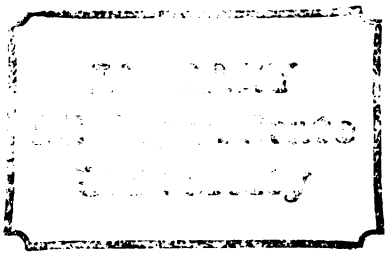

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I. Effects Of Brain Or Carotid Body Hypoxia And Hypercapnia On Pulmonary Hemodynamics
II. Effects Of Histamine On Lung Water And Hemodynamics Before And After Adrenergic Blockade

presented by

Neil C. Olson

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of the requirements for

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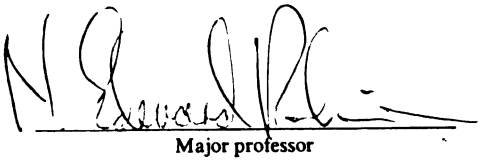

Major professor

Date March 11, 1982

I. EFFECTS OF BRAIN OR CAROTID BODY HYPOXIA AND HYPERCAPNIA ON PULMONARY HEMODYNAMICS

II. EFFECTS OF HISTAMINE ON LUNG WATER AND HEMODYNAMICS BEFORE AND AFTER ADRENERGIC BLOCKADE

By

Neil C. Olson

A DISSERTATION

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ABSTRACT

I. EFFECTS OF BRAIN OR CAROTID BODY HYPOXIA AND HYPERCAPNIA ON PULMONARY HEMODYNAMICS

II. EFFECTS OF HISTAMINE ON LUNG WATER AND HEMODYNAMICS BEFORE AND AFTER ADRENERGIC BLOCKADE

By

Neil C. Olson

There are no reports in the literature of the effects of local brain hypoxia and hypercapnia on pulmonary hemodynamics and reports concerning the role of the carotid bodies are controversial. Therefore, a better understanding of pulmonary vascular control by the brain and carotid bodies is needed. This is particularly true during pathophysiological states such as the adult respiratory distress syndrome. Thus, the main purpose of this investigation was to evaluate the effects of local brain or carotid body hypoxia, hypercapnia, and hypoxia-hypercapnia on pulmonary hemodynamics and attempt to relate these findings to the adult respiratory distress syndrome.

Numerous etiologies have been proposed for the adult respiratory distress syndrome including brain hypoxia and release of humoral agents. In the latter, histamine is a likely candidate. Therefore, another purpose of this investigation was to evaluate the effects of histamine on lung water and hemodynamics both before and after adrenergic blockade.

All experiments were performed on anesthetized dogs. Following ligation of collateral vessels (supplying blood to the brain), brain

hypoxia or hypercapnia or both were induced by pumping arterial autologous blood through an extracorporeal lung to the external carotid arteries for 5 min or 2 hours. Five min hypoxia increased cardiac output, central blood volume, total peripheral resistance, mean pulmonary artery, left atrial, pulmonary artery pulse, and mean aortic pressures. However, these effects were not maintained during 2 hours hypoxia. Pulmonary vascular resistance and lung extravascular thermal volume were unchanged during 5 min and 2 hours of brain hypoxia. I conclude that 5 min of brain hypoxia and/or hypercapnia does not increase pulmonary vascular resistance but may increase microvascular hydrostatic pressure secondary to increased pulmonary blood volume and in this way could cause pulmonary edema and alveolar hemorrhage similar to that observed in the adult respiratory distress syndrome. Failure of these effects to be maintained for 2 hours may reflect deterioration of the preparation.

The carotid bodies were perfused bilaterally with hypoxic and/or hypercapnic blood by pumping arterial autologous blood through an extracorporeal lung to the common carotid arteries. Carotid body hypoxia decreased cardiac output while pulmonary vascular resistance, mean aortic pressure and total peripheral resistance increased. During hypoxia-hypercapnia mean pulmonary artery and aortic pressures increased as did pulmonary vascular and total peripheral resistances. Following alpha blockade with phentolamine pulmonary vascular resistance failed to increase during carotid body hypoxia or hypoxia-hypercapnia. I conclude that carotid body hypoxia and hypoxia-hypercapnia reflexly increase pulmonary vascular resistance and left ventricular afterload, that these

effects are mediated by alpha adrenergic receptors, and that carotid body stimulation could potentiate the effects of brain hypoxia on pulmonary hemodynamics and thus increase lung water.

