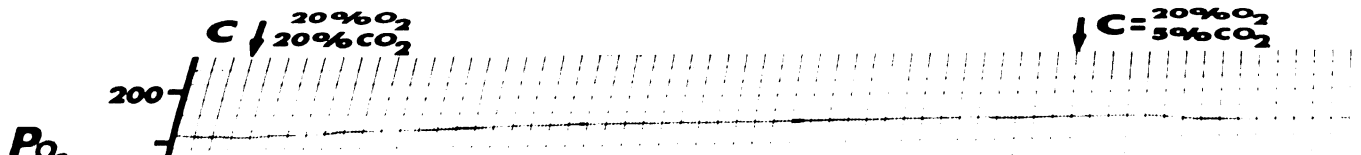
A typical response to carotid chemoreceptor stimulation with the hypercapnic gas mixture after vagotomy is shown in Figure 4. After an initial control period, ventilation with 20% O_2 - 20% CO_2 was begun. The P_{O_2} of the sinus blood rose slightly, probably due to the effect of hydrogen ion on oxygen dissociation (Bohr effect). While carotid sinus pressure remained unchanged, systemic and brachial artery perfusion pressure increased markedly. The pH of the sinus blood decreased from 7.28 to 6.94. Brachial and cephalic outflows were not significantly altered. After returning to the control gas mixture, systemic pressure and brachial artery perfusion pressure rapidly returned to control levels.

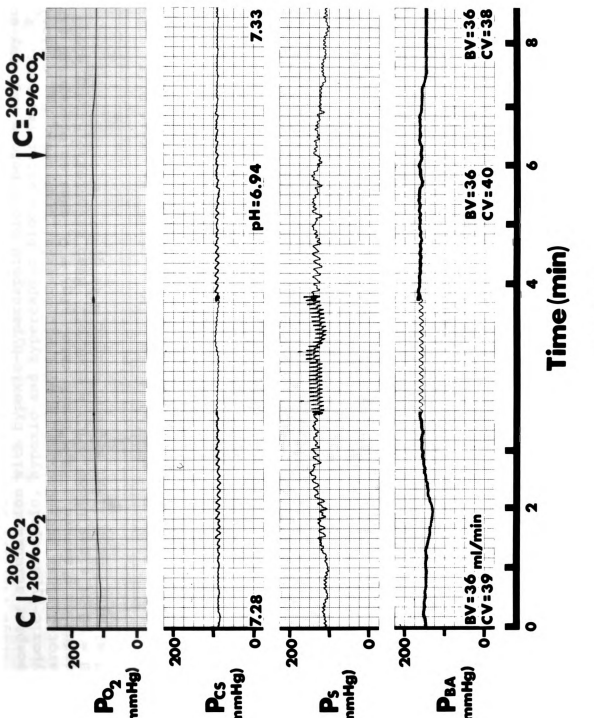
Intestine

Table 3 shows the average responses of systemic blood pressure, heart rate and the vascular responses of the ileal

Figure 4. Representative forelimb vascular response to carotid chemoreceptor stimulation with hypercapnic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.
P_{CS} = carotid sinus pressure.
pH = pH of sinus blood.
P_S = systemic arterial pressure.
BV = brachial vein flow.
CV = cephalic vein flow.
P_{BA} = brachial artery pressure.




C 20%O2 20%CO2
C= 20%O2 5%CO2
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CV=40
BV=36
CV=38
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6
8
Time (min)

Figure 4

Table 3. Average vascular response of ileal segment of intestine to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_{MA} = ileal segment perfusion pressure. HR = heart rate. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean mesenteric artery blood flow = 17 ml/min. Mean ileal segment weight = 44 g.

Table 3. Average vascular responses ot ileal segment of intestine to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_{MA} = ileal segment perfusion pressure. HR = heart rate. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean mesenteric artery blood flow = 17 ml/min. Mean ileal segment weight = 44 g.

VENTILATORY MIXTURE (ISOLATED LUNG)	P_{CS}	P_S	Mean Diff. ± SE.	P_{MA}	Mean Diff. ± SE.	HR	Mean Diff. ± SE.	P_{O_2}	pH
				BEFORE VAGOTOMY					
20% O_2 - 2½% CO_2 (C)	122	120		79		166		111	7.38
			15%*± 6.9		5 ± 3.5		-8 ± 5.8		
0% O_2 - 20% CO_2	119	135		84		158		17	6.98
				AFTER VAGOTOMY					
20% O_2 - 2½% CO_2 (C)	111	116		111		166		150	7.39
			42**± 6.5		41**± 13.7		-4 ± 2.6		
0% O_2 - 20% CO_2	112	158		152		162		18	6.96
20% O_2 - 2½% CO_2 (C)	112	111		125		168		151	7.40
			22**± 5.5		15**± 4.1		-6 ± 2.6		
0% O_2 - 5% CO_2	112	133		140		162		15	7.32
20% O_2 - 2½% CO_2 (C)	103	101		118		169		155	7.39
			25**± 4.2		20**± 10.3		3 ± 3.0		
20% O_2 - 20% CO_2	104	126		138		172		133	6.91

*P < 0.05 (Student's t-test for paired observations), n = 5.

**P < 0.05 (Student's t-test for paired observations), n = 9.

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segment to perfusion of the carotid chemoreceptors with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood following vagotomy. The only significant response produced before vagotomy was an increase in systemic arterial pressure. The changes in heart rate before vagotomy were insignificant. Following vagotomy increases in systemic pressure and ileal segment perfusion pressure occurred during ventilation with each of the experimental gases. Systemic arterial pressure increased to a greater extent (36%) during hypoxic-hypercapnic stimulation than during hypoxic alone (20%) or hypercapnic stimulation alone (25%). Similarly, a greater increase in ileal segment perfusion pressure occurred during hypoxic-hypercapnic (37%) than during hypoxia only (12%) or hypercapnia alone (17%). No significant changes in heart rate were observed.

A typical response of the isolated ileal segment and systemic blood pressure to carotid body chemoreceptor stimulation with the hypoxic-hypercapnic gas mixture after vagotomy is shown in Figure 5. During the control period the extracorporeal lung was ventilated with 20% O_2 - 2 % CO_2. After changing the ventilatory gas to 0% O_2 - 20% CO_2 systemic arterial pressure and perfusion pressure of the ileal segment increased markedly while carotid sinus pressure remained unchanged. The pH of the blood perfusing the carotid sinuses decreased from 7.45 to 7.00. In this animal fluctuations in the intraluminal pressure of the ileal segment appeared to

Figure 5. Representative vascular response of ileal segment to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood in a vagotomized dor.

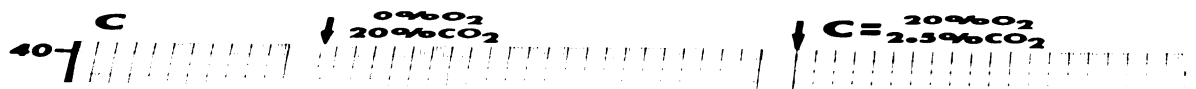
M = intraluminal pressure of ileal segment.

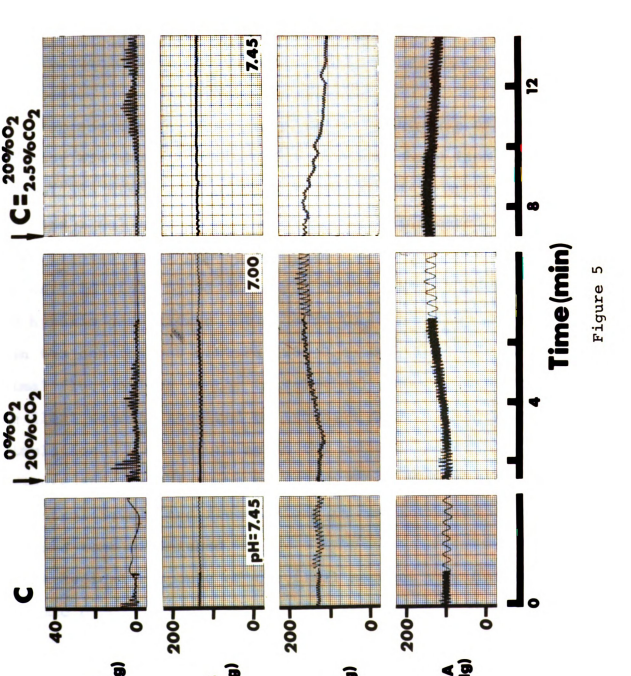
P_{CS} = carotid sinus pressure.

pH = pH of sinus blood.

P_S = systemic arterial pressure.

P_{MA} = ileal segment perfusion pressure.




C
0%O2
20%CO2
C=
20%O2
2.5%CO2
M
(mmHg)
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0
PCS
(mmHg)
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pH=7.45
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Figure 5

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decrease during chemoreceptor stimulation. Following the return to the control gas, systemic pressure and ileal segment perfusion pressure rapidly returned toward control levels and fluctuations in the intraluminal pressure increased in magnitude.

Representative responses produced by hypoxia after vagotomy are shown in Figure 6. Upon switching from the control gas mixture to 0% O_2 - 5% CO_2 systemic arterial pressure and ileal segment perfusion pressure increased markedly while carotid sinus pressure remained unchanged. The pH of the carotid sinus blood decreased from 7.46 to 7.36 because the hypoxic gas mixture (0% O_2 - 5% CO_2) contained more CO_2 than the control gas mixture (20% O_2 - $2\frac{1}{2}$% CO_2). In this animal fluctuations in the intraluminal pressure and tone of the ileal segment appeared to increase during chemoreceptor stimulation. Upon returning to the control gas, systemic pressure and ileal segment perfusion pressure rapidly returned to control levels and fluctuations in the intraluminal pressure and tone diminished.

A typical response of the ileal segment vasculature and systemic blood pressure to carotid chemoreceptor stimulation with hypercapnic blood is presented in Figure 7. After a control period, the extracorporeal lung was ventilated with 20% O_2 - 20% CO_2. The pH of the sinus blood decreased from 7.42 to 6.91. Systemic pressure and ileal segment perfusion pressure increased markedly while carotid sinus pressure showed

Figure 6. Representative vascular response of ileal segment to carotid chemoreceptor stimulation with hypoxic blood in a vagotomized dog.

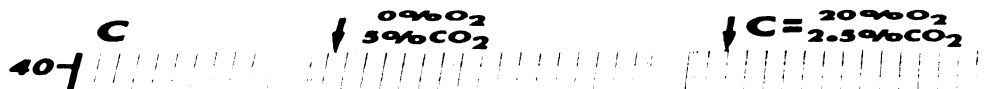
M = intraluminal pressure of ileal segment.

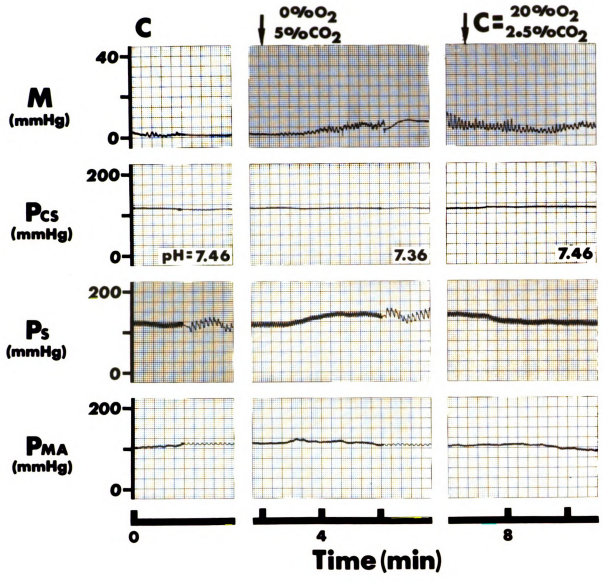
P_{CS} = carotid sinus pressure.

pH = pH of sinus blood.

P_S = systemic arterial pressure.

P_{MA} = ileal segment perfusion pressure.




C
0%O2
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C=20%O2
2.5%CO2
M
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PCS
(mmHg)
200
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pH=7.46
7.36
7.46
PS
(mmHg)
200
0
PMA
(mmHg)
200
0
0
4
8
Time (min)

Figure 6

Figure 7. Representative vascular response of ileal segment to carotid chemoreceptor stimulation with hypercapnic blood in a vagotomized dog.

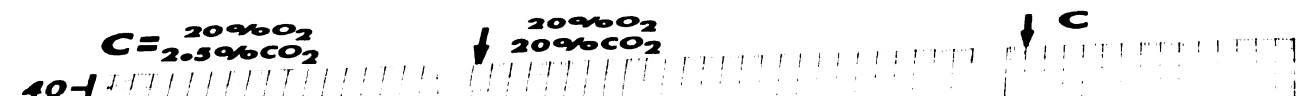
M = intraluminal pressure of ileal segment.

P_{CS} = carotid sinus pressure.

pH = pH of sinus blood.

P_S = systemic arterial pressure.

P_{MA} = ileal segment perfusion pressure.



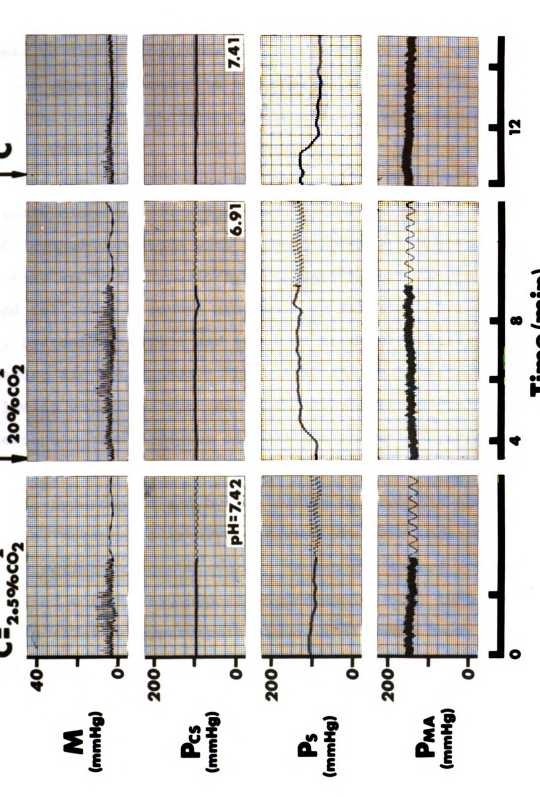

C= 20%O2 2.5%CO2
20%O2 20%CO2
C
M (mmHg)
Pcs (mmHg)
Ps (mmHg)
PMA (mmHg)
40
0
200
0
200
0
200
0
pH=7.42
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Figure 7

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little change. Intraluminal pressure fluctuations did not appear to differ significantly from those of the control period. Upon returning to the control gas, systemic pressure and ileal segment perfusion pressure rapidly returned to control values.

The average responses of the superior mesenteric artery, systemic blood pressure and heart rate to perfusion of the carotid chemoreceptors with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood following vagotomy are shown in Table 4. Before vagotomy, systemic pressure and superior mesenteric artery perfusion pressure did not change. The heart rate was also unchanged. Following vagotomy, systemic pressure increased during hypoxic-hypercapnic chemoreceptor stimulation and with hypercapnic stimulation alone. Systemic pressure increased by 37% during hypoxic-hypercapnic and by 23% during hypercapnia alone. Superior mesenteric artery perfusion pressure increased with each experimental gas mixture. Mesenteric artery pressure increased more during hypoxic-hypercapnia (50%) than during hypoxia (17%) or hypercapnia alone (15%). The heart rate was not altered significantly by any maneuver.

Kidney

Table 5 shows the average responses of the kidney, systemic blood pressure and heart rate to perfusion of the

Table 4. Average responses of superior mesenteric artery to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_{SMA} = superior mesenteric artery pressure. HR = heart rate. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean superior mesenteric artery blood flow = 174 ml/min.

Table 4. Average responses of superior mesenteric artery to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_{SMA} = superior mesenteric artery pressure. HR = heart rate. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean superior mesenteric artery blood flow = 174 ml/min.

VENTILATORY MIXTURE (ISOLATED LUNG)	P_{CS}	P_S	Mean Diff. ± SE.	P_{SMA}	Mean Diff. ± SE.	HR	Mean Diff. ± SE.	P_{O_2}	pH
			BEFORE VAGOTOMY						
20% O_2 - 2½% CO_2 (C)	121	128		106		152		104	7.35
			14 ± 5.0		13 ± 8.4		7 ± 2.9		
0% O_2 - 20% CO_2	119	142		119		159		17	6.97
			AFTER VAGOTOMY						
20% O_2 - 2½% CO_2 (C)	104	102		102		140		92	7.35
			38**± 7.1		51**± 10.0		3 ± 1.9		
0% O_2 - 20% CO_2	105	140		153		143		13	6.92
20% O_2 - 2½% CO_2 (C)	117	115		101		144		93	7.38
			15 ± 7.6		17**± 5.6		-2 ± 1.9		
0% O_2 - 5% CO_2	114	130		118		142		12	7.27
20% O_2 - 2½% CO_2 (C)	104	101		108		141		105	7.40
			23**± 3.2		18**± 4.2		2 ± 2.2		
20% O_2 - 20% CO_2	104	124		126		143		111	6.90

*$P < 0.05$ (Student's t-test for paired observations), n = 3.

**$P < 0.05$ (Student's t-test for paired observations), n = 4.

Table 2. Average kidney response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_R = renal artery pressure. HR = heart rate. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean renal artery blood flow = 110 ml/min.

	P_{CS}	P_S	Mean Diff.	P_R	Mean Diff.	HR	Mean Diff.	P_{O_2}	pH

Table 5. Average kidney response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_R = renal artery pressure. HR = heart rate. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. (C) = control. Mean renal artery blood flow = 110 ml/min.

VENTILATORY MIXTURE (ISOLATED LUNG)	P_{CS}	P_S	Mean Diff. ± SE.	P_R	Mean Diff. ± SE.	HR	Mean Diff. ± SE.	P_{O_2}	pH
				BEFORE VAGOTOMY					
20% O_2 - 2½% CO_2 (C)	116	120		80		151		121	7.38
			19*± 2.3		48*± 18.7		1 ± 1.9		
0% O_2 - 20% CO_2	117	139		128		152		18	6.98
				AFTER VAGOTOMY					
20% O_2 - 2½% CO_2 (C)	105	102		91		142		112	7.36
			32* ± 5.6		59* ± 13.9		7*± 3.5		
0% O_2 - 20% CO_2	105	134		150		149		19	6.93
20% O_2 - 2½% CO_2 (C)	103	101		87		145		113	7.34
			19* ± 5.8		43* ± 15.2		6 ± 4.1		
0% O_2 - 5% CO_2	104	120		130		151		14	7.26
20% O_2 - 2½% CO_2 (C)	101	99		86		148		120	7.35
			23* ± 3.8		38* ± 2.9		-2 ± 1.3		
20% O_2 - 20% CO_2	103	122		124		146		123	6.87

*$P < 0.05$ (Student's t-test for paired observations), n = 10.