The effects of 90 min intravenous histamine with and without alpha (phentolamine) or beta (propranolol) receptor blockade on lung water and hemodynamics were also studied. Histamine with and without alpha blockade decreased central blood volume, pulmonary artery wedge, and mean aortic pressures; pulmonary vascular resistance increased while lung extravascular thermal volume was unchanged. Histamine with propranolol decreased mean aortic pressure, cardiac index, and central blood volume. Pulmonary vascular resistance increased and lung extravascular thermal volume was unchanged. In all experiments postmortem extravascular lung water to extravascular dry weight ratio was unchanged from control values. I conclude that histamine has little or no effect on lung microvascular permeability, does not increase lung water, and that these responses are not modified by reflex beta or alpha receptor stimulation on the microvascular membrane. Thus, histamine cannot be considered a likely mediator of the massive increase in lung water and permeability that occur in the adult respiratory distress syndrome.

DEDICATION

With love to Peggy, Jennifer, and Stephanie

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TABLE OF CONTENTS

TABLE OF CONTENTS--continued

TABLE OF CONTENTS--continued

TABLE OF CONTENTS--continued

LIST OF TABLES

LIST OF TABLES--continued

LIST OF TABLES--continued

TABLE

LIST OF FIGURES

LIST OF FIGURES

INTRODUCTION

In the last two decades a life-threatening pulmonary complication has emerged. The condition, which usually follows hemorrhagic shock and trauma, has been given a wide variety of names including the adult respiratory distress syndrome, shock lung, and capillary leak syndrome (19). That the etiology remains an enigma is evidenced by the numerous hypotheses proposed. One hypothesis, proposed by Moss and Stein (167), is that severe hemorrhagic shock may cause brain hypoxia thus impairing oxidative metabolism in the hypothalamus leading to increased sympathetic outflow to postcapillary vessels and increasing pulmonary vascular resistance. Increased postcapillary tone would increase microvascular hydrostatic pressure and cause pulmonary congestion, edema, hemorrhage, and hypoxemia (i.e., adult respiratory distress syndrome).

There is considerable circumstantial evidence in the literature which suggests that the brain has the ability to increase pulmonary vascular resistance during systemic hypoxemia and/or hypercapnia and that this response may be regulated by the autonomic nervous system. However, no reports exist describing these specific effects. This research is designed to quantitate the change in pulmonary vascular resistance during periods of brain hypoxia, hypercapnia, and hypoxia-hypercapnia and to attempt to elucidate the mechanisms involved.

This investigation is of considerable significance because if hypoxic and/or hypercapnic stimulation of the brain (either directly or reflexly through stimulation of peripheral chemoreceptors) increases pulmonary vascular resistance then neuropharmacologic agents with actions on the brain (e.g., hypothalamus) may become an important modality in the prevention or treatment of pulmonary edema and alveolar hemorrhage during periods of systemic hypoxia and/or hypercapnia.

The primary objectives of this investigation were to determine the effects of local brain or carotid body hypoxia and/or hypercapnia on pulmonary vascular resistance both before and after carotid sinus nerve section and cervical vagotomy. Secondary objectives were to localize the site of resistance response, by use of an alpha adrenergic blocker (phentolamine) determine if autonomic mechanisms cause these changes, and measurement of lung extravascular thermal volume and central blood volume during brain hypoxia.

Another objective of this investigation was to evaluate the effects of histamine on lung water and hemodynamics with and without alpha or beta receptor blockade. This study was performed for 2 reasons. First, histamine is one of several humoral agents that may be involved in mediating the adult respiratory distress syndrome and second, the effect of histamine on lung water during alpha or beta receptor blockade has not been reported.

The first several sections of the literature review contain material relevant to functional anatomy, pulmonary hemodynamics, lung fluid balance and pulmonary edema. Subsequent sections present background information on the adult respiratory distress syndrome with particular emphasis on the

brain's ability to alter pulmonary hemodynamics and cause pulmonary edema and alveolar hemorrhage. The centrineurogenic hypothesis proposed by Moss and Stein (167) is considered in detail. In addition, histamine is discussed as it relates to the adult respiratory distress syndrome and vascular permeability in general.

LITERATURE REVIEW

I. Functional Anatomy

Pulmonary Vessels

The pulmonary circulation originates at the pulmonary semilunar valves and extends to the junction of the pulmonary veins and left atrium. Included in this system is a short pulmonary trunk, right and left pulmonary arteries and their lobar branches, arterioles, capillaries, venules, small and large pulmonary veins (115).