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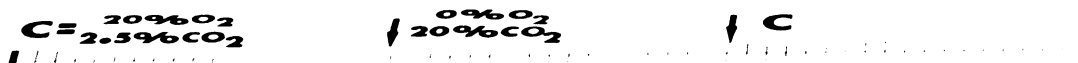
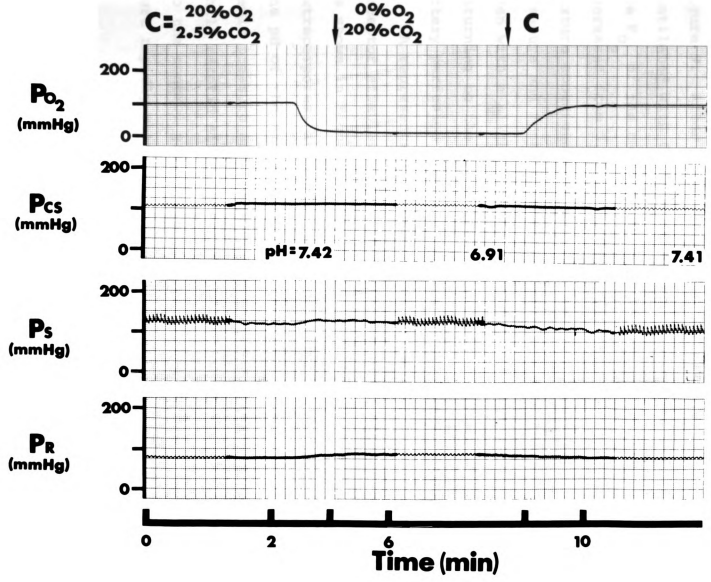
carotid chemoreceptors with hypoxic-hypercapnic blood before vagotomy and with hypoxic-hypercapnic, hypoxic and hypercapnic blood after vagotomy. Systemic arterial pressure and renal artery perfusion pressure increased before vagotomy, while the heart rate was unchanged. Following vagotomy, systemic pressure and renal artery perfusion pressure increased significantly during each experimental maneuver. The only change in heart rate was a slight increase during chemoreceptor stimulation with combined hypoxia and hypercapnia. The increase in systemic pressure was greater during hypoxic-hypercapnia (31%) than during hypoxia (19%) or hypercapnia alone (23%). Similarly, renal artery perfusion pressure increased more during the combined hypoxic-hypercapnia (65%) than during hypoxia (49%) or hypercapnia alone (44%).

Figure 8 presents a representative record during chemoreceptor stimulation with hypoxic-hypercapnic blood following vagotomy. After a control period during which the extracorporeal lung was ventilated with 20% O_2 - $2\frac{1}{2}$% CO_2, ventilation was changed to 0% O_2 - 20% CO_2. The pH of the carotid sinus blood decreased from 7.42 to 6.91. As the O_2 tension of the carotid sinus blood fell, systemic arterial pressure and renal artery perfusion pressure increased while carotid sinus pressure remained constant. Upon returning to the control gas, systemic pressure and renal artery perfusion pressure returned to near control values.

Figure 8. Representative kidney response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.
P_{CS} = carotid sinus pressure.
P_S = systemic arterial pressure.
P_R = renal artery pressure.
pH = pH of sinus blood.




C= 20%O2 2.5%CO2
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chemorecept

A typical renal vascular response to carotid chemoreceptor stimulation with hypoxic blood after vagotomy is shown in Figure 9. After a control period the extracorporeal lung was ventilated with 0% O_2 - 5% CO_2 which produced a decrease in the P_{O_2} of the carotid sinus blood. The pH of the sinus blood decreased from 7.37 to 7.30, again, because the hypoxic gas mixture contained more CO_2 than the control mixture. Systemic pressure and renal artery perfusion pressure increased markedly even with a slight rise in carotid sinus pressure. After returning to the control gas, systemic pressure and renal artery perfusion pressure rapidly decreased to control values.

A representative response of the kidney to carotid chemoreceptor stimulation with hypercapnic blood after vagotomy is shown in Figure 10. Following a control period, the extracorporeal lung was ventilated with 20% O_2 - 29% CO_2. The pH of the sinus blood decreased from 7.39 to 6.87. Systemic pressure and renal artery perfusion pressure increased while carotid sinus pressure remained constant. Upon returning to the control gas, systemic pressure and renal artery pressure rapidly returned to control levels.

Heart

The average responses of the coronary vasculature, systemic pressure and left ventricular contractile force to chemoreceptor stimulation by hypoxic-hypercapnic blood in

Figure 9. Representative kidney response to carotid chemoreceptor stimulation with hypoxic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.
P_{CS} = carotid sinus pressure.
P_S = systemic arterial pressure.
P_R = renal artery pressure.
pH = pH of sinus blood.

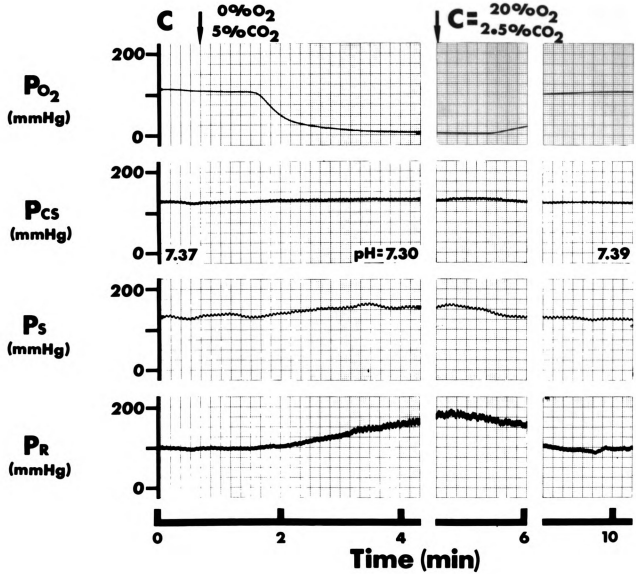
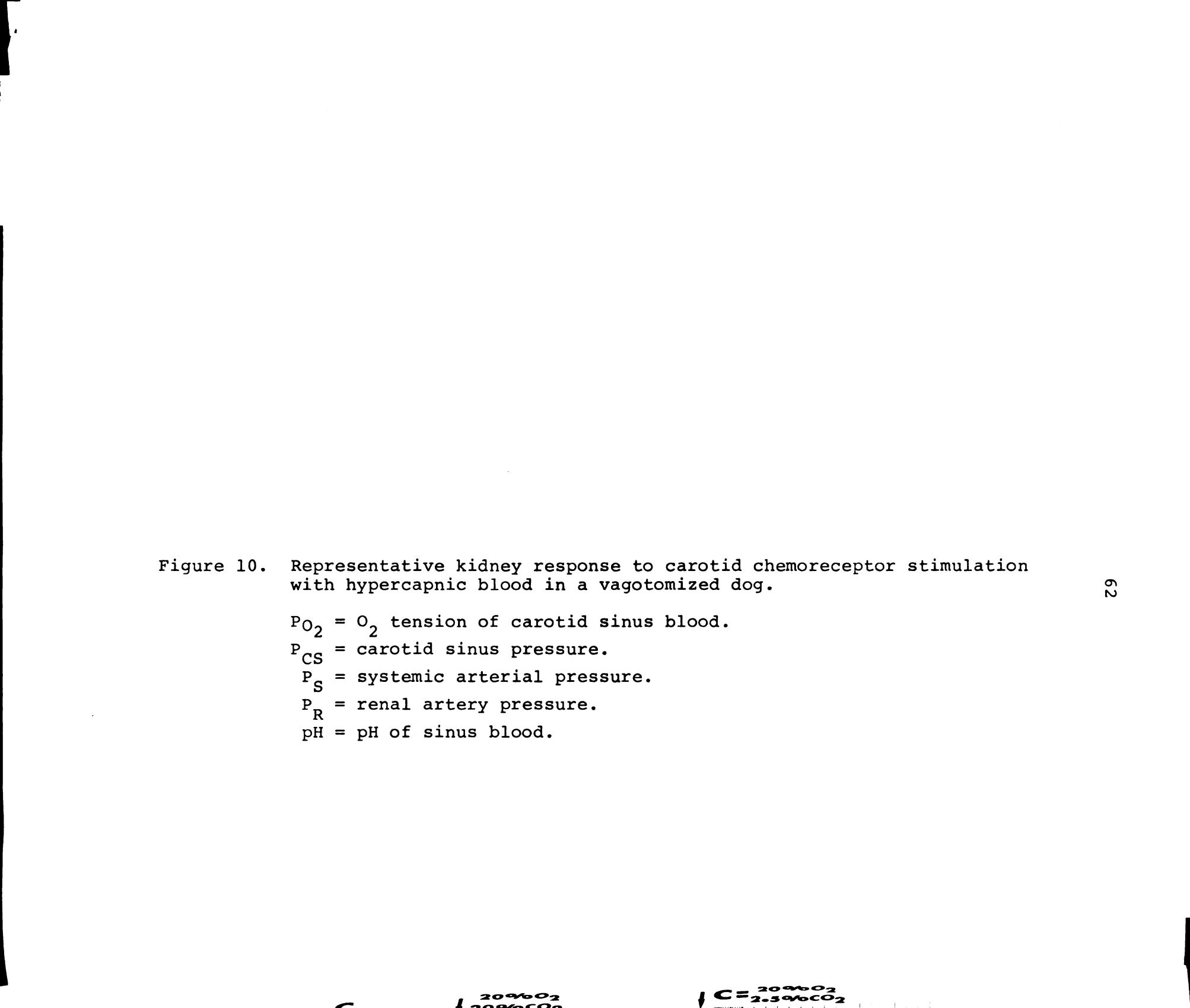

C
0%O2
5%CO2
C=
20%O2
2.5%CO2
200
0
PO2
(mmHg)
PCS
(mmHg)
7.37
pH=7.30
7.39
PS
(mmHg)
PR
(mmHg)
0
2
4
6
10
Time (min)

Figure 9

Figure 10. Representative kidney response to carotid chemoreceptor stimulation with hypercapnic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.
P_{CS} = carotid sinus pressure.
P_S = systemic arterial pressure.
P_R = renal artery pressure.
pH = pH of sinus blood.



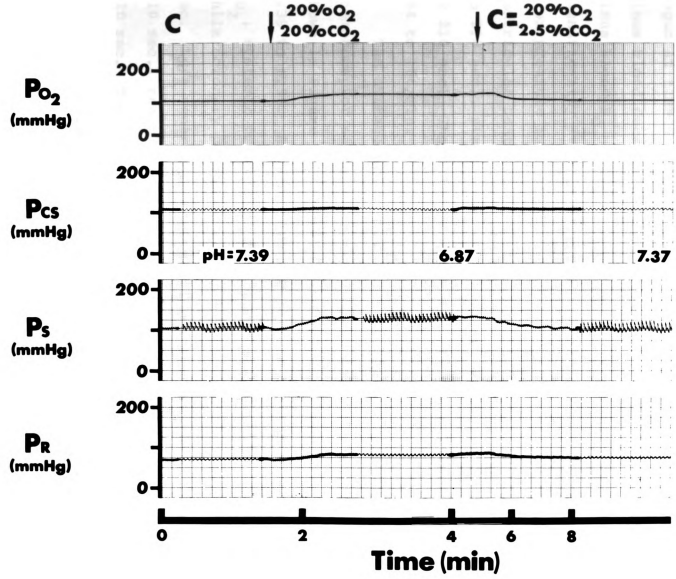

C
20%O2
20%CO2
C=
20%O2
2.5%CO2
200
0
PO2
(mmHg)
PCS
(mmHg)
pH=7.39
6.87
7.37
PS
(mmHg)
PR
(mmHg)
0
2
4
6
8
Time (min)

Figure 10

ten animals before vagotomy are shown in Figure 11. During the control period the extracorporeal lung was ventilated with 20% O_2 - 2½% CO_2. Ventilation with 0% O_2 - 20% CO_2 was then begun at time 0 seconds (Figure 11). The pH of the carotid sinus blood decreased from 7.44 to 6.96. As the carotid sinus blood P_{O_2} fell, systemic arterial pressure increased significantly from 60 to 210 sec. while coronary artery perfusion pressure rose significantly only at 60 and 90 sec. Left ventricular contractile force decreased significantly from 90 to 210 sec., stabilizing at a point 9% below the control value by 210 sec. The heart rate was significantly lowered from 164 to 156/min.

The average effects of the same hypoxic-hypercapnic chemoreceptor stimulus in ten animals following vagotomy are shown in Figure 12. Carotid sinus blood pH decreased from 7.39 to 6.95. Accompanying the fall in carotid sinus blood P_{O_2}, systemic pressure increased markedly from 60 to 210 sec. while coronary perfusion pressure rose slightly only at 60 sec. Left ventricular contractile force decreased from 90 to 210 sec., reaching a point 19% below the control value by 210 sec. There was no significant change in heart rate (159 to 157/min).

The average responses to hypoxic chemoreceptor stimulation in ten animals after vagotomy are presented in Figure 13. Carotid sinus blood pH decreased slightly from 7.36 to 7.32. As the carotid sinus blood P_{O_2} fell, systemic pressure

Figure 11. Average coronary vascular response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy.

P_{COR} = coronary perfusion pressure.

P_S = systemic arterial pressure.

P_{O_2} = O_2 tension of carotid sinus blood.

LVCF = left ventricular contractile force.

Mean coronary blood flow = 118 ml/min.

n = 10.

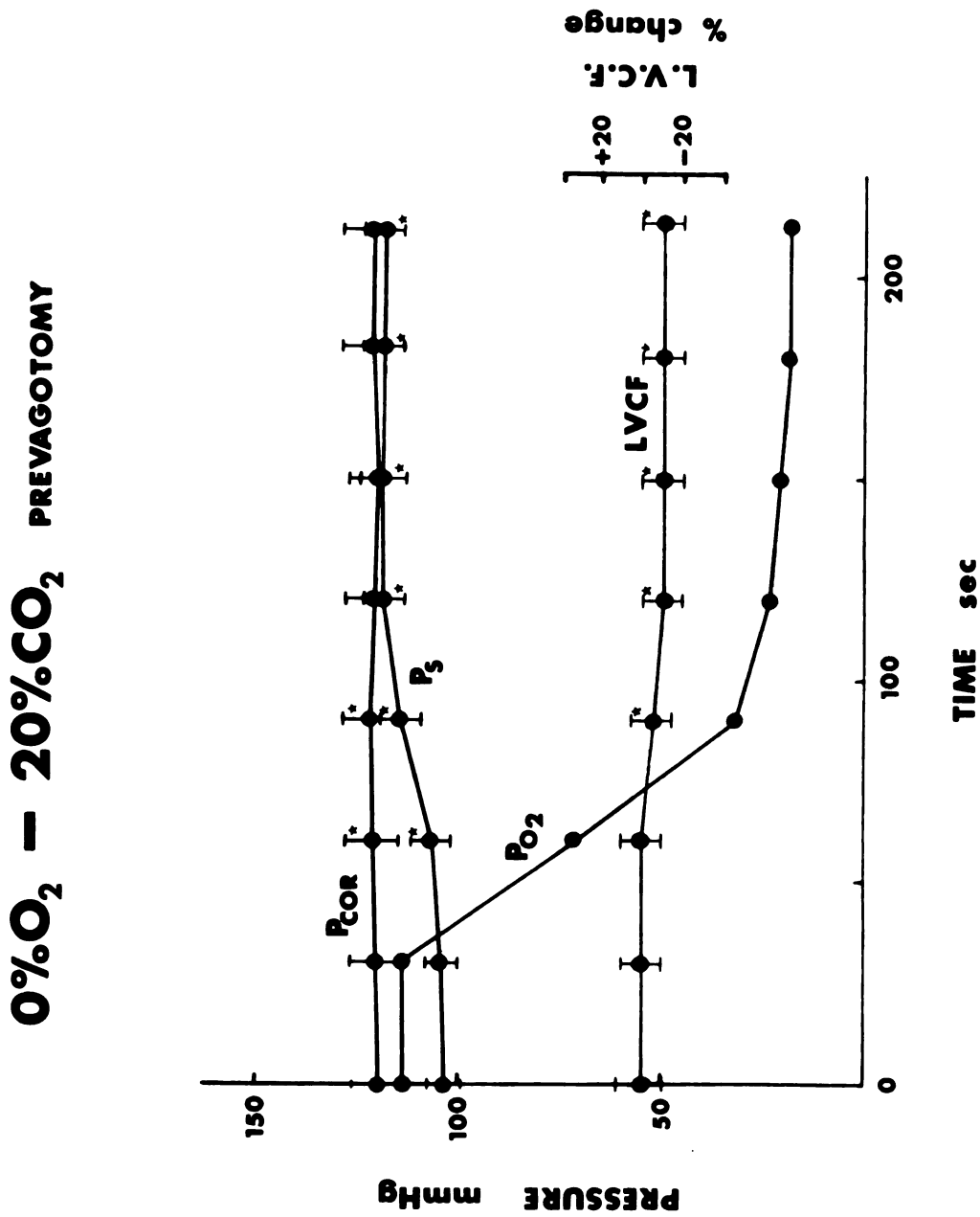

0%O2 — 20%CO2 PREVAGOTOMY
PRESSURE mmHg
150
100
50
0
100
200
TIME sec
PCOR
PS
PO2
LVCF
L.V.C.F.
% change
+20
-20
Means ± SE.
* P<.05 (Student's t test for paired observations)

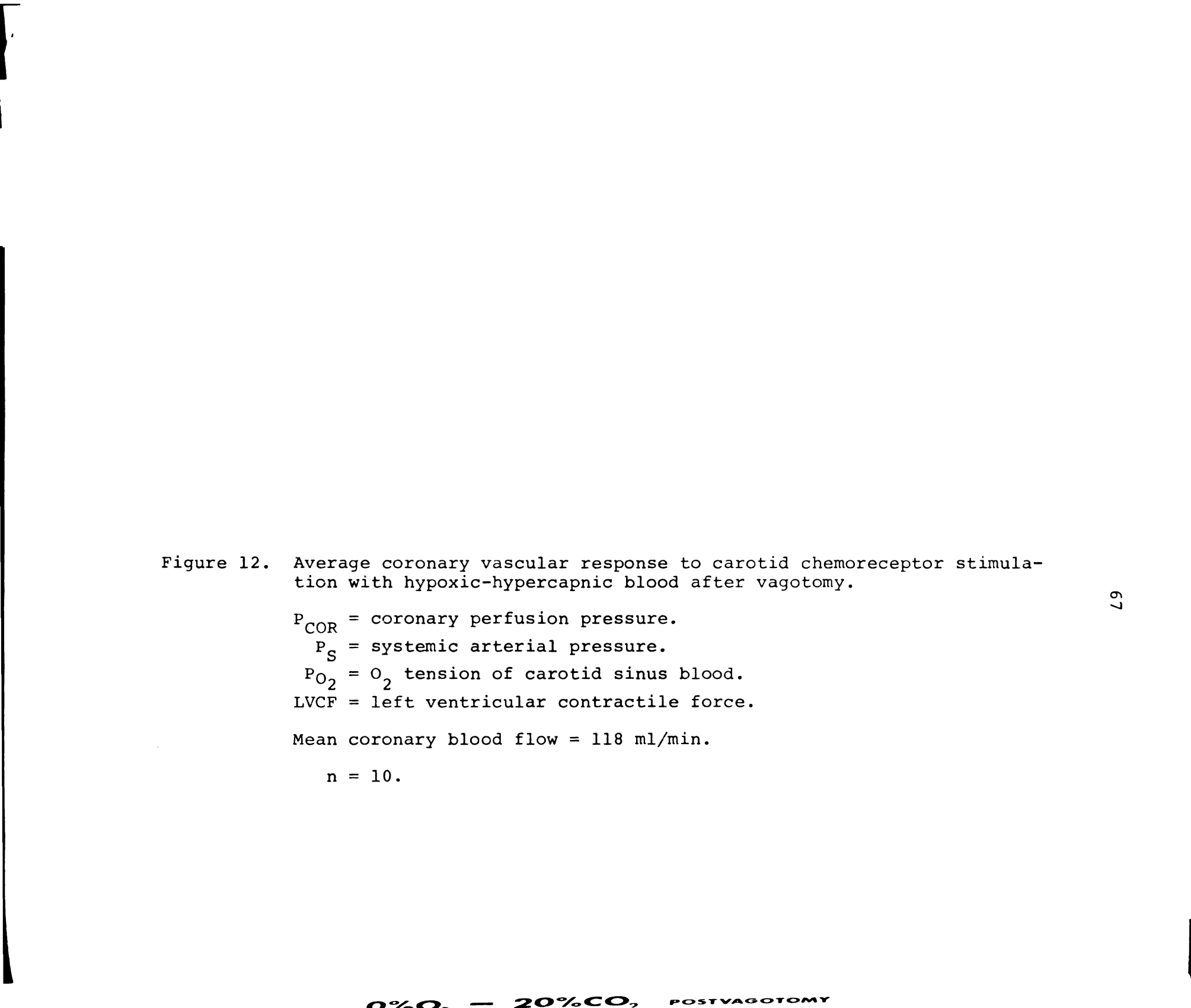
Figure 11

Figure 12. Average coronary vascular response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood after vagotomy.

P_{COR} = coronary perfusion pressure.
P_S = systemic arterial pressure.
P_{O_2} = O_2 tension of carotid sinus blood.
LVCF = left ventricular contractile force.

Mean coronary blood flow = 118 ml/min.

n = 10.



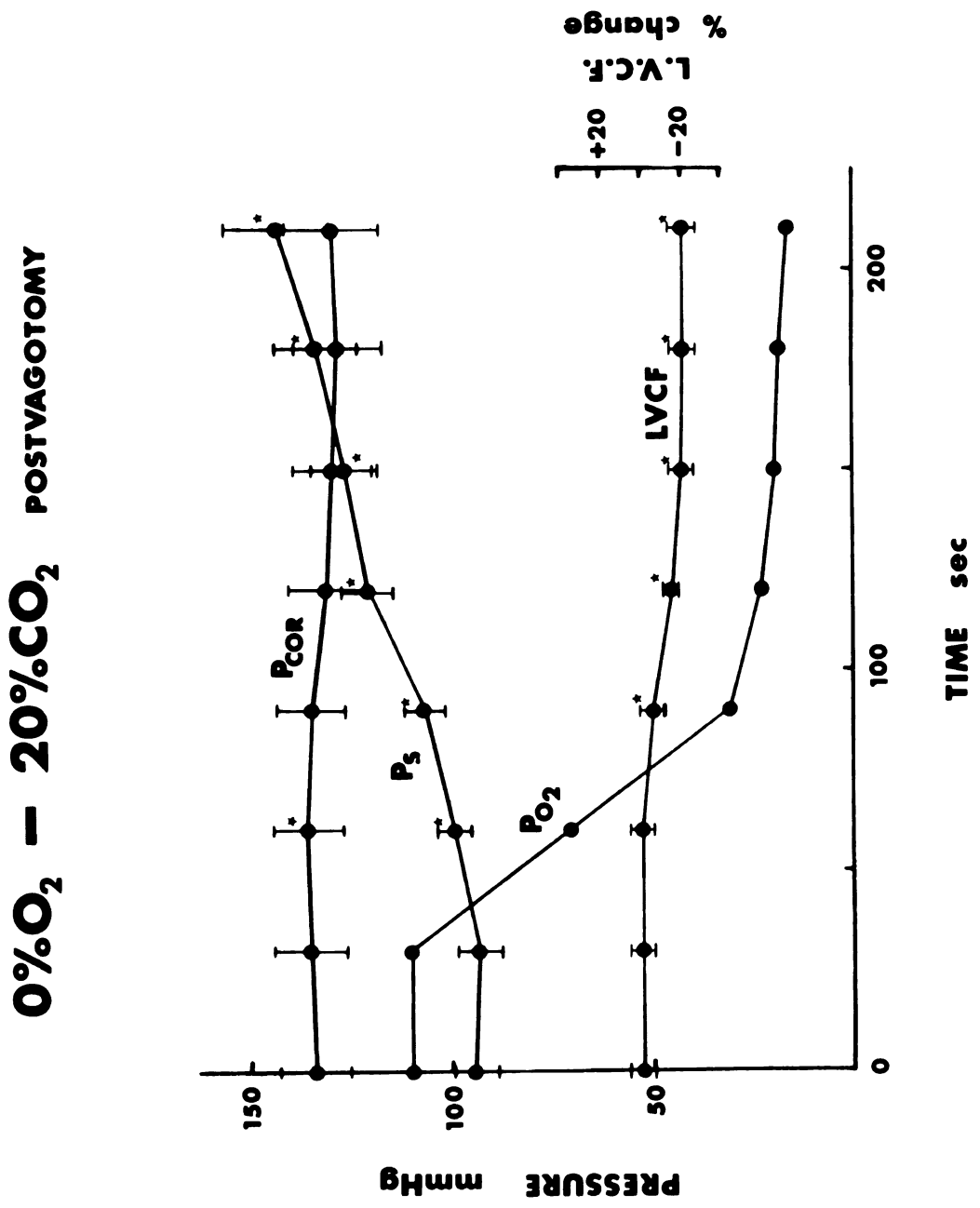
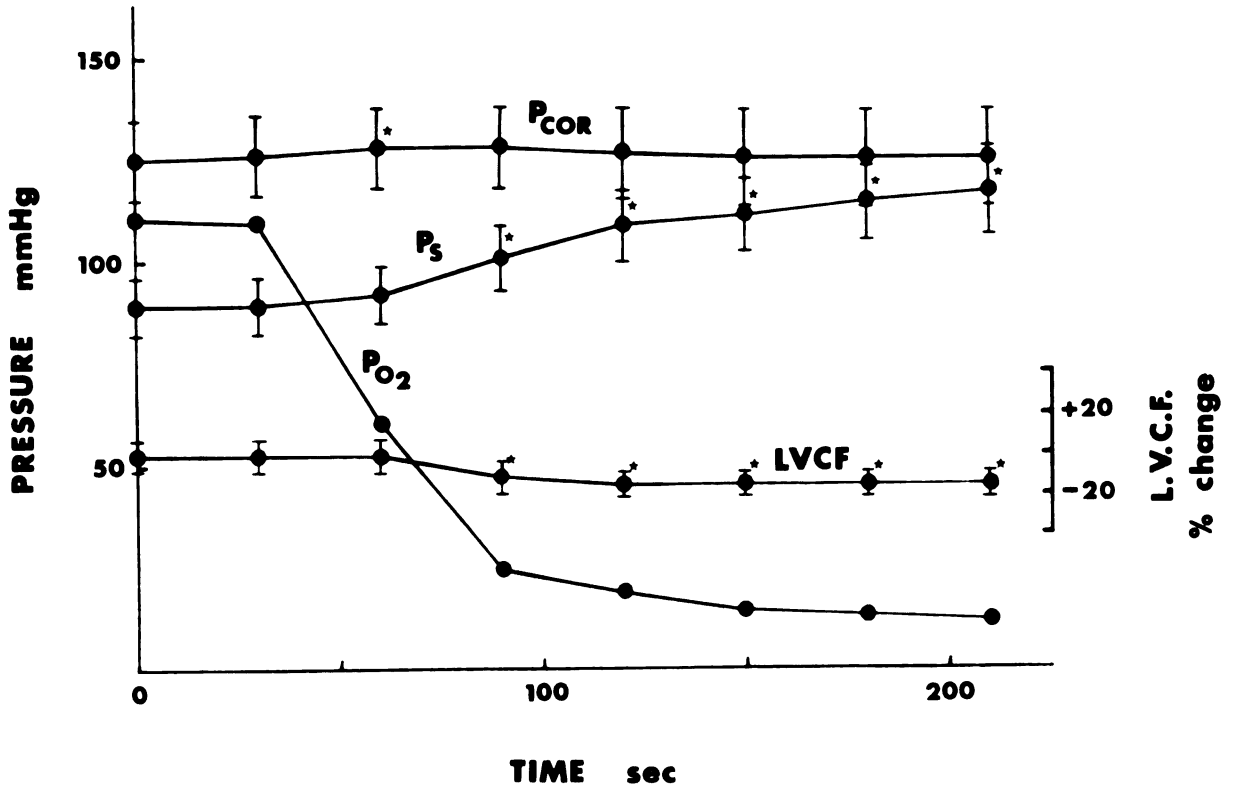

0%O2 — 20%CO2 POSTVAGOTOMY
PRESSURE mmHg
150
100
50
0
100
200
TIME sec
PCOR
PS
PO2
LVCF
L.V.C.F. % change
+20
−20
Means ± SE.
* P<.05 (Student's t test for paired observations)

Figure 12

Figure 13. Average coronary vascular response to carotid chemoreceptor stimulation with hypoxic blood after vagotomy.

P_{COR} = coronary perfusion pressure.
P_S = systemic arterial pressure.
P_{O_2} = O_2 tension of carotid sinus blood.
LVCF = left ventricular contractile force.
Mean coronary blood flow = 118 ml/min.
n = 10.

$0\%O_2 - 5\%CO_2$ POSTVAGOTOMY



Means ± SE.

** P<.05 (Student's t test for paired observations)*

Figure 13

increased significantly from 90 to 210 sec. Coronary sinus perfusion pressure was significantly increased at 60 sec but then gradually decreased during the remainder of the experimental period. Left ventricular contractile force decreased significantly from 90 sec onward, reaching a point 14% below control by 210 sec. The heart rate was unchanged (158 to 157/min).

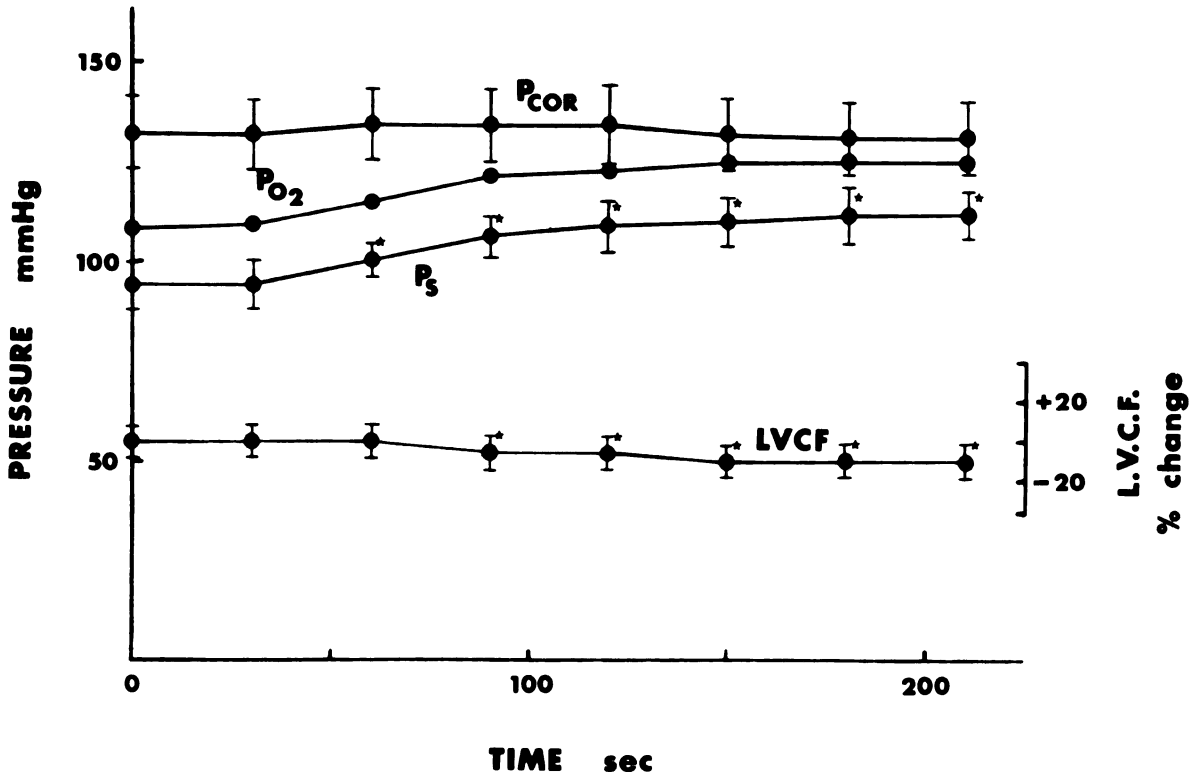
The average responses to hypercapnic chemoreceptor stimulation in nine dogs after vagotomy are presented in Figure 14. The P_{O_2} of the carotid sinus blood rose, probably due to the Bohr effect. The sinus blood pH decreased from 7.37 to 6.92. Systemic pressure increased significantly from 60 sec onward while coronary perfusion pressure showed no significant change. Left ventricular contractile force decreased significantly from 90 sec onward, reaching a point 9% below control by 210 sec. The heart rate was unchanged (158/min).

A second series of heart studies was carried out on vagotomized animals in which graded carotid chemoreceptor stimulation was accomplished by perfusing the chemoreceptors with the combined hypoxic-hypercapnic blood and with blood having varying degrees of hypoxia and hypercapnia. Figure 15 is a representative record showing the responses of the systemic pressure, coronary perfusion pressure and left ventricular contractile force to ventilation of the extracorporeal lung with the hypoxic-hypercapnic gas (0% O_2 - 20% CO_2) after vagotomy. Following the control period, ventilation

Figure 14. Average coronary vascular response to carotid chemoreceptor stimulation with hypercapnic blood after vagotomy.

P_{COR} = coronary perfusion pressure.
P_S = systemic arterial pressure.
P_{O_2} = O_2 tension of carotid sinus blood.
LVCF = left ventricular contractile force.
Mean coronary blood flow = 118 ml/min.
n = 9.

$20\%O_2 - 20\%CO_2$ POSTVAGOTOMY



Means ± SE.

**P<.05 (Student's t test for paired observations)*

Figure 14

Figure 15. Representative coronary vascular response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.
pH = pH of sinus blood.
P_S = systemic arterial pressure.
LVCF = left ventricular contractile force.
P_{COR} = coronary perfusion pressure.

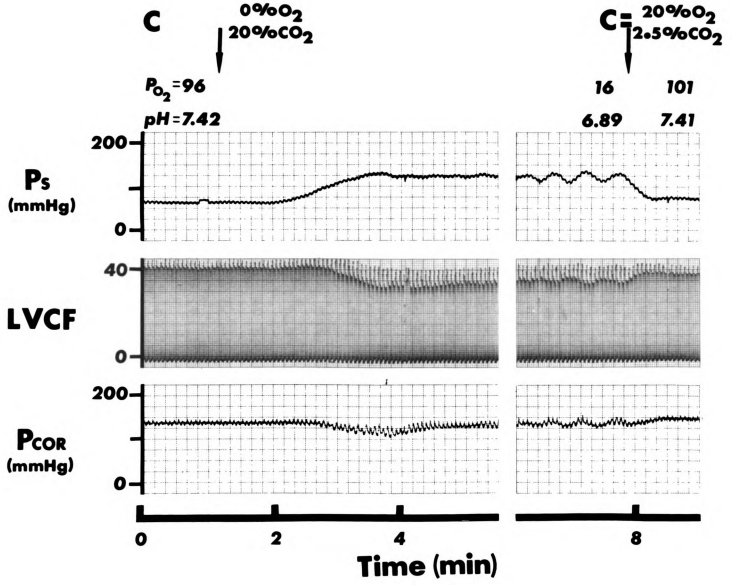

C
0%O2
20%CO2
C
20%O2
2.5%CO2
PO2=96
pH=7.42
16
101
6.89
7.41
200
Ps
(mmHg)
0
40
LVCF
0
200
PCOR
(mmHg)
0
0
2
4
8
Time (min)

Figure 15

with the experimental gas was begun and the typical marked rise in systemic arterial pressure was observed as the pH and P_{O_2} of the sinus blood fell. Left ventricular contractile force decreased remaining well below the control level. In this animal, the coronary perfusion pressure showed a transient decrease followed by a return to near control value. Upon returning to the control gas, systemic pressure rapidly decreased toward control as the carotid sinus pH and P_{O_2} returned to control values. Left ventricular contractile force increased as the coronary perfusion pressure rose to a level slightly above the control level.

Figure 16 is a representative record showing responses to a reduced degree of hypoxic-hypercapnia (10% O_2 - 10% CO_2). Following the control period the extracorporeal lung was ventilated with the experimental gas, which produced roughly 50% of the fall in carotid sinus blood pH and P_{O_2} obtained with the previous gas mixture. At a constant carotid sinus pressure, systemic pressure increased. Left ventricular contractile force fell slightly while coronary perfusion pressure was unchanged. Upon returning to the control gas, systemic pressure rapidly returned to control. Left ventricular contractile force rose to a level above control while coronary perfusion pressure remained unaltered.

Representative responses produced by chemoreceptor stimulation with a less hypercapnic gas mixture (20% O_2 - 10% CO_2) than that employed in the first series of coronary

Figure 16. Representative coronary vascular response to carotid chemoreceptor stimulation with less hypoxic-hypercapnic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.

pH = pH of sinus blood.

P_S = systemic arterial pressure.

LVCF = left ventricular contractile force.

P_{COR} = coronary perfusion pressure.

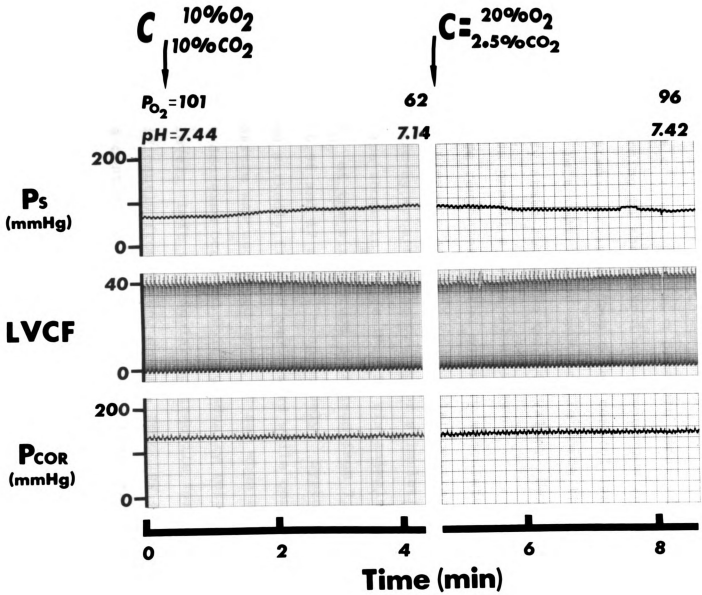

C
10%O2
10%CO2
C=
20%O2
2.5%CO2
PO2=101
62
96
pH=7.44
7.14
7.42
200
0
PS
(mmHg)
40
0
LVCF
200
0
PCOR
(mmHg)
0
2
4
6
8
Time (min)

Figure 16

studies (20% O_2 - 20% CO_2) is shown in Figure 17. At a constant carotid sinus pressure, systemic pressure rose as the sinus blood pH fell. Left ventricular contractile force decreased while coronary perfusion pressure remained unchanged. Returning to the control gas produced a rapid decrease in systemic pressure toward the control level and an increase in left ventricular contractile force that reached a steady state above the control value. Coronary artery perfusion pressure remained unchanged.

The average responses of the coronary vasculature, systemic blood pressure and left ventricular contractile force to hypoxic-hypercapnic chemoreceptor stimulation following vagotomy are shown in Figure 18. In six animals, the mean pH and P_{O_2} of the sinus blood decreased from 7.43 and 105 mm Hg to 6.96 and 17 mm Hg, respectively. Systemic pressure increased markedly from 60 sec onward while coronary perfusion pressure was unchanged until 90 sec when a transient insignificant decrease occurred which gradually returned to the control level. Left ventricular contractile force decreased significantly from 90 sec onward, reaching a point 27% below the control level. No change in heart rate was observed (141/min).