In the adult human being three types of pulmonary arteries are described based upon the histology of the arterial wall (115). The wall of elastic arteries, which are greater than 1000 μm external diameter, consist predominantly of elastic fibrils with some muscle fibers and collagen. Examples of this type of artery include the pulmonary trunk, right and left pulmonary arteries and their lobar branches. The wall of muscular arteries, whose external diameter is between 100 and 1000 μm, consist of smooth muscle fibers interposed between internal and external elastic laminae. The muscular pulmonary arteries lie close to the bronchioles, respiratory bronchioles and alveolar ducts. The wall of arterioles, which include precapillary vessels less than 100 μm external diameter, initially has a thin layer of smooth muscle that subsequently disappears so that the wall consists solely of an endothelial lining and a single elastic lamina. Pulmonary arterioles supply blood to alveolar ducts and alveoli.

Precapillary vessels accompany the dichotomous branching of the airways to the level of the terminal bronchioles and from this point divide extensively to form the capillary bed (242). The pulmonary capillaries are lined by an endothelial layer and surrounded by alveoli lined with epithelium. This capillary network is so dense that it is regarded by some as a sheet of flowing blood interrupted in places by "posts" much like an underground parking garage (242).

Pulmonary venules are postcapillary vessels less than 100 μm external diameter with a histologic structure identical to arterioles. They are formed in the area of the bronchioles and pass into the connective tissue septa between secondary lobules to enter pulmonary veins. The media of pulmonary veins is somewhat irregular in thickness consisting of oblique, circularly arranged smooth muscle fibers and collagen while the adventitia is thick and fibrous. Near the venoatrial junction cardiac muscle appears in the walls of the pulmonary veins (115). Von Hayek (116) has observed cardiac muscle fibers accompanying pulmonary veins as far back as the hilum. The degree of muscularization of pulmonary vessels as well as their distribution within the lung is quite species dependent (85,158). The pulmonary arteries in man, dog and rabbit contain more smooth muscle than veins of comparable size. However, in other species such as the guinea-pig, cat, pig and calf, both arteries and veins have abundant smooth muscle (127). Only in rabbits and cattle does the pulmonary circulation contain thick walled precapillary vessels reminiscent of systemic arterioles (85). McLaughlin and co-workers (158) found large variation in the distribution of smooth muscle within pulmonary vessels of several species of animals. They urged extreme caution when comparing

findings from other species with human beings since equally marked physiologic, pathologic and biochemical differences may also exist. It is interesting that of the species examined (i.e., cattle, sheep, pig, dog, cat, monkey, horse, rat, rabbit and guinea-pig), the pulmonary vascular architecture in the horse most closely resembled that found in human-beings (158).

The pulmonary arteries also give rise to branches which do not accompany the dichotomous branching of the airways. These are called supernumerary arteries which actually outnumber the conventional ones, providing 25 to 40% of the total cross-sectional area of the pulmonary arterial bed (170). They serve as a collateral source of blood to the terminal respiratory units (i.e., structures distal to and including respiratory bronchioles), particularly following obstruction of conventional pulmonary arteries (192).

Bronchial Vessels

Whereas pulmonary arteries deliver mixed venous blood to the lung at low vascular pressures, the bronchial arteries deliver systemic arterial blood at high vascular pressures. Bronchial arteries vary in number and origin. Three arteries are usually found, one for the right lung and two for the left lung, originating from the thoracic aorta (48) or one of its major branches (161). Bronchial arteries supply blood to the bronchial tree, nervous, lymphoid, and connective tissues within the lung (32,161). The bronchial arteries also supply the pleura of some species, including human beings (161), cattle, sheep, and swine (158).

The existence of direct anastomotic connections between pulmonary arteries and bronchial arteries is controversial and may be species dependent (158). Despite this controversy, however, it is generally accepted that anastomoses between bronchial and pulmonary vessels may occur in the precapillary, capillary and postcapillary pulmonary bed (170). Approximately 30% of the bronchial arterial supply is returned through the bronchial, azygos, or intercostal veins into the right atrium. The remaining 70% is returned to the left atrium through the pulmonary veins and thus constitutes a right to left shunt (170). Although bronchial flow is only approximately 1% of the cardiac output in the normal lung (32), considerable increases in flow may occur during such maladies as neoplasia, congenital anomalies and inflammation (170).