Figure 19 shows the average responses to chemoreceptor stimulation with a reduced degree of hypoxic-hypercapnia (10% O_2 - 10% CO_2). The mean pH and P_{O_2} of the carotid sinus blood decreased from 7.45 and 108 mm Hg to 7.15 and 63 mm Hg,

Figure 17. Representative coronary vascular response to carotid chemoreceptor stimulation with hypercapnic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.

pH = pH of sinus blood.

P_S = systemic arterial pressure.

LVCF = left ventricular contractile force.

P_{COR} = coronary perfusion pressure.

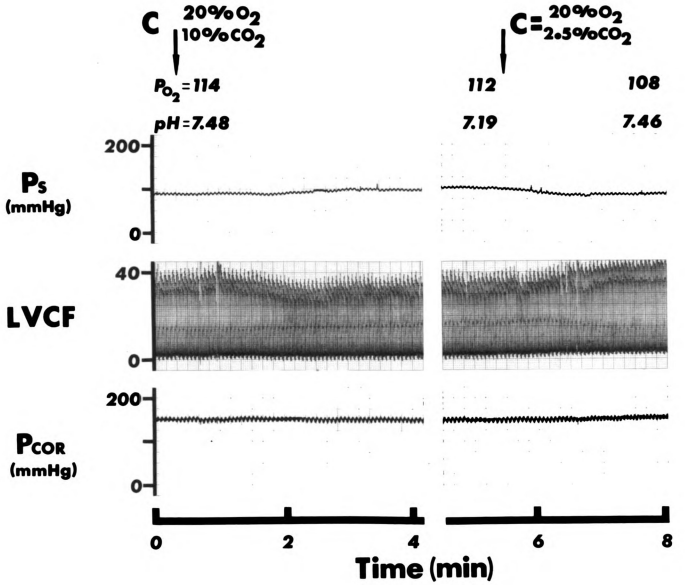

C
20%O2
10%CO2
C=20%O2
2.5%CO2
Po2=114
112
108
pH=7.48
7.19
7.46
200
Ps
(mmHg)
0
40
LVCF
0
200
PCOR
(mmHg)
0
0
2
4
6
8
Time (min)

Figure 17

Figure 18. Average coronary vascular response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood after vagotomy.

P_S = systemic arterial pressure.

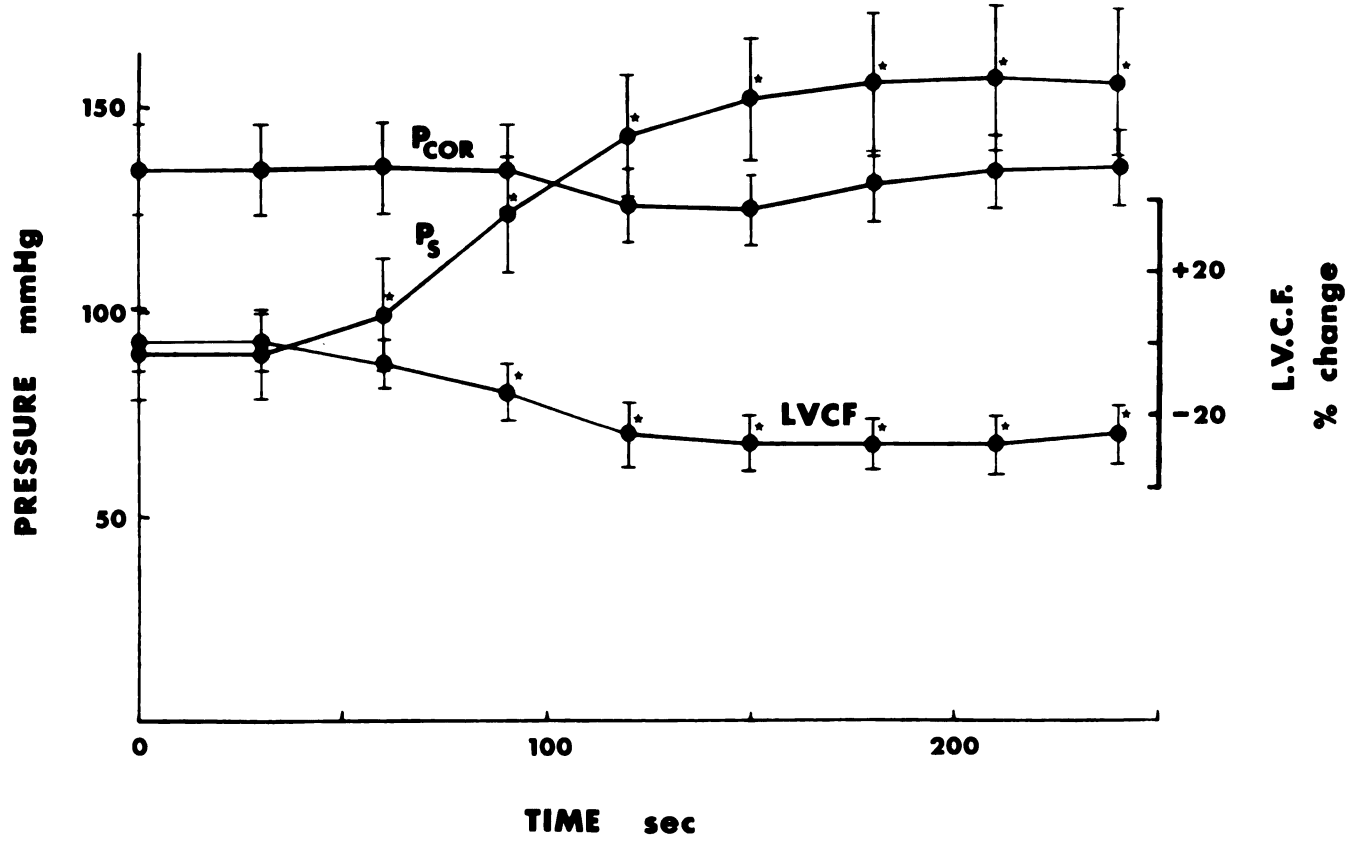
P_{COR} = coronary perfusion pressure.

LVCF = left ventricular contractile force.

Mean coronary blood flow = 115 ml/min.

n = 6.

$0\%O_2 - 20\%CO_2$ POSTVAGOTOMY



Means ± SE.

** P<.05 (Student's t test for paired observations)*

Figure 18

Figure 19. Average coronary vascular response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood after vagotomy.

P_S = systemic arterial pressure.

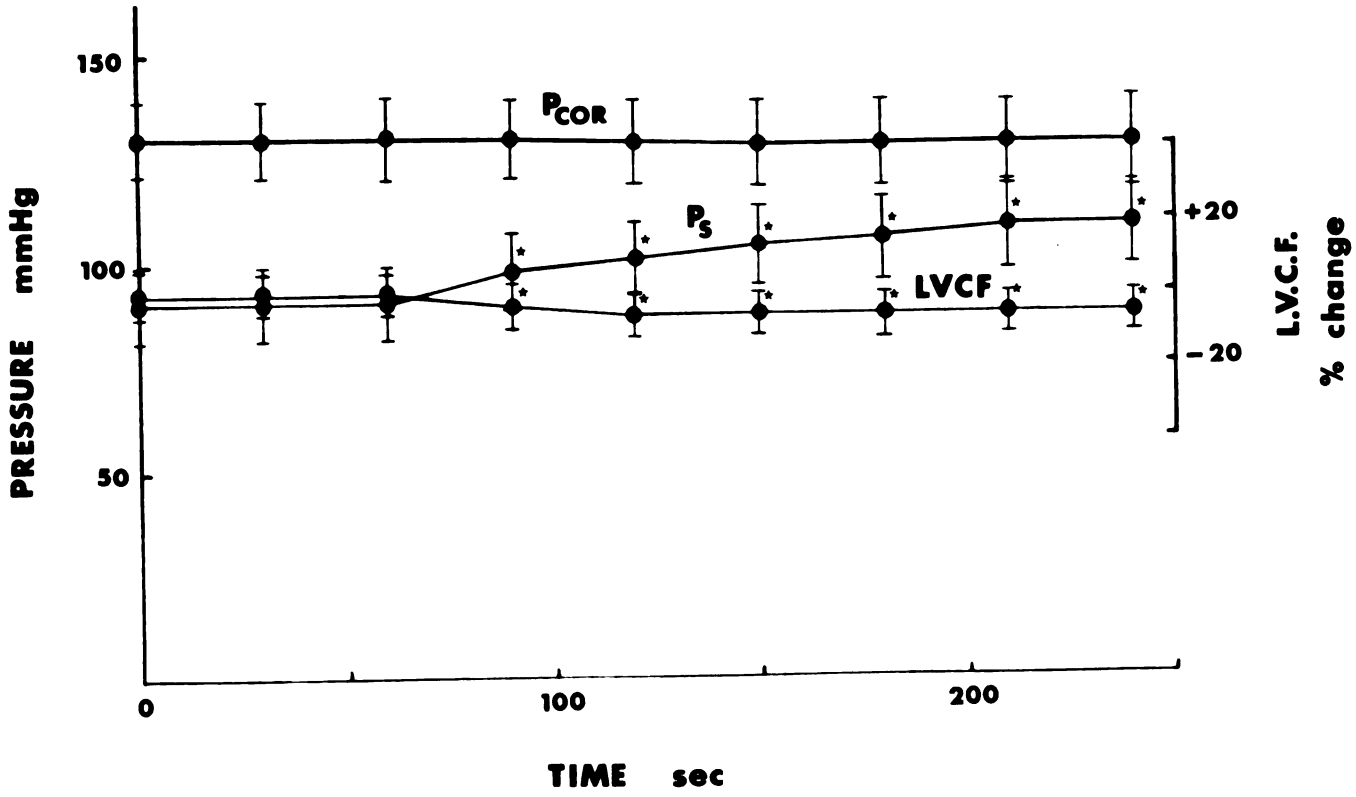
P_{COR} = coronary perfusion pressure.

LVCF = left ventricular contractile force.

Mean coronary blood flow = 115 ml/min.

n = 6.

$10\%O_2 - 10\%CO_2$ POSTVAGOTOMY



Means ± SE.

** P<.05 (Student's t test for paired observations)*

Figure 19

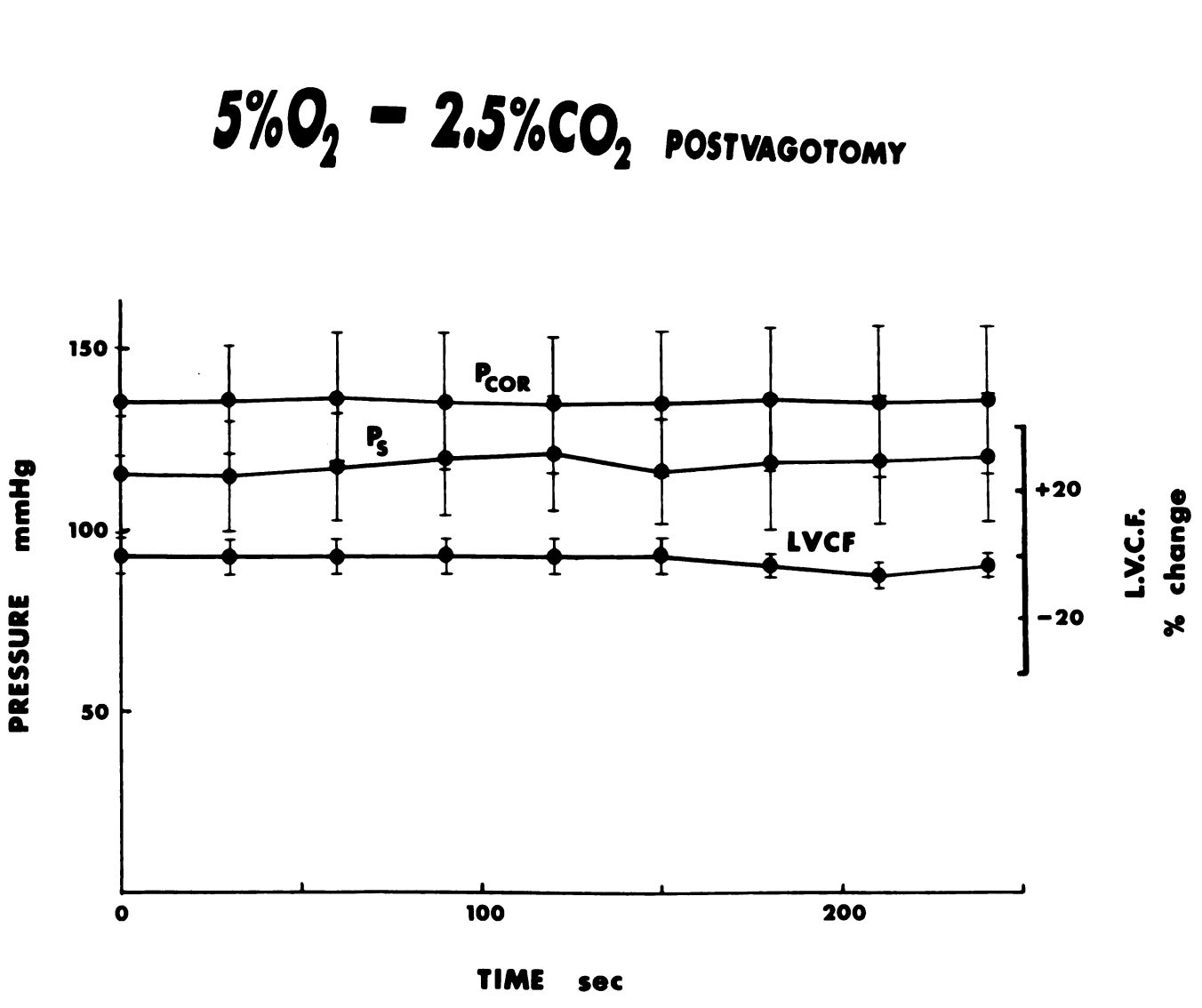
respectively. Systemic arterial pressure increased from 90 sec on while there was no change in coronary perfusion pressure. Left ventricular contractile force decreased significantly from 90 sec onward, reaching a point 5% below the control level. The change in heart rate from 140 to 142/min was not significant.

The average responses to varying degree of hypoxic chemoreceptor stimulation are shown in Figures 20 and 21. Hypoxic stimulation by 5% O_2 - $2\frac{1}{2}$% CO_2 in two animals and 10% O_2 - $2\frac{1}{2}$% CO_2 in three animals produced no changes in systemic pressure, coronary perfusion pressure or left ventricular contractile force. During carotid sinus hypoxia induced by 5% O_2 the mean pH and P_{O_2} of the carotid sinus blood were altered from 7.44 and 111 mm Hg to 7.45 and 38 mm Hg, respectively. During hypoxia induced by 10% O_2 the mean pH and P_{O_2} were altered from 7.44 and 111 mm Hg to 7.43 and 45 mm Hg, respectively. Changes in heart rate during ventilation with 5% O_2 (139 to 141/min) and 10% O_2 (154 to 151/min) were not significant.

Figure 22 shows the average responses to a lesser degree of hypercapnic chemoreceptor stimulation. Systemic pressure increased from 60 sec onward. Coronary perfusion pressure varied with signigicant increases only at 60, 90, 180 and 210 sec. Left ventricular contractile force declined gradually becoming significant at 150 sec. By 240 sec it was 6% below the control value. The pH and P_{O_2} of the carotid sinus blood

Figure 20. Average coronary vascular response to carotid chemoreceptor stimulation with hypoxic blood after vagotomy.

P_S = systemic arterial pressure.
P_{COR} = coronary perfusion pressure.
LVCF = left ventricular contractile force.
Mean coronary blood flow = 124 ml/min.
n = 2.



Means ± SE.

** p<.05 (Student's t test for paired observations)*

Figure 20

Figure 21. Average coronary vascular response to carotid chemoreceptor stimulation with a less hypoxic blood after vagotomy.

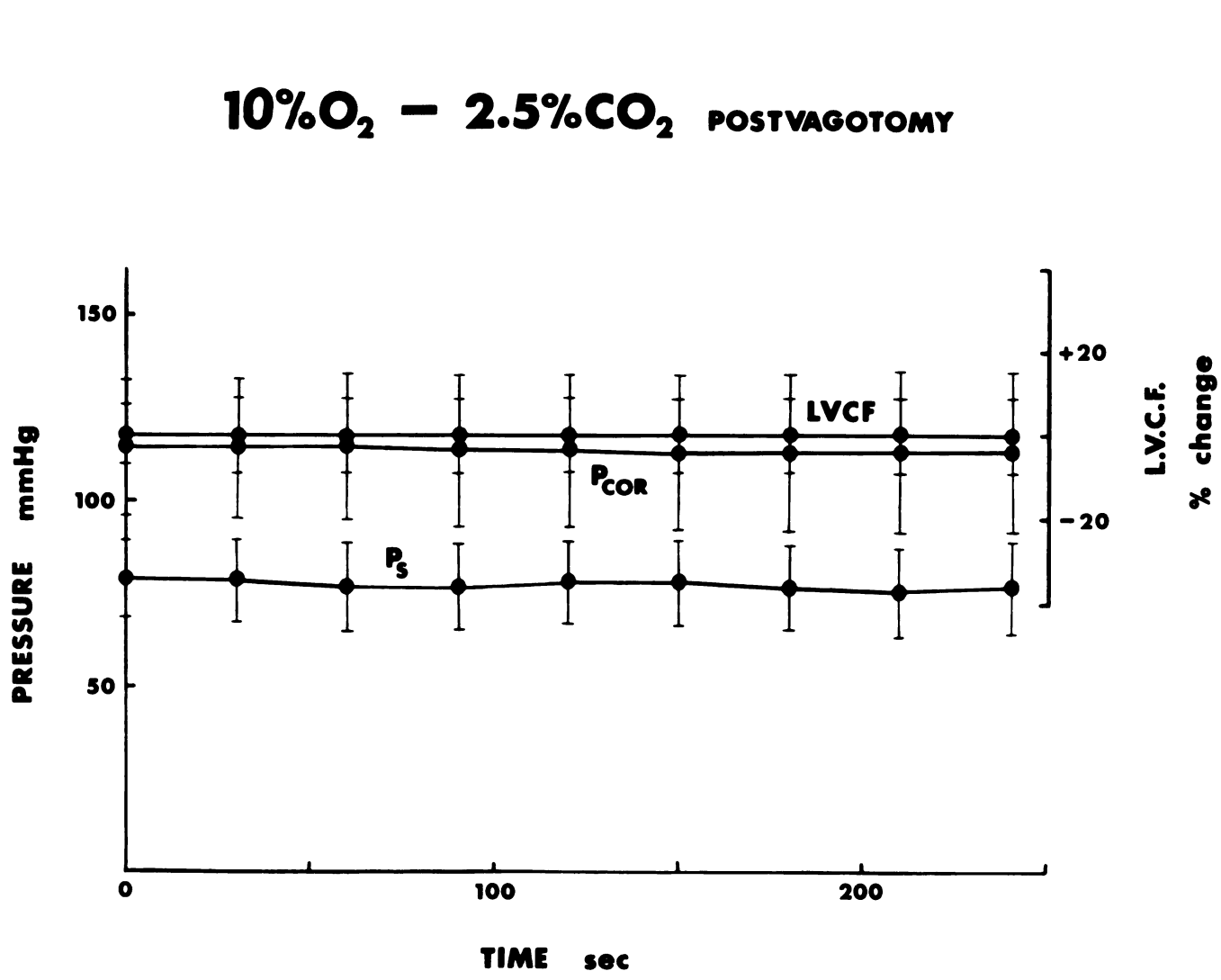
P_S = systemic arterial pressure.

P_{COR} = coronary perfusion pressure.

LVCF = left ventricular contractile force.

Mean coronary blood flow = 131 ml/min.

n = 3.



Means ± SE.

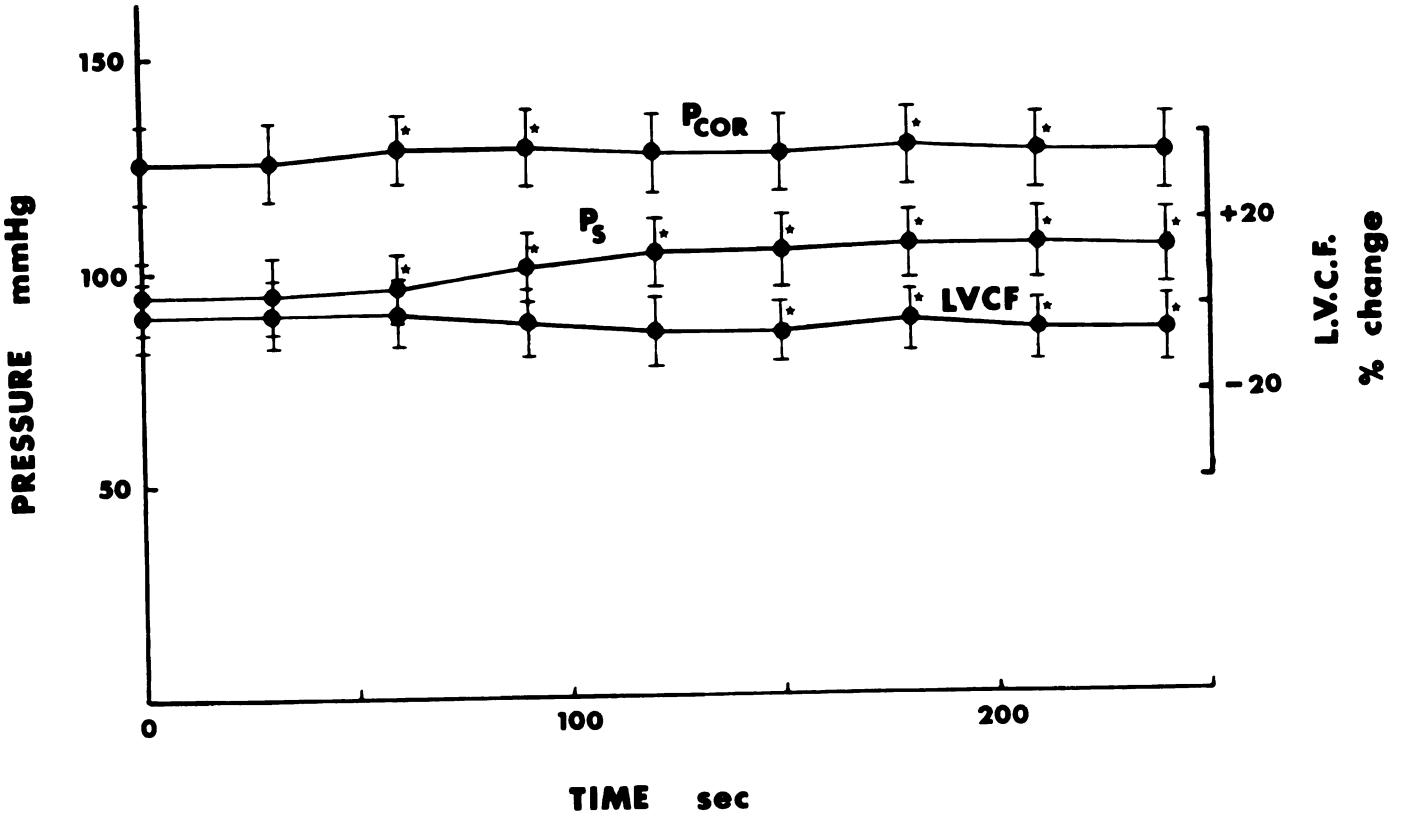
** P<.05 (Student's t test for paired observations)*

Figure 21

Figure 22. Average coronary vascular response to carotid chemoreceptor stimulation with hypercapnic blood after vagotomy.

P_S = systemic arterial pressure.
P_{COR} = coronary perfusion pressure.
LVCF = left ventricular contractile force.
Mean coronary blood flow = 115 ml/min.
n = 6.

$20\%O_2 - 10\%CO_2$ POSTVAGOTOMY



Means ± SE.

** p<.05 (Student's t test for paired observations)*

Figure 22

changed from 7.45 to 109 mm Hg to 7.17 and 112 mm Hg, respectively. The heart rate remained constant (141/min).

An additional parameter, the Q-T interval of the EKG, was monitored in the second heart study. Data from six animals showed no significant alteration of the lead II Q-T interval by any of the chemoreceptor stimuli.

Gracilis--Hindpaw

Table 6 presents the data from two animals showing the responses of the isolated, perfused hindpaw and gracilis muscle to perfusion of the carotid chemoreceptors with hypoxic-hypercapnic blood before and after vagotomy. The data show that systemic pressure, hindpaw and gracilis perfusion pressure are increased during chemoreceptor stimulation before and after vagotomy. Figure 23 is a representative tracing showing the responses of the hindpaw, gracilis muscle and systemic blood pressure to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood after vagotomy. After a control period the isolated lung was ventilated with 0% O_2 - 20% CO_2. As systemic arterial pressure rose, carotid sinus perfusion pressure was maintained as constant as possible. Gracilis artery and cranial tibial artery perfusion pressure increased during stimulation. Upon returning to the control gas, systemic pressure, gracilis artery and paw perfusion pressure returned to control levels.

Table 6. Average responses of isolated hindpaw and gracilis muscle to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before and after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_{paw} = hindpaw perfusion pressure. $P_{gracilis}$ = gracilis artery pressure. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. Mean hindpaw blood flow = 26 ml/min. Mean gracilis artery blood flow = 11 ml/min.

	VENTILATORY MIXTURE (ISOLATED LUNG)	P_{CS}	P_S	P_{paw}	$P_{gracilis}$	P_{O_2}	pH
		BEFORE VAGOTOMY					
DOG #1	20% O_2 - 2½% CO_2 (C)	129	129	93	109	110	7.51
	0% O_2 - 20% CO_2	125	139	127	129	24	7.10
DOG #2	20% O_2 - 2½% CO_2 (C)	99	103	100	65	104	-
	0% O_2 - 20% CO_2	101	135	105	96	24	7.07
		AFTER VAGOTOMY					
DOG #1	20% O_2 - 2½% CO_2 (C)	134	125	120	143	118	-
	0% O_2 - 20% CO_2	133	132	135	156	30	-
DOG #2	20% O_2 - 2½% CO_2 (C)	86	110	115	133	112	-
	0% O_2 - 20% CO_2	87	121	128	152	28	-

Figure 23. Representative responses of isolated hindpaw and gracilis muscle to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood in a vagotomized dog.

P_{O_2} = O_2 tension of carotid sinus blood.

pH = pH of sinus blood.

P_S = systemic arterial pressure.

P_{CS} = carotid sinus pressure.

$P_{gracilis}$ = gracilis artery perfusion pressure.

P_{paw} = hindpaw perfusion pressure.

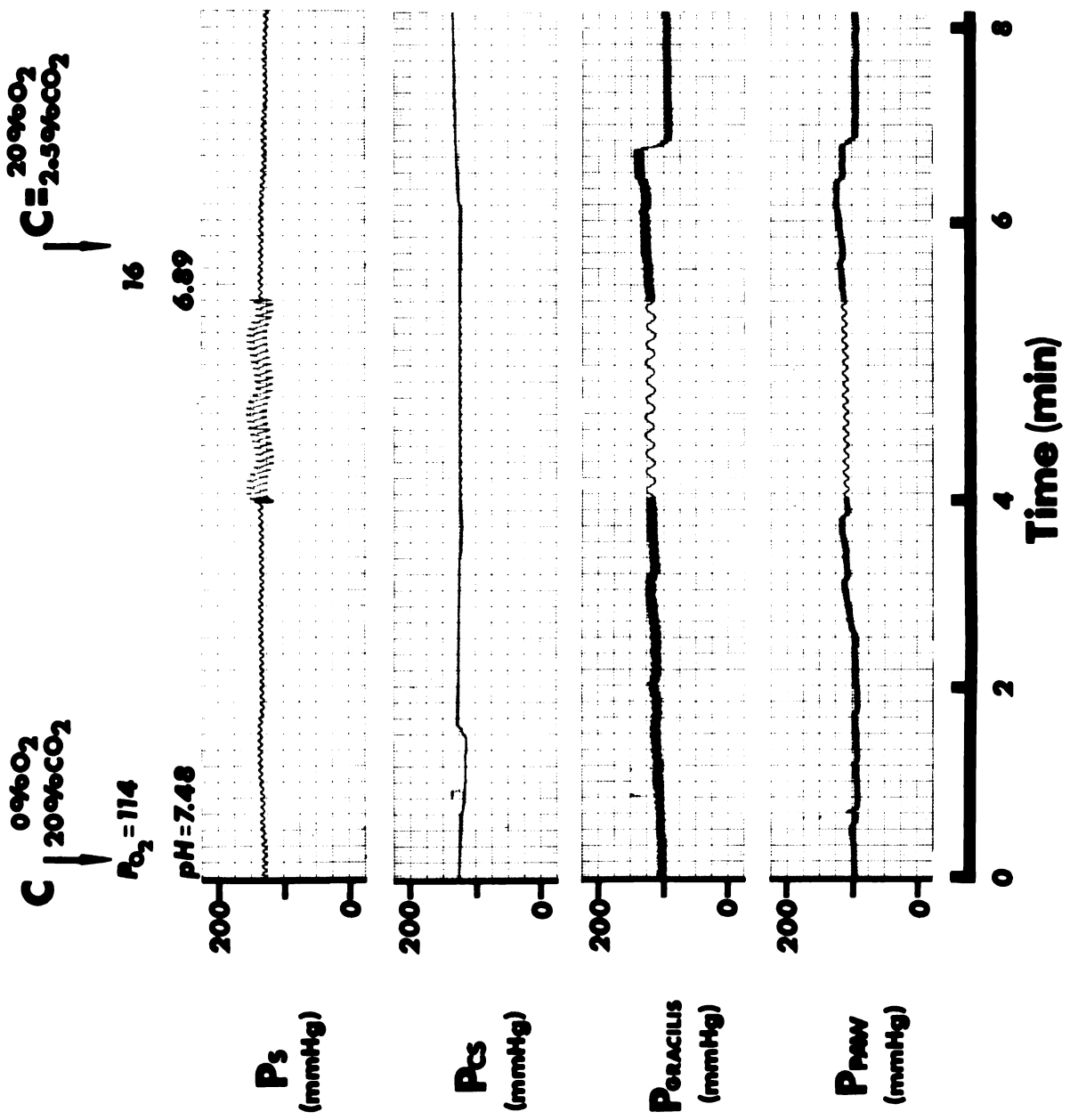

C 0%O2 20%CO2
PO2=114
pH=7.48
C=20%O2 2.5%CO2
16
6.89
PS (mmHg)
PCS (mmHg)
PBACILLUS (mmHg)
PH2O (mmHg)
200
0
0
2
4
6
8
Time (min)

Figure 23

Table 7 presents the results from the three animals in the second series of hindpaw studies in which the skin of the hindpaw was circumferentially sectioned and the cranial tibial arteries perfused. Hindpaw perfusion pressure did not appear to change during stimulation before vagotomy and only increased slightly following vagotomy.

The results from the two animals in the third series of studies are presented in Table 8. In this series the hindpaw skin remained intact and the paw was perfused through the cranial tibial artery. The data show that the systemic pressure and paw perfusion pressure increased during chemoreceptor stimulation before and after vagotomy. Figure 24 is a representative record of the responses from the third series of hindpaw studies. Before vagotomy, ventilation of the isolated lung with 0% O_2 - 20% CO_2 produced increases in systemic pressure and paw perfusion pressure. Ventilation with the same gas mixture following vagotomy produced a greater increase in systemic pressure and paw perfusion pressure. Ventilation with 10% O_2 - 10% CO_2 produced a lesser degree of hypoxic-hypercapnia. This induced a smaller increase in systemic pressure and paw perfusion pressure.

Table 7. Average hindpaw response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before and after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_{paw} = hindpaw perfusion pressure. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. Mean hindpaw blood flow = 41 ml/min.

	VENTILATORY MIXTURE (ISOLATED LUNG)	P_{CS}	P_S	P_{paw}	P_{O_2}	pH
		BEFORE VAGOTOMY				
DOG #1	20% O_2 - 2½% CO_2 (C)	100	132	85	106	-
	0% O_2 - 20% CO_2	100	148	85	20	-
DOG #2	20% O_2 - 2½% CO_2 (C)	145	167	145	116	-
	0% O_2 - 20% CO_2	148	173	150	21	-
DOG #3	20% O_2 - 2½% CO_2 (C)	100	116	75	98	7.57
	0% O_2 - 20% CO_2	100	130	75	16	6.99
		AFTER VAGOTOMY				
DOG #1	20% O_2 - 2½% CO_2 (C)	114	142	90	100	-
	0% O_2 - 20% CO_2	115	180	93	19	-
DOG #2	20% O_2 - 2½% CO_2 (C)	147	157	128	123	-
	0% O_2 - 20% CO_2	150	169	138	23	-
DOG #3	20% O_2 - 2½% CO_2 (C)	105	128	85	113	7.46
	0% O_2 - 20% CO_2	107	150	88	19	6.98

Table 8. *Average hindpaw response to carotid chemoreceptor stimulation* with hypoxic-hypercapnic blood before and after vagotomy. P_{CS} = carotid sinus pressure. P_S = systemic arterial pressure. P_{paw} = hindpaw perfusion pressure. P_{O_2} = O_2 tension of carotid sinus blood. pH = pH of sinus blood. Mean hindpaw blood flow = 44 ml/min.

	VENTILATORY MIXTURE (ISOLATED LUNG)	P_{CS}	P_S	P_{paw}	P_{O_2}	pH
		BEFORE VAGOTOMY				
DOG #1	20% O_2 - 2½% CO_2 (C)	125	132	102	100	7.51
	0% O_2 - 20% CO_2	128	155	123	19	7.06
DOG #2	20% O_2 - 2½% CO_2 (C)	135	130	100	114	7.47
	0% O_2 - 20% CO_2	133	160	120	28	7.03
		AFTER VAGOTOMY				
DOG #1	20% O_2 - 2½% CO_2 (C)	119	120	130	97	7.50
	0% O_2 - 20% CO_2	120	167	172	18	7.03
DOG #2	20% O_2 - 2½% CO_2 (C)	105	105	145	98	7.44
	0% O_2 - 20% CO_2	110	190	193	22	7.06

Figure 24. Representative hindpaw response to carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before and after vagotomy.

P_{O_2} = O_2 tension of carotid sinus blood.

pH = pH of sinus blood.

P_S = systemic arterial pressure.

P_{CS} = carotid sinus pressure.

P_{paw}= hindpaw perfusion pressure.

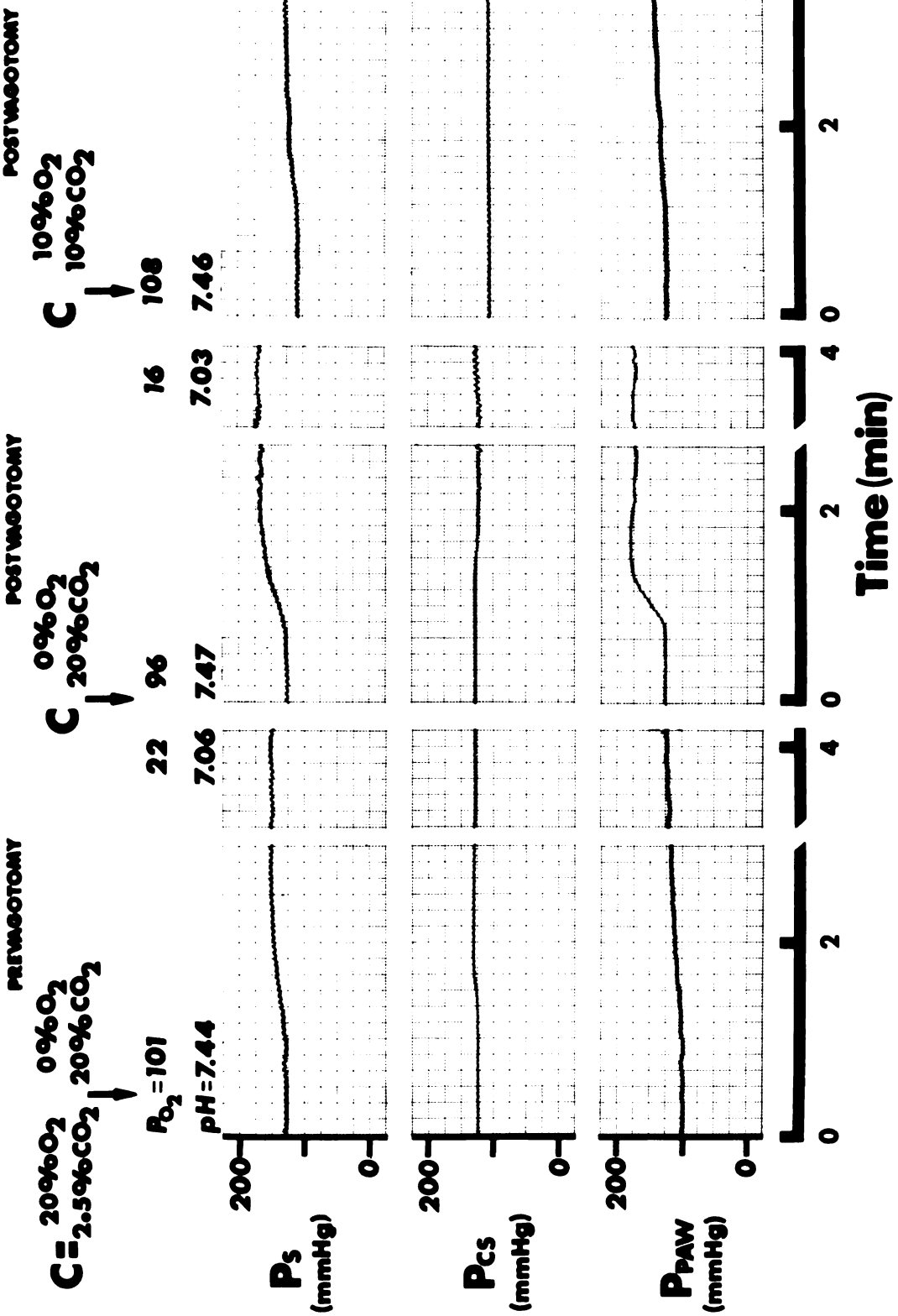

PREMASOTOMY
POSTMASOTOMY
POSTMASOTOMY
C 20%O2 2.5%CO2
0%O2 20%CO2
0%O2 20%CO2
10%O2 10%CO2
PaO2=101
pH=7.44
22
7.06
96
7.47
16
7.03
108
7.46
62
7.14
PS (mmHg)
PCS (mmHg)
PPAW (mmHg)
200
0
0
2
4
Time (min)

Figure 24

DISCUSSION

Carotid body stimulation by hypoxic-hypercapnic blood before vagotomy increased vascular resistance in the kidney but caused no change in resistance in the forelimb, intestine or coronary vasculature (Table 9). After vagotomy, hypoxic, hypercapnic and hypoxic-hypercapnic stimulation of the carotid bodies increased vascular resistance in the forelimb, intestine and kidney but not in the heart. Systemic arterial pressure increased during hypoxic-hypercapnic chemoreceptor stimulation before vagotomy and increased after vagotomy during stimulation with hypoxia, hypoxic-hypercapnia and hypercapnia. Heart rate was not consistently affected by chemoreceptor stimulation either before or after vagotomy.

This study differs from other investigations of the reflex vascular effects of carotid chemoreceptor stimulation in that selective, physiologic stimuli were applied to the innervated carotid bodies rather than to the entire animal. Selective stimulation was accomplished by varying the oxygen and carbon dioxide tension of autologous blood perfusing the carotid sinuses. This was done by means of an extracorporeal lung ventilated with various O_2 and CO_2 gas mixtures. The use of this approach probably results in peripheral responses

Table 9. Change in vascular resistance in forelimb, ileum, kidney and coronary vascular beds during carotid chemoreceptor stimulation before and after vagotomy.

Ventilatory Mixture (Isolated Lung)	Forelimb	Ileum	Kidney	Coronary
PERCENT CHANGE IN VASCULAR RESISTANCE BEFORE VAGOTOMY				
0% O_2 - 20% CO_2	4.8 ± 2.3†	4.3 ± 4.0†	56.0 ± 21.7*	-
PERCENT CHANGE IN VASCULAR RESISTANCE AFTER VAGOTOMY				
0% O_2 - 20% CO_2	21.7 ± 7.6*†	32.9 ± 13.8*	68.5 ± 16.5*	-
0% O_2 - 5% CO_2	9.9 ± 4.0*†	13.1 ± 3.8*†	47.3 ± 15.5*	-
20% O_2 - 20% CO_2	9.5 ± 2.3*†	17.4 ± 9.8*	44.7 ± 15.4*	-

Values are means ± SE.

*$P < 0.05$ (Student's t test for paired observations).

$P < 0.05$ vs. kidney values (Student's t test modified for unpaired observations and unequal variances).

-No significant change (Student's t test for paired observations).

which are more representative of chemoreceptor induced responses in the intact animal than responses evoked by unilateral carotid sinus perfusion (46), or bilateral perfusion with heterologous blood (21) or pharmacologic agents (46). The importance of using a bilateral preparation is suggested by the work of Sagawa and Watanabe (56) showing that impulses generated in the left and right carotid sinus nerves during baroreceptor stimulation summate in the central nervous system.

It is possible that ligation of both internal carotid arteries in the surgical preparation reduced the blood flow to the central vasomotor areas (57,58). However, Green and Rapela (75) reported that because of the extensive collateral blood supply provided by the vertebral arteries, bilateral common carotid artery occlusion did not lower vertebral artery perfusion pressure more than to about 90% of systemic arterial pressure.

The use of the carotid sinus perfusion circuit containing an isolated lung has two advantages over procedures previously employed to determine the effects of carotid body chemoreceptor stimulation. First, the method allows the use of autologous blood and eliminates the necessity of using stagnated blood or non-physiologic perfusates. Second, it permits rapid changes in local blood gas content without detectable changes in systemic blood gas concentrations. Normal systemic blood gas content is maintained because the blood leaving the sinus perfusion circuit is returned to the animal's venous

circulation via the jugular vein. Since the volume of blood flowing through the perfusion circuit is relatively small, amounting to less than 5% of the animal's cardiac output, abnormalities in the O_2 and CO_2 content of the blood are corrected during passage through the animal's pulmonary circulation.

While many investigators have reported the reflex responses to carotid chemoreceptor stimulation few studies have employed selective carotid body stimulation. This makes a comparison of the data inappropriate since alteration of the systemic O_2 and CO_2 blood gas content could produce a combination of three effects: 1) local vascular effects (60, 62-64), 2) reflex vascular effects due to central nervous system chemoreceptor stimulation (4), and 3) reflex effects due to peripheral arterial chemoreceptor stimulation (4). Of the few studies in which selective carotid chemoreceptor stimulation was used, most employed pharmacologic or non-physiologic rather than physiologic stimuli which also renders a strict comparison with our findings inappropriate.

The comparison of results is also complicated by the use of different anesthetics. Some investigators employ chloralose anesthesia (23,40,42,46) while we employed pentobarbital anesthesia in the present study. Pentobarbital is reported to depress centrally mediated reflexes while chloralose exaggerates these reflexes (52). Recently, Cox (73,74) compared the influences of chloralose and pentobarbital anesthesia on

cardiovascular function in the dog. The results showed chloralose anesthesia to produce no change in systemic hemodynamics. The heart rate responses to hypotension and hypertension were exaggerated. The results showed that the only hemodynamic effects of pentobarbital anesthesia were a significant increase in heart rate and slight decrease in stroke volume. Pentobarbital depressed smooth muscle reactivity and reduced the sensitivity of the peripheral mechanoreceptor reflexes.

The effects of carotid chemoreceptor stimulation were studies before and following vagotomy. This was done in order to determine the role of the carotid chemoreceptors without the reflex buffering influences of the aortic baroreceptors and chemoreceptors. Efforts were made to maintain a constant perfusion pressure in the carotid sinuses to prevent excitation of the carotid sinus baroreceptors.

The rise in vascular resistance, during chemoreceptor stimulation, observed in the kidney before vagotomy and in the forelimb, intestine and kidney following vagotomy appears to be the result of active changes in blood vessel caliber. An active change is indicated since resistance rose concomitant with an increased transmural pressure which would favor a passive decrease in vascular resistance. Increases in vascular resistance might have been augmented by increases in blood viscosity via changes in hematocrit subsequent to splenic discharge. The present findings suggest that carotid chemoreceptor stimulation results in responses that are

mediated over sympathetic nerves with a contribution from increases in circulating catecholamines. The possibility of a withdrawal of parasympathetic activity can be ruled out since only a small proportion of the resistance vessels of the body receive parasympathetic innervation (70). Therefore, its effect on total vascular resistance is small. Sympathoadrenal mediation is indicated by the time course of the response to chemoreceptor stimulation. The rise in systemic arterial pressure and organ perfusion pressure concurrent with the change in blood gas tension, as indicated by the sinus P_{O_2}, suggests a neurogenic constrictor response. Frequently, a distinct secondary rise in pressure was observed. This was attributed to an increase in circulating catecholamines subsequent to adrenal discharge.

The increases in vascular resistance in the forelimb and intestine following vagotomy were similar in magnitude. However, the kidney vasculature appeared to be the most responsive to chemoreceptor stimulation of all of the vascular beds studied. Haddy and Scott (71) showed a greater sensitivity in the kidney to the systemic administration of epinephrine and norepinephrine than in the intestine or hindlimb. The greater responsiveness of the kidney could be related to an augmenting pressor action of angiotension subsequent to the release of renin. Vander (72) reported direct electrical stimulation of renal nerves and intravenous infusions of

norepinephrine and epinephrine, while keeping aortic pressure constant, to increase renin release from the kidney.

The responses evoked from the forelimb, kidney and intestinal vasculature during carotid chemoreceptor stimulation are directionally similar to the responses induced by carotid sinus hypotension. In the present study, a 30% increase in renal vascular resistance was produced when carotid sinus perfusion pressure was reduced from 102 to 47 mm Hg. Similarly, Fronek (65) reported increased mesenteric artery resistance during carotid sinus hypotension. DiSalvo et al. (59) reported increases in forelimb skin (56%) and muscle (31%) vascular resistances when perfusion pressure in the isolated carotid sinuses was reduced from 108 to 59 mm Hg.

Brachial and cephalic venous outflows in the forelimb study, where total limb inflow was constant, showed no change from control during chemoreceptor stimulation. The absence of a change in brachial and cephalic venous outflows during the increase in forelimb vascular resistance indicates that the muscle and skin vascular beds contributed about equally to the increase in forelimb resistance. Calvelo et al. reported increased vascular resistance in the gracilis muscle during carotid chemoreceptor stimulation with nicotine and cyanide. However, they reported that chemoreceptor stimulation induced vasodilation in the hindpaw (skin) that was unchanged or augmented by pharmacologic alpha blockade. This response in the skin vasculature is different from the results

obtained in the present work in which only constriction was seen. These differences could be explained if we failed to separate the skin and muscle in the forelimb. To test this possibility we employed an isolated skin and muscle preparation in the hindlimb similar to that used by Calvelo et al. (23). The results of these preliminary studies confirmed the vasoconstriction in skin. The discrepancy in these reports has yet to be resolved and could possibly be related to the anesthesia employed, that is, pentobarbital versus chloralose.[1]

The responses of the coronary vasculature to carotid chemoreceptor stimulation were investigated in two studies. One study examined the responses to stimulation with the hypoxic, hypoxic-hypercapnic and hypercapnic stimuli employed in the previous studies on the forelimb, intestine and kidney. The second study examined the responses of the coronary vasculature to chemoreceptor stimulation with blood that was less hypoxic, less hypoxic-hypercapnic or less hypercapnic than was employed in the first study. Carotid chemoreceptor stimulation before and following vagotomy produced no consistent changes in coronary vascular resistance. Hackett et al. (46) recently reported reflex coronary vasodilation during

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[1]In one experiment, using the same hindpaw preparation and anesthetic as that employed by Calvelo et al. we again observed vasoconstriction in skin during chemoreceptor stimulation.

carotid chemoreceptor stimulation with nicotine and cyanide, and during carotid sinus nerve stimulation. Ventricular pacing and AY-21,011 (a myocardio-selective beta-receptor antagonist) were used to minimize the chronotropic and inotropic responses to chemoreceptor stimulation. They reported that the intravenous administration of atropine blocked the reflex coronary dilator response and proposed the efferent pathway mediating the response to be through vagal cholinergic fibers. This difference in findings might be attributable to a differing response to physiologic versus pharmacologic chemoreceptor stimulation. DiSalvo et al. (61) reported no change in coronary vascular resistance in a natural flow coronary preparation when pressure in the isolated carotid sinuses was lowered from 87 to 48 mm Hg.

Since our data indicate no consistent change in coronary vascular resistance during carotid body stimulation concomitant with a fall in left ventricular contractile force, it appears that factors which produce vasoconstriction acted along with those producing vasodilation. The factors favoring vasoconstriction in this constant coronary blood flow preparation include 1) a decreased vasodilator metabolite concentration due to a fall in heart metabolism as indicated by the fall in ventricular contractile force (62) (the change in contractile force will be discussed in detail later), 2) a myogenic vasoconstriction (Bayliss effect) in response to an increased transmural pressure resulting from a fall in extravascular

pressure subsequent to a decrease in contractile force (66, 67), and 3) a decreased sympathetic tone to the heart (66). The factors favoring vasodilation include 1) an increase in circulating catecholamines and 2) a passive increase in vessel caliber due to a fall in extravascular pressure resulting from a decreased ventricular contractile force. The lack of a response in coronary resistance suggests that the above factors balance out to produce no net change.

The decrease in left ventricular contractile force observed during chemoreceptor stimulation was greater following vagotomy than before. DeGeest et al. (48) reported that hypoxic chemoreceptor stimulation before vagotomy diminished left ventricular contractile force in the paced, isovolumetric heart. However, they found the negative inotropic effect elicited by chemoreceptor stimulation to be abolished by cervical vagotomy suggesting mediation mainly by vagal pathways. Downing et al. (43) have also reported a decreased left ventricular contractility during hypoxic carotid chemoreceptor stimulation following vagotomy, however, these investigators did not study contractility before vagotomy. These investigators suggest the disparity in findings to be due to possible differences in the magnitude of concomitant excitation of the respiratory and vasomotor centers during chemoreceptor stimulation. They reported that, after vagotomy, it is likely that a diminution of sympathetic tone represents

the primary cardiac reflex effect of carotid chemoreceptor stimulation. Excitation of the respiratory centers resulting from chemoreceptor stimulation also tends to increase cardiac sympathetic activity thus producing a secondary cardiac effect. They conclude that in some cases the secondary cardiac effects due to respiratory center excitation may predominate over the primary cardiac effect of chemoreceptor stimulation. Hackett et al. (61) reported an increase in left ventricular dP/dt during unilateral carotid chemoreceptor stimulation with nicotine and cyanide before and after vagotomy. This difference in findings might again be attributable to a differing response to physiologic versus pharmacologic chemoreceptor stimulation.

While the data from these studies indicate a sympathoadrenal mediated vasoconstriction in the peripheral vasculature, the results indicate a concomitant selective diminution of sympathetic tone to the heart.

Mechanical factors in the heart could have contributed to the decrease in ventricular contractile force produced by carotid chemoreceptor stimulation. A diminished cardiac sympathetic tone could have been augmented by an increase in afterload of the heart since systemic pressure increased as contractile force fell.

Heart rate was measured during chemoreceptor stimulation before and after vagotomy in all experiments. The data indicated no consistent changes in heart rate during chemoreceptor

stimulation with any of the experimental gas mixtures. These results differ from the findings of many investigators (39,40-43),48) using a similar preparation with controlled ventilation. When respiration is controlled, carotid chemoreceptor stimulation produced bradycardia. Daly and Scott (40) and Downing (42) proposed that the primary reflex effect of carotid chemoreceptor stimulation on heart rate is a vagally induced bradycardia. This reflex bradycardia can be over-ridden by secondary mechanisms evoked by concomitant increases in respiration, changes in arterial pressure and circulating catecholamines (40,42,55). Since we held ventilatory rate and volume constant our findings on heart rate could be due to the type of anesthetic employed. Daly and Scott (40) and Downing (42) used chloralose anesthesia while our work was carried out with pentobarbital.

Carotid chemoreceptor stimulation with combined hypoxia and hypercapnia following vagotomy caused a greater increase in forelimb, intestine and kidney vascular resistance than was produced by hypoxia or hypercapnia alone (Table 9). Hypoxic-hypercapnic blood caused a 26% increase in forelimb vascular resistance while hypoxic or hypercapnic blood alone increased resistance by 12% and 11%, respectively. Before vagotomy, hypoxic-hypercapnic chemoreceptor stimulation increased renal vascular resistance by 56%. Following vagotomy, hypoxic-hypercapnic stimulation caused a 69% increase in renal resistance, while hypoxia and hypercapnia alone increased

resistance by 48% and 45%, respectively. Similarly, combined hypoxic-hypercapnic chemoreceptor stimulation caused a 33% increase in ileal vascular resistance, while hypoxia alone increased resistance by 13% and hypercapnia increased resistance by 17%.

The rise in systemic arterial pressure during carotid chemoreceptor stimulation may have resulted either from an increase in total peripheral resistance or cardiac output or a combination of both. Since cardiac output was not measured in this study it was not possible to determine total peripheral resistance. The reflex buffering effect produced by the aortic baro- and chemoreceptors probably attenuated the rise in systemic pressure before vagotomy. Although intestinal, skin and muscle vascular resistance was unchanged during chemoreceptor stimulation before vagotomy, kidney resistance was markedly elevated. Increases in resistance in other vascular beds which were not measured may also have contributed to a rise in total peripheral resistance. Following vagotomy, a rise in resistance in the intestine, kidney, skin and muscle also contributes to the rise in peripheral resistance during chemoreceptor stimulation.

SUMMARY AND CONCLUSIONS

The purpose of this study was to determine the reflex effects of selective, physiologic stimulation of the carotid body chemoreceptors on the vascular resistance of the forelimb, kidney, intestine and heart. Selective physiologic chemoreceptor stimulation was accomplished by varying the gas content of autologous blood perfusing the isolated carotid sinuses by means of an extracorporeal lung ventilated with various O_2 and CO_2 gas mixtures.

The reflex responses to carotid chemoreceptor stimulation were studied in the dog before and following vagotomy. Systemic arterial pressure increased during chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy. Following vagotomy, systemic pressure increased during carotid body stimulation with hypoxic, hypoxic-hypercapnic and hypercapnic blood. Carotid chemoreceptor stimulation with hypoxic-hypercapnic blood before vagotomy increased vascular resistance in the kidney but caused no change in resistance in the forelimb, intestine or coronary vasculature. After vagotomy, hypoxic, hypoxic-hypercapnic and hypercapnic chemoreceptor stimulation increased vascular resistance in the forelimb, intestine and kidney but not in the heart.

During hypoxic-hypercapnic chemoreceptor stimulation following vagotomy vascular resistance in the kidney increased 69% while forelimb and ileal resistance increased 26% and 33%, respectively. The absence of a change in skeletal muscle and skin blood flow in the forelimb preparation indicated that the skin and muscle vascular beds contributed about equally to the increase in forelimb resistance. To further examine the effects of chemoreceptor stimulation on the skin and skeletal muscle vasculature a gracilis muscle and hindpaw preparation was employed. The results of these preliminary studies indicated vasoconstriction in muscle and skin during hypoxic-hypercapnic chemoreceptor stimulation.

The rise in vascular resistance observed in the kidney before vagotomy and in the forelimb, intestine and kidney following vagotomy appeared to be the result of active changes in blood vessel caliber. The responses appear to be mediated over sympathetic nerves with a contribution from increased circulating catecholamines.

Changes in left ventricular contractile force during chemoreceptor stimulation were measured in a heart preparation having a constant coronary blood flow. Left ventricular contractile force decreased during chemoreceptor stimulation before and after vagotomy but larger reductions in contractile force were observed following vagotomy. The decrease in contractile force appears to be primarily the result of a

diminished sympathetic tone to the heart possibly augmented by an increased afterload. Heart rate was not consistently affected by chemoreceptor stimulation either before or following vagotomy.

These studies suggest that carotid body chemoreceptor stimulation increases systemic arterial pressure in part by increasing total peripheral resistance. The studies also indicate that hypoxia and hypercapnia act on the carotid body chemoreceptors to elicit changes in autonomic outflow to the vasculature similar to changes induced by lowering the pressure in the carotid sinuses.

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APPENDICES

APPENDIX A

RAW DATA

LIST OF ABBREVIATIONS

(For APPENDIX A)

P_{CS} = carotid sinus pressure (mm Hg)

P_S = systemic arterial pressure (mm Hg)

P_{BA} = brachial artery pressure (mm Hg)

P_{MA} = mesenteric artery or ileal segment perfusion pressure (mm Hg)

P_{SMA} = superior mesenteric artery pressure (mm Hg)

P_R = renal artery pressure (mm Hg)

CSP = carotid sinus pressure (mm Hg)

F_{BV} = brachial vein blood flow (ml/min)

F_{CV} = cephalic vein blood flow (ml/min)

F_{MA} = mesenteric artery blood flow (ml/min)

F_{SMA} = superior mesenteric artery blod flow (ml/min)

F_R = renal artery blood flow (ml/min)

HR = heart rate (beats/min)

P_{O_2} = O_2 tension of the carotid sinus blood (mm Hg)

pH = pH of the carotid sinus blood

$t^M a$ = ileal segment intraluminal pressure (mm Hg), t and a are qualitative assessments of ileal tone and activity, respectively, (scale: 0 - 4)

FORELIMB

	20% O_2 - 5% CO_2 (control) Prevagotomy								Room Air Prevagotomy							
Dog #	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH
1	119	120	110	48.0	76.0	192	68	7.27	116	115	100	48.0	84.0	192	52	7.50
2	120	110	95	44.0	48.0	138	118	7.27	115	107	88	42.0	48.0	135	118	7.58
3	126	135	120	54.0	71.3	180	100	7.27	121	130	117	56.0	70.0	176	96	7.54
4	120	122	134	66.4	17.6	188	106	7.31	120	120	134	62.0	16.4	184	102	7.50
5	100	110	88	48.0	40.0	192	127	7.25	110	110	84	48.0	40.0	186	129	7.59
6	122	137	80	56.0	67.7	174	130	7.32	125	126	80	56.0	66.0	168	128	7.63
7	139	163	118	54.0	53.6	171	136	7.35	142	150	118	56.0	51.6	162	139	7.59
8	135	140	150	46.4	4.8	152	117	7.28	123	130	159	47.2	1.2	164	122	7.53
9	163	155	157	45.6	57.6	216	129	7.29	140	147	149	46.8	56.0	201	132	7.62
10	128	134	133	46.4	50.4	147	125	7.32	132	138	122	48.8	50.4	144	130	7.64
Mean	127	133	119	50.9	48.7	175	116	7.28	124	127	115	51.1	48.4	171	115	7.57

FORELIMB

Dog #	20% O_2 - 5% CO_2 (control) PREVAGOTOMY								0% O_2 - 20% CO_2 PREVAGOTOMY							
	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH
1	119	120	110	48.0	76.0	192	68	7.27	115	112	134	48.0	72.0	172	37	7.11
2	120	110	95	44.0	48.0	138	118	7.27	115	112	102	42.0	48.0	132	16	6.95
3	126	135	120	54.0	71.3	180	100	7.27	110	150	130	53.3	67.2	180	25	6.98
4	120	122	134	66.4	17.6	188	106	7.31	102	173	138	68.0	16.8	196	16	6.97
5	100	110	88	48.0	40.0	192	127	7.25	105	126	87	50.0	42.4	198	11	6.88
6	122	137	80	56.0	67.7	174	130	7.32	116	164	83	58.0	70.0	171	22	6.96
7	139	163	118	54.0	53.6	171	136	7.35	136	190	120	52.0	57.2	172	26	7.01
8	135	140	150	46.4	4.8	152	117	7.28	138	174	162	45.6	4.4	148	10	6.92
9	163	155	157	45.6	57.6	216	129	7.29	140	165	156	44.0	60.0	222	14	6.96
10	128	134	133	46.4	50.4	147	125	7.32	130	148	129	47.6	51.2	150	14	7.05
Mean	127	133	119	50.9	48.7	175	116	7.28	121	151	124	50.9	48.9	174	19	6.98

FORELIMB

	20% O_2 - 5% CO_2 (control) PREVAGOTOMY								0% O_2 - 5% CO_2 PREVAGOTOMY							
Dog #	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH
1	115	118	112	44.0	76.0	192	68	7.27	115	91	128	48.0	72.0	168	26	7.34
2	116	113	100	44.8	48.0	136	118	7.28	113	103	103	44.0	46.4	132	12	7.26
3	122	136	127	56.0	70.0	168	103	7.24	112	140	127	55.6	72.0	176	20	7.30
4	122	135	140	70.0	15.2	188	106	7.31	112	151	145	68.0	14.4	192	13	7.30
5	115	108	85	48.8	43.6	196	118	7.22	110	103	87	48.0	40.0	200	8	7.23
6	124	132	78	56.0	71.6	170	131	7.28	115	136	72	60.0	72.8	159	16	7.31
7	144	165	116	52.0	56.8	171	126	7.32	135	176	115	61.0	57.0	171	19	7.38
8	131	127	170	42.4	5.6	156	113	7.30	135	150	183	40.0	8.0	153	5	7.31
9	140	158	140	41.6	63.2	228	120	7.29	141	161	136	41.6	64.0	231	12	7.31
10	130	128	117	47.6	51.2	152	126	7.34	128	138	129	45.6	51.6	144	11	7.34
Mean	126	132	119	50.3	50.1	176	113	7.29	122	135	123	51.2	49.8	173	14	7.31

FORELIMB

	20% O_2 - 5% CO_2 (control) PREVAGOTOMY								20% O_2 - 20% CO_2 PREVAGOTOMY							
Dog #	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O2}	pH	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O2}	pH
1	110	100	110	44.0	78.4	180	67	7.27	104	87	128	44.0	80.0	171	92	7.20
2	118	106	110	44.0	48.4	144	116	7.28	114	104	125	44.0	48.0	144	130	6.94
3	124	134	129	54.8	71.7	172	100	7.23	113	149	138	60.0	64.0	176	114	6.89
4	122	130	150	66.4	15.2	188	97	7.31	112	154	161	68.0	15.2	192	115	6.97
5	120	98	94	48.0	40.0	192	113	7.23	110	102	96	48.8	41.6	195	134	6.85
6	120	132	75	60.0	72.0	164	122	7.30	114	151	77	64.0	75.3	168	144	6.92
7	153	175	114	52.0	58.4	168	126	7.36	146	184	114	52.0	60.8	168	152	6.96
8	153	119	193	36.0	9.6	162	103	7.30	133	128	193	33.6	11.6	162	127	6.89
9	142	153	130	38.0	65.2	228	120	7.29	146	156	140	37.6	65.6	231	149	6.92
10	125	137	133	47.6	51.6	141	121	7.31	121	152	138	47.2	52.0	141	143	6.92
Mean	127	128	124	49.1	51.1	175	109	7.29	121	137	131	49.9	51.4	175	130	6.95

FORELIMB

	20% O_2 - 5% CO_2 (control) POSTVAGOTOMY								0% O_2 - 20% CO_2 POSTVAGOTOMY							
Dog #	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH
1	95	81	94	43.2	81.6	156	106	7.27	115	120	180	44.0	80.0	150	28	-
2	90	98	161	36.0	44.0	148	120	-	95	190	188	38.0	42.0	150	14	6.94
3	121	131	120	46.0	54.8	152	103	-	115	178	150	48.0	56.0	164	22	6.91
4	148	150	160	44.0	12.0	168	102	-	130	195	197	46.0	12.0	180	17	-
5	73	85	96	48.0	40.8	186	127	7.22	70	123	134	48.0	40.0	-	11	6.84
6	123	117	82	58.0	70.8	148	119	7.29	122	170	114	58.0	74.0	156	28	6.98
7	142	143	103	48.8	60.0	150	130	-	136	165	110	50.0	61.6	140	28	6.96
8	118	120	175	28.8	17.2	153	109	-	121	160	173	28.0	19.6	148	15	6.87
9	111	120	134	46.4	54.1	200	127	7.27	112	119	145	46.8	55.6	196	12	6.92
10	136	140	120	43.2	57.2	129	126	-	132	159	125	34.0	66.0	135	11	6.91
11	141	140	86	64.0	118.0	156	101	7.29	143	164	85	70.0	128.0	156	21	6.95
12	117	104	109	44.0	70.0	124	117	7.36	115	125	118	42.0	68.0	144	24	6.94
13	113	117	103	-	-	-	114	7.26	115	154	105	-	-	-	22	6.95
Mean	118	119	119	45.8	55.8	156	115	7.28	117	156	140	46.1	58.6	156	19	6.92

FORELIMB

	20% O_2 - 5% CO_2 (control) POSTVAGOTOMY								0% O_2 - 5% CO_2 POSTVAGOTOMY							
Dog #	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH
1	85	87	130	42.0	78.0	164	110	-	80	105	195	44.0	77.6	148	20	7.27
2	90	125	162	34.0	40.0	153	113	7.23	90	145	163	36.0	40.0	147	10	7.29
3	115	127	125	45.2	51.6	160	100	7.27	117	143	133	44.0	53.6	164	17	7.25
4	140	137	160	44.0	12.0	164	88	-	135	155	170	44.0	12.0	176	13	-
5	72	53	105	48.0	38.0	195	110	7.20	75	65	114	48.0	40.0	192	7	7.19
6	125	120	83	55.2	70.4	147	120	7.23	120	143	100	57.2	70.0	147	17	7.30
7	140	139	112	48.0	59.2	144	126	7.27	139	145	117	50.0	60.0	144	20	7.30
8	108	75	178	23.2	20.4	153	100	7.24	107	134	183	22.4	22.8	153	9	7.27
9	110	105	139	44.0	55.6	204	117	7.28	108	88	141	40.8	56.8	192	11	7.31
10	140	135	127	32.0	68.0	129	117	7.27	138	149	138	32.0	68.0	132	7	7.28
11	148	148	87	66.0	124.0	156	91	7.25	147	158	87	66.0	124.0	156	15	7.28
12	112	77	95	40.0	68.4	135	130	7.33	113	102	103	44.0	69.2	136	20	7.34
13	110	116	108	-	-	-	112	-	109	123	112	-	-	-	14	7.25
Mean	115	111	124	43.5	57.1	159	110	7.25	114	127	135	44.0	57.8	157	14	7.27

FORELIMB

	20% O_2 - 5% CO_2 (control) POSTVAGOTOMY								20% O_2 - 20% CO_2 POSTVAGOTOMY							
Dog #	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH	P_{CS}	P_S	P_{BA}	F_{BV}	F_{CV}	HR	P_{O_2}	pH
1	84	78	128	40.0	78.0	164	108	7.30	73	68	170	40.8	76.0	156	126	6.91
2	90	112	155	36.0	39.2	150	113	7.23	91	131	158	36.0	40.0	153	134	7.19
3	114	116	124	43.6	51.2	164	99	7.23	117	123	130	42.0	51.2	168	117	6.89
4	132	108	168	43.2	12.8	168	70	-	130	158	176	43.6	12.0	184	84	-
5	70	42	113	48.0	38.0	186	120	7.21	70	38	123	48.0	38.0	192	133	6.81
6	122	105	95	55.6	68.8	144	118	7.30	119	125	107	55.2	68.4	152	132	6.94
7	140	133	115	50.0	59.2	144	120	7.28	139	150	127	52.0	58.4	144	153	6.92
8	120	42	187	20.0	21.2	144	106	7.28	110	105	200	22.4	21.6	156	126	6.85
9	107	83	138	40.8	58.4	204	120	7.28	108	96	158	41.6	56.0	204	146	6.88
10	137	127	137	28.0	72.0	132	114	7.29	133	135	145	28.0	68.0	136	141	6.87
11	150	155	90	62.0	128.0	157	91	7.29	148	158	93	66.0	126.0	181	107	6.96
12	112	83	97	44.0	68.0	132	132	-	114	106	105	44.0	73.0	138	150	6.91
13	107	116	110	-	-	-	114	-	101	101	145	-	-	-	124	6.83
Mean	114	100	127	42.6	57.9	157	110	7.27	112	115	141	43.3	57.4	164	129	6.91

INTESTINE

(Ileal Segment)

	20% O_2 - 2½% CO_2 (control PREVAGOTOMY								0% O_2 - 20% CO_2 PREVAGOTOMY								
Dog #	P_{CS}	P_S	P_{MA}	HR	P_{O_2}	PH	t	M a	P_{CS}	P_S	P_{MA}	HR	P_{O_2}	pH	t	M a	F_{MA}
1	125	113	105	144	-	7.42	0	0	115	150	118	138	15	7.00	0	0	18
2	115	116	87	152	103	7.41	0	0	117	143	100	156	15	6.96	0	0	11
3	150	153	65	172	105	7.22	3	3	148	160	65	174	17	6.97	3	3	16
4	123	118	65	160	126	7.45	1	2	120	125	65	132	22	7.00	1	1	15
5	95	98	73	204	109	7.42	0	2	95	98	70	192	17	6.95	0	3	24
Mean	122	120	79	166	111	7.38	0.8	1.4	119	135	84	158	17	6.95	0.8	1.4	17

INTESTINE

(Ileal Segment)

	20% O_2 - 2½% CO_2 (control) POSTVAGOTOMY								0% O_2 - 20% CO_2 POSTVAGOTOMY								
Dog #	P_{CS}	P_S	P_{MA}	HR	P_{O_2}	pH	t	M a	P_{CS}	P_S	P_{MA}	HR	P_{O_2}	pH	t	M a	F_{MA}
1	100	130	116	180	112	7.24	0	0	103	188	257	176	20	6.97	0	0	28
2	113	123	107	148	215	7.40	0	0	115	190	160	156	17	6.96	2	1	14
3	114	115	113	174	208	7.34	0	0	120	170	125	168	21	6.96	1	1	7
4	130	125	158	204	240	7.38	0	1	125	153	177	204	26	7.01	2	1	16
5	110	110	95	144	100	7.49	0	0	115	160	142	138	14	6.94	0	1	18
6	63	60	135	144	100	7.50	2	2	65	115	165	144	14	6.89	0	0	11
7	145	150	105	160	-	7.33	1	1	141	160	115	156	-	6.97	4	1	16
8	133	130	100	156	118	7.45	0	2	133	163	140	135	22	7.00	0	0	15
9	94	100	71	184	109	7.38	0	2	90	120	83	180	10	6.93	0	0	24
Mean	111	116	111	166	150	7.39	0.3	0.9	112	158	152	162	18	6.96	1.0	0.7	17

INTESTINE

(Ileal Segment)

	20% O_2 - 2½% CO_2 (control) POSTVAGOTOMY								0% O_2 - 5% CO_2 POSTVAGOTOMY								
Dog #	P_{CS}	P_S	P_{MA}	HR	P_{O2}	pH	t	M a	P_{CS}	P_S	P_{MA}	HR	P_{O2}	pH	t	M a	F_{MA}
1	100	100	147	180	115	7.27	1	1	100	134	180	176	14	7.32	0	0	28
2	115	108	137	148	210	7.38	2	2	112	130	158	144	12	7.38	0	0	14
3	105	105	115	172	202	7.36	2	2	104	115	118	164	15	7.30	0	0	7
4	118	125	177	208	245	7.43	0	1	119	156	186	210	20	7.38	1	2	16
5	116	108	135	144	102	7.44	0	1	115	125	135	144	14	7.32	0	1	18
6	75	80	141	152	103	7.47	0	1	75	137	170	144	13	7.30	1	0	11
7	160	158	105	168	-	7.36	2	1	160	160	108	162	-	7.27	3	1	16
8	120	116	88	150	113	7.45	0	2	120	132	102	126	17	7.32	1	1	15
9	102	96	78	192	114	7.43	3	3	102	108	104	192	11	7.32	0	0	24
Mean	112	111	125	168	151	7.40	1.1	1.6	112	133	140	162	15	7.32	0.6	0.6	17

INTESTINE

(Ileal Segment)

	20% O_2 - 2½% CO_2 (control) POSTVAGOTOMY								20% O_2 - 20% CO_2 POSTVAGOTOMY								
Dog #	P_{CS}	P_S	P_{MA}	HR	P_{O_2}	pH	t	M a	P_{CS}	P_S	P_{MA}	HR	P_{O_2}	pH	t	M a	F_{MA}
1	101	105	158	188	117	7.29	1	1	103	150	180	192	142	6.91	2	2	28
2	96	95	140	150	220	7.42	3	2	97	135	150	165	-	-	-1	3	14
3	90	87	100	176	203	7.39	0	0	90	115	100	176	128	6.90	0	1	7
4	120	131	170	204	225	7.43	0	1	124	162	181	204	-	6.95	0	1	16
5	93	78	105	156	100	7.44	0	0	96	90	205	156	122	6.89	0	1	18
6	45	45	143	141	111	-	2	2	45	70	155	153	137	6.84	2	2	11
7	158	150	100	160	-	7.34	1	2	158	160	108	160	-	6.92	1	1	16
8	123	23	76	152	112	7.41	1	1	124	134	80	138	140	6.93	0	0	15
9	100	98	74	192	112	7.42	0	2	100	120	83	204	128	6.91	3	3	24
Mean	103	101	118	169	155	7.39	0.9	1.3	104	126	138	172	133	6.91	0.8	1.3	17

INTESTINE

(Superior Mesenteric Artery)

20% O_2 - 2½% CO_2 (control)
PREVAGOTOMY

Dog #	P_{CS}	P_S	P_{SMA}	HR	P_{O_2}	pH
1	127	136	115	180	127	-
2	-	-	-	-	-	-
3	115	130	100	156	78	7.32
4	120	117	104	120	107	7.38
Mean	121	128	106	152	104	7.35

0% O_2 - 20% CO_2
PREVAGOTOMY

P_{CS}	P_S	P_{SMA}	HR	P_{O_2}	pH	F_{SMA}
125	160	134	182	12	6.98	262
-	-	-	-	-	-	-
115	140	123	168	29	7.10	140
118	125	100	126	9	6.82	180
119	142	119	159	17	6.97	194

20% O_2 - 2½% CO_2 (control)
POSTVAGOTOMY

1	115	113	88	168	90	7.46
2	75	73	117	120	-	7.29
3	110	110	110	156	80	7.31
4	115	110	93	115	105	7.33
Mean	104	102	102	140	92	7.35

0% O_2 - 20% CO_2
POSTVAGOTOMY

114	160	144	168	6	6.96	262
79	127	148	126	-	5.89	112
113	138	150	162	26	7.01	140
114	135	170	114	6	6.82	180
105	140	153	143	13	6.92	174

INTESTINE

(Superior Mesenteric Artery)

20% O_2 - 2½% CO_2 (control)
POSTVAGOTOMY

Dog #	P_{CS}	P_S	P_{SMA}	HR	P_{O_2}	pH
1	115	118	105	162	107	7.46
2	75	65	133	120	-	7.40
3	120	118	105	156	70	7.31
4	115	108	92	115	104	7.35
Mean	117	115	101	144	93	7.38

0% O_2 - 5% CO_2
POSTVAGOTOMY

P_{CS}	P_S	P_{SMA}	HR	P_{O_2}	pH	F_{SMA}
115	143	120	162	7	7.36	262
-	-	-	-	-	-	112
118	138	114	150	21	7.25	140
110	108	120	114	7	7.21	180
114	130	118	142	12	7.27	174

20% O_2 - 2½% CO_2 (control)
POSTVAGOTOMY

Dog #	P_{CS}	P_S	P_{SMA}	HR	P_{O_2}	pH
1	114	118	98	160	94	7.46
2	75	65	133	126	-	7.40
3	115	115	105	156	100	7.34
4	113	105	96	115	120	7.38
Mean	104	101	108	141	105	7.40

20% O_2 - 20% CO_2
POSTVAGOTOMY

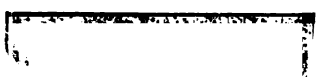
P_{CS}	P_S	P_{SMA}	HR	P_{O_2}	pH	F_{SMA}
114	146	125	168	129	6.94	262
78	93	145	132	-	6.88	112
112	130	114	156	100	6.95	140
110	125	118	114	104	6.81	180
104	124	126	143	111	6.90	174

KIDNEY

	20% O_2 - 2½% CO_2 (control) PREVAGOTOMY						0% O_2 - 20% CO_2 PREVAGOTOMY						
Dog #	P_{CS}	P_S	P_R	HR	P_{O_2}	pH	P_{CS}	P_S	P_R	HR	P_{O_2}	pH	F_R
1	92	90	73	138	95	7.38	93	110	188	138	12	6.95	100
2	104	114	82	162	105	7.42	105	130	98	162	17	7.03	140
3	130	144	83	200	140	7.37	134	150	92	192	43	7.10	150
4	131	130	67	168	113	7.36	128	155	87	174	23	6.88	104
5	100	100	64	136	170	7.32	95	115	62	136	9	6.92	56
6	108	113	100	168	130	7.33	106	134	213	162	21	6.97	90
7	135	138	89	156	117	7.35	138	145	96	160	21	6.90	152
8	132	140	83	120	112	7.43	136	163	90	116	14	6.96	112
9	135	135	88	132	136	7.41	135	160	250	144	9	6.88	85
10	96	98	75	132	92	7.38	95	124	100	132	14	7.18	108
Mean	116	120	80	151	121	7.38	117	139	128	152	18	6.98	110

KIDNEY

	20% O_2 - 2½% CO_2 (control) POSTVAGOTOMY						0% O_2 - 20% CO_2 POSTVAGOTOMY						
Dog #	P_{CS}	P_S	P_R	HR	P_{O_2}	pH	P_{CS}	P_S	P_R	HR	P_{O_2}	pH	F_R
1	76	70	73	126	96	7.34	75	98	193	126	11	6.90	100
2	114	117	77	168	103	7.32	115	128	88	168	11	6.91	116
3	99	93	98	186	120	7.31	100	114	208	192	53	7.11	150
4	102	101	153	156	114	7.33	103	138	205	150	37	6.86	104
5	95	93	65	121	170	7.37	100	125	85	153	9	6.88	64
6	84	78	112	168	120	7.31	81	84	137	164	23	6.93	76
7	115	120	75	132	90	7.38	115	142	86	138	10	6.84	132
8	157	155	90	108	109	7.42	161	204	175	116	13	6.97	112
9	130	120	105	124	118	7.41	127	171	218	139	7	6.95	90
10	75	73	57	132	82	7.39	73	134	108	144	13	6.97	108
Mean	105	102	91	142	112	7.36	105	134	150	149	19	6.93	105



KIDNEY

	20% O_2 - 2½% CO_2 (control) POSTVAGOTOMY						0% O_2 - 5% CO_2 POSTVAGOTOMY						
Dog #	P_{CS}	P_S	P_R	HR	P_{O_2}	pH	P_{CS}	P_S	P_R	HR	P_{O_2}	pH	F_R
1	78	73	75	126	103	7.30	78	88	88	128	10	7.26	94
2	109	110	75	168	107	7.34	110	118	83	168	9	7.26	116
3	100	103	98	192	129	7.31	104	120	255	204	47	7.29	150
4	115	108	84	168	114	7.34	113	125	154	156	20	7.18	104
5	100	105	100	121	117	7.32	106	129	140	156	6	7.22	88
6	88	83	93	168	130	7.31	85	87	120	164	17	7.25	76
7	130	125	93	144	107	7.38	132	126	96	144	6	7.24	152
8	111	104	81	108	114	7.41	110	113	100	108	10	7.25	112
9	128	130	100	126	117	7.37	130	158	183	138	5	7.30	90
10	70	68	68	132	89	7.32	67	133	82	144	10	7.31	108
Mean	103	101	87	145	113	7.34	104	120	130	151	14	7.26	109

KIDNEY

	20% O_2 - 2½% CO_2 (control) POSTVAGOTOMY						20% O_2 - 20% CO_2 POSTVAGOTOMY						
Dog #	P_{CS}	P_S	P_R	HR	P_{O_2}	pH	P_{CS}	P_S	P_R	HR	P_{O_2}	pH	F_R
1	73	63	71	128	103	7.33	77	75	81	126	123	6.84	94
2	108	106	69	168	102	7.39	110	133	83	168	125	6.87	116
3	85	80	102	204	152	7.35	86	95	225	192	133	6.95	150
4	108	105	115	156	114	7.32	106	130	178	160	116	6.83	104
5	97	93	75	121	178	7.31	104	128	100	121	117	6.81	88
6	100	103	95	164	130	7.32	96	107	108	162	137	6.87	76
7	135	133	98	150	109	7.31	138	145	106	150	123	6.87	152
8	113	115	84	112	105	7.39	115	148	100	112	126	6.90	112
9	127	128	79	141	122	7.39	128	168	170	138	137	6.89	85
10	67	65	70	136	89	7.34	65	95	84	131	93	6.91	108
Mean	101	99	86	148	120	7.35	103	122	124	146	123	6.87	109

KIDNEY

PREVAGOTOMY

	Control			Low CSP			Control			High CSP			
Dog #	P_{CS}	P_S	P_R	P_{CS}	P_S	P_R	P_{CS}	P_S	P_R	P_{CS}	P_S	P_R	F_R
1	103	108	69	65	113	71	103	108	69	200	93	66	140
2	133	131	70	43	153	75	131	133	74	208	113	75	104
3	125	118	100	35	146	150	121	126	112	215	102	93	90
4	125	133	86	37	151	91	129	133	84	197	123	81	152
5	137	137	84	40	157	88	140	140	83	209	110	78	112
6	140	134	100	43	178	155	140	134	95	207	109	83	120
Mean	127	127	85	44	150	105	127	129	86	206	108	79	120

POSTVAGOTOMY

1	114	108	80	68	133	95	115	108	81	200	62	68	116
2	106	105	76	68	159	145	106	105	73	206	70	61	104
3	75	56	100	34	67	126	75	75	121	225	38	77	76
4	130	133	99	43	162	117	136	134	99	200	118	89	152
5	118	123	85	35	160	97	118	118	100	190	83	68	84
6	70	72	63	35	88	69	71	83	66	195	53	57	108
Mean	102	100	84	47	128	108	104	104	90	203	71	70	107

CORONARY VASCULATURE--STUDY 1

0% O_2 - 20% CO_2 (PREVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"
1	102	100	100	107	110	112	115	117
2	101	103	105	113	112	114	117	108
3	103	102	111	130	132	134	128	128
4	130	132	138	146	152	155	150	150
5	100	100	100	109	115	115	113	113
6	104	104	108	107	108	107	105	105
7	100	103	110	115	120	120	120	120
8	96	96	96	104	105	105	104	105
9	81	83	85	90	96	98	100	100
10	115	115	117	120	126	127	127	125
Mean	103	104	108	114	118	119	118	117

CORONARY ARTERY PRESSURE

1	155	157	158	164	165	163	167	170
2	106	105	107	108	109	111	113	113
3	115	117	121	122	125	128	128	127
4	141	141	143	144	142	140	140	138
5	95	96	100	103	108	111	112	115
6	133	135	135	138	140	140	140	141
7	97	99	99	98	95	97	96	93
8	120	120	119	118	117	116	115	115
9	100	100	100	100	100	102	117	119
10	125	125	125	120	112	93	90	88
Mean	119	120	121	122	121	120	122	122

LEFT VENTRICULAR CONTRACTILE FORCE

1	24	24	23	22	22	22	22	22
2	17	17	17	15	15	15	15	15
3	17	17	17	17	16	16	16	16
4	23	23	23	21	20	20	20	20
5	17	17	17	17	16	16	16	16
6	18	18	18	17	17	17	17	17
7	31	31	31	30	30	29	29	28
8	25	25	25	24	24	24	23	23
9	31	31	31	30	29	29	30	30
10	18	18	17	16	15	14	13	12
Mean	22	22	22	21	20	20	20	20

CORONARY VASCULATURE--STUDY 1

0% O_2 - 20% CO_2 (POSTVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"
1	80	80	82	83	90	92	102	118
2	107	110	120	131	140	143	146	146
3	90	93	100	126	150	165	175	195
4	113	110	110	123	138	165	195	215
5	84	84	90	100	105	101	103	105
6	110	109	110	110	105	102	100	95
7	75	75	90	90	97	100	101	-
8	105	105	105	110	125	124	126	131
9	63	62	75	125	135	140	143	140
10	108	105	105	117	125	138	140	140
Mean	94	93	99	112	121	127	133	

CORONARY ARTERY PRESSURE

1	148	149	150	152	155	156	157	156
2	164	166	167	170	175	178	185	186
3	137	138	139	140	143	146	150	140
4	135	136	135	140	139	139	140	140
5	92	93	95	95	95	95	100	97
6	158	159	158	162	155	161	162	160
7	85	85	91	90	93	95	92	-
8	113	114	116	118	117	120	117	115
9	140	140	143	115	90	90	85	85
10	160	160	162	158	150	113	80	82
Mean	133	134	136	134	131	129	127	129

LEFT VENTRICULAR CONTRACTILE FORCE

1	17	17	17	16	16	15	15	16
2	24	23	22	20	18	18	17	17
3	18	18	18	15	14	13	12	11
4	21	21	21	20	19	18	18	16
5	24	24	24	24	24	24	24	24
6	21	21	21	20	19	20	20	20
7	15	15	15	14	13	12	12	-
8	25	25	25	24	19	18	18	17
9	26	26	26	23	20	18	18	18
10	21	21	21	19	18	14	11	11
Mean	21	21	21	20	18	17	17	17

CORONARY VASCULATURE--STUDY 1

0% O_2 - 5% CO_2 (POSTVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"
1	95	92	86	93	93	92	92	
2	105	106	101	110	122	128	130	133
3	110	106	110	134	157	162	165	165
4	112	115	120	133	140	146	155	175
5	45	47	50	55	68	70	75	75
6	75	75	74	75	77	80	80	82
7	70	70	73	85	90	92	95	93
8	101	103	101	108	112	116	124	123
9	78	80	105	115	115	115	115	115
10	100	100	100	100	105	106	109	113
Mean	89	89	92	101	108	111	114	117

CORONARY ARTERY PRESSURE

1	153	152	155	157	159	160	158	157
2	155	157	156	160	164	164	166	170
3	135	135	136	135	136	141	146	148
4	133	135	135	136	136	133	137	133
5	114	115	115	115	115	116	114	113
6	135	136	138	140	136	137	136	135
7	70	71	75	75	74	74	75	74
8	130	130	130	130	130	128	127	126
9	75	75	75	65	55	50	50	50
10	150	150	154	153	151	150	145	143
Mean	125	126	127	127	126	125	125	125

LEFT VENTRICULAR CONTRACTILE FORCE

1	17	16	15	15	15	15	14	14
2	29	29	28	27	24	23	22	21
3	16	15	13	13	13	11	11	11
4	21	21	21	20	20	19	19	19
5	20	20	20	20	20	20	20	20
6	19	19	19	19	19	19	19	19
7	18	18	17	16	16	16	16	16
8	27	27	27	26	25	23	25	25
9	28	28	28	19	15	14	14	14
10	19	19	19	19	19	19	18	17
Mean	21	21	21	19	18	18	18	18

CORONARY VASCULATURE--STUDY 1

20% O_2 - 20% CO_2 (POSTVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"
1	100	98	101	104	108	108	110	116
2	-	-	-	-	-	-	-	-
3	110	110	115	138	141	146	148	142
4	110	110	110	118	122	123	130	133
5	81	80	87	95	98	101	101	99
6	70	70	75	80	80	80	78	78
7	102	99	110	110	105	105	105	105
8	102	105	104	106	108	106	107	105
9	68	68	97	100	103	102	107	107
10	105	105	106	115	118	120	120	120
Mean	94	94	101	107	109	110	112	112

CORONARY ARTERY PRESSURE

1	164	162	165	168	170	168	165	165
2	-	-	-	-	-	-	-	-
3	148	147	147	146	148	146	146	144
4	142	142	141	146	143	143	137	137
5	100	99	100	98	97	96	95	93
6	150	151	154	153	154	155	154	155
7	82	80	81	80	78	80	77	77
8	132	132	132	133	135	132	134	134
9	133	136	139	135	137	135	135	135
10	135	140	142	142	140	137	138	139
Mean	132	132	134	133	134	132	131	131

LEFT VENTRICULAR CONTRACTILE FORCE

1	22	22	21	21	20	20	19	19
2	-	-	-	-	-	-	-	-
3	16	16	16	15	14	14	14	14
4	22	22	22	21	20	20	20	19
5	23	23	23	23	22	22	22	22
6	24	24	24	23	23	23	22	22
7	18	18	17	17	17	16	16	16
8	28	28	27	27	26	26	26	26
9	27	27	27	26	26	25	25	25
10	20	20	20	18	17	17	16	16
Mean	22	22	22	21	21	20	20	20

CORONARY VASCULATURE--STUDY 2

0% O_2 - 20% CO_2 (PREVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"	240"
1	96	97	99	105	107	113	116	118	125
2	105	105	105	106	106	107	108	108	109
3	120	120	140	138	143	145	150	150	150
4	136	140	150	162	167	165	170	168	167
5	95	95	96	97	104	108	112	115	118
6	116	120	125	134	134	134	133	133	133
Mean	111	113	119	124	127	129	132	132	134

CORONARY ARTERY PRESSURE

1	150	150	150	152	153	153	150	151	155
2	128	129	130	131	131	129	128	127	126
3	125	125	130	120	132	140	145	148	148
4	125	126	125	132	135	140	139	139	137
5	138	138	138	137	135	130	128	127	125
6	81	83	84	84	85	87	88	93	97
Mean	125	125	126	126	129	130	130	131	131

LEFT VENTRICULAR CONTRACTILE FORCE

1	43	42	43	41	39	38	37	37	36
2	24	24	24	22	20	19	19	18	18
3	14	14	14	13	13	12	12	13	13
4	37	37	37	33	31	31	30	30	30
5	32	32	32	32	31	29	29	29	29
6	35	34	30	26	26	27	27	27	27
Mean	31	31	30	28	27	26	26	26	26

CORONARY VASCULATURE--STUDY 2

0% O_2 - 20% CO_2 (POSTVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"	240"
1	67	67	70	90	118	133	128	126	127
2	91	91	90	91	95	96	96	100	98
3	62	64	70	125	160	175	178	178	175
4	133	134	157	182	192	195	205	203	200
5	80	80	85	115	125	133	135	131	132
6	105	105	122	140	168	180	192	205	205
Mean	90	90	99	124	143	152	156	157	156

CORONARY ARTERY PRESSURE

1	131	130	131	132	115	108	115	125	125
2	144	144	146	150	150	149	149	148	148
3	86	86	86	88	90	95	98	100	101
4	140	140	140	134	134	134	140	146	152
5	130	132	135	127	119	120	123	125	123
6	170	170	170	170	145	145	158	158	160
Mean	134	134	135	134	126	125	131	134	135

LEFT VENTRICULAR CONTRACTILE FORCE

1	44	44	44	45	41	36	35	37	37
2	25	25	25	24	21	20	20	19	20
3	36	36	34	30	25	22	26	26	27
4	41	41	35	32	28	28	28	28	28
5	35	35	35	30	25	27	27	27	27
6	40	38	37	31	-	-	-	-	-
Mean	37	37	35	32	28	27	27	27	28

CORONARY VASCULATURE--STUDY 2

5% O_2 - 2½% CO_2 (POSTVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"	240"
1	132	130	132	135	137	130	135	135	135
2	100	100	102	103	105	101	100	100	103
Mean	116	115	117	119	121	116	118	118	119

CORONARY ARTERY PRESSURE

1	120	120	118	116	115	114	115	113	114
2	150	150	154	154	153	154	155	155	155
Mean	135	135	136	135	134	134	135	134	135

LEFT VENTRICULAR CONTRACTILE FORCE

1	37	37	37	37	37	37	36	35	36
2	33	33	33	33	33	33	33	33	33
Mean	35	35	35	35	35	35	35	34	35

CORONARY VASCULATURE--STUDY 2

10% O_2 - $2\frac{1}{2}$% CO_2 (POSTVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"	240"
1	77	77	78	80	80	82	81	80	83
2	98	98	97	95	96	95	95	95	95
3	62	60	56	55	59	56	56	54	53
Mean	79	78	77	77	78	78	77	76	77

CORONARY ARTERY PRESSURE

1	123	123	124	124	125	125	125	126	126
2	143	143	143	144	143	143	143	142	142
3	80	79	76	75	74	72	71	70	70
Mean	115	115	115	114	114	113	113	113	113

LEFT VENTRICULAR CONTRACTILE FORCE

1	37	37	37	37	37	37	37	37	37
2	24	24	24	24	24	24	24	24	24
3	33	33	33	33	33	33	33	33	33
Mean	47	47	47	47	47	47	47	47	47

CORONARY VASCULATURE--STUDY 2

20% O_2 - 10% CO_2 (POSTVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"	240"
1	75	75	77	80	80	80	80	78	78
2	95	96	97	98	100	98	99	99	99
3	66	65	72	82	90	94	96	96	95
4	125	125	125	135	136	140	140	140	140
5	95	96	99	100	101	100	100	100	98
6	105	105	105	110	114	114	113	115	115
Mean	94	94	96	101	104	104	105	105	104

CORONARY ARTERY PRESSURE

1	127	127	127	128	127	126	127	126	125
2	139	139	139	140	140	141	142	141	140
3	90	90	95	93	91	90	92	91	93
4	120	120	123	124	123	122	122	122	123
5	122	123	126	125	125	124	125	125	125
6	157	157	157	159	156	156	157	159	158
Mean	126	126	128	128	127	127	128	127	127

LEFT VENTRICULAR CONTRACTILE FORCE

1	40	40	40	40	39	39	29	39	39
2	23	23	23	22	22	22	22	22	22
3	37	37	37	37	37	37	37	37	37
4	40	40	40	40	40	38	39	38	38
5	31	31	32	31	30	30	31	30	30
6	42	42	42	41	37	38	40	39	40
Mean	36	36	36	35	34	34	35	34	34

CORONARY VASCULATURE--STUDY 2

10% O_2 - 10% CO_2 (POSTVAGOTOMY)

SYSTEMIC ARTERIAL PRESSURE

Dog #	C	30"	60"	90"	120"	150"	180"	210"	240"
1	67	68	69	76	80	83	84	85	87
2	92	91	92	95	95	94	93	94	94
3	68	70	67	86	92	95	103	105	103
4	125	125	127	133	137	146	150	156	156
5	87	87	87	87	90	92	92	93	93
6	105	105	106	115	114	115	116	115	115
Mean	91	91	91	98	101	104	106	108	108

CORONARY ARTERY PRESSURE

1	128	129	129	129	128	127	128	128	128
2	141	142	142	143	145	145	134	145	145
3	96	95	93	94	90	87	89	88	87
4	123	124	125	124	122	120	118	117	117
5	125	126	125	125	126	127	128	127	125
6	165	164	165	164	164	164	162	163	163
Mean	130	130	130	130	129	128	128	128	128

LEFT VENTRICULAR CONTRACTILE FORCE

1	40	40	40	40	39	39	39	40	38
2	28	28	28	26	26	26	25	26	26
3	38	38	37	37	36	34	35	36	37
4	41	40	40	40	40	39	38	27	27
5	33	33	33	32	32	32	32	32	31
6	42	42	42	38	38	39	39	39	40
Mean	37	37	37	36	35	35	35	35	35

APPENDIX B

STATISTICAL METHODS

STATISTICAL METHODS

Since in every dog a control period preceded each experimental maneuver, each animal served as its own control. To statistically analyze the data the Student's t test for paired observations was used. This approach was used in order to eliminate the source of extraneous variance existing from pair to pair. This was done by calculating the variance of the differences rather than that among the individuals within each sample.

The parameters analyzed by this statistical method included the systemic arterial pressure, organ perfusion pressure, blood flow, heart rate and left ventricular contractile force data. The animal's control data for each of the above parameters were used as one of the paired values while the data obtained during the experimental maneuver were used as the other value. The mean for the controls was designated $\bar{x}_1$ and the mean for the experimentals designated $\bar{x}_2$. The mean difference between the values was $\bar{x}_1 - \bar{x}_2$ which also equaled $\bar{d}$. $S_{\bar{d}}$ equaled the standard error of the mean paired difference and was calculated from

$$S_{\bar{d}} = \sqrt{\frac{\sum_j D_j^2 - \left(\sum_j D_j\right)^2/n}{n\,(n-1)}}$$

The test statistic (t) = $\frac{\bar{d}}{s_{\bar{d}}}$. The hypothesis being tested was

$$H_0 : \mu_d = 0, \quad H_A : \mu_d \neq 0$$

If the sample t was greater than the tabulated value with which it was compared, then the null hypothesis was rejected and the alternative accepted. For this study a significance level of .05 was used.

In the case of the comparison of the percent changes in vascular resistance (Table 9), the t test modified for unpaired observations and unequal variances was used. A sufficiently accurate approximation for determining a significant value of t' was calculated from

$$t' = \frac{w_1 t_1 + w_2 t_2}{w_1 + w_2}$$

where $w_1 = s_1^2/n_1$, $w_2 = s_2^2/n_2$, and t_1 and t_2 are the values of Student's t for $n_1 - 1$ and $n_2 - 1$ degrees of freedom at the .05 significance level. This approximation erred slightly on the conservative side in that the value of t' required for significance may have been slightly too large.

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