Innervation and Receptors

The pulmonary circulation is innervated by the sympathetic and parasympathetic nervous systems (115,121,194). In the parasympathetic system, preganglionic efferent fibers have their origin in the dorsal vagal nuclei within the medulla. These fibers descend in the vagus nerve and synapse with ganglia located around blood vessels. Short post-ganglionic fibers then innervate vascular smooth muscle (115,194). Sympathetic preganglionic efferent fibers traveling to the lung originate in the intermediolateral horns of thoracic spinal cord segments two through six. They synapse with cell bodies of postganglionic fibers in the second to sixth spinal ganglia, middle cervical, or stellate ganglia (115). Postganglionic sympathetic fibers emanating from these ganglia and the vagus nerves contribute to the formation of an extrapulmonary (i.e., anterior and posterior pulmonary plexuses) plexus at the roots of

the lungs (170). The extrapulmonary plexuses are continued within the lung parenchyma as two main intrapulmonary plexuses, one along conducting airways and the other along the pulmonary artery and its branches (161). The sympathetic postganglionic vasoconstrictor fibers are adrenergic and the parasympathetic vasodilator fibers are cholinergic. Murray (170) and Fishman (83) consider these vasodilator fibers to be physiologically unimportant in adult human beings.

It should be emphasized that tremendous variability in the innervation of the mammalian lung exists between species (117,194). Extrapolation of physiologic responses or anatomic distribution of nerves from one species to another must therefore be done with considerable caution (194). Despite species variability, some generalizations can be made regarding the pattern of innervation of pulmonary vessels (66,85). 1) Both sympathetic and parasympathetic fibers are found in close association with pulmonary vessels. 2) The arteries have a more widespread and complete innervation than the veins. 3) The pulmonary vascular innervation in most species is relatively sparse when compared with bronchial or other systemic arteries. 4) The density of nerve fibers is greatest in the larger elastic vessels, less in muscular arteries, and absent in vessels less than 30 μm. 5) Both alpha and beta adrenergic receptors are present; however the alpha receptors predominate (17,229,232). 6) The small intrapulmonary veins are minimally supplied with nerves in comparison to the small precapillary vessels. The calf appears to be an exception because the small veins are more profusely innervated than the smaller arteries (117).

Lymphatics and Lymph Nodes

The lungs are provided with an abundant supply of lymphatics surpassing the number found in several other organs including the liver, kidney, and spleen (161). Grossly, the lymphatics can be divided into a superficial and deep network. The superficial network supplies the visceral pleura and the deep network accompanies the cartilagenous airways as well as branches of the pulmonary arteries and veins (161). The two networks anastomose in the pleura and at the hilum (115).

Histologically, the walls of larger lymphatics consist of collagen, elastic fibrils, smooth muscle and an endothelial lining. The smaller lymphatics consist of a fibro-elastic coat and an endothelial lining while lymph capillaries consist only of an endothelium (115). Valves, formed by intimal folds, within the lymphatics, are numerous in the pleura and hilar region but infrequent or absent in the lung parenchyma (161). Lymphatics extend at least to the level of the terminal bronchioles (145) but are not present in the walls of alveolar sacs or alveoli (115,161). Lymph vessels between adjacent terminal respiratory units are called juxta-alveolar lymphatics and these constitute the distal blind-ended tubules of the lymphatic system (145). Pulmonary capillaries within the inter-alveolar septum have been estimated to be between 100 μm and 1000 μm from the nearest juxta-alveolar lymphatic (170).

Lymph is formed by normal lungs (26,237) and proceeds toward the hilum along bronchial, arterial, and venous lymph vessels. Exception to this centripetal pattern occurs in the pleura (145). Lymph from the lung drains into tracheobronchial lymph nodes, thoracic duct, and finally the right atrium. Recently, Parker et al. (179) estimated total

lymph flow for the normal dog lung to be approximately 0.07 ml/min/100 gm wet lung weight. The normal concentration of albumin in lung lymph is approximately 80% and the larger globulins approximately 50% of the plasma albumin and globulin concentration, respectively. The total protein concentration in lung lymph is approximately two-thirds the plasma concentration. This is consistent with the concept that protein molecules are sieved according to their molecular size (26,219).

Lung Ultrastructure

The alveolar epithelium is continuous with airway epithelium. Three cell types constitute the alveolar epithelium. Type I cells (squamous pneumocytes) consist of a nucleus with long thin cytoplasmic extensions that cover approximately 95% of the total alveolar surface (239). Type II cells (granular pneumocytes) are more numerous than type I cells but because of their cuboidal shape occupy less than 5% of the alveolar surface (170). Unlike type I cells, type II cells undergo mitosis and are rich in mitochondria, endoplasmic reticulum, Golgi apparatus, and osmiophilic lamellated bodies. The latter have been associated with the production and removal of surfactant (238). Type II cells can differentiate into type I cells and appear to be the main cell type involved in the repair of injured alveolar epithelium. Type III cells (alveolar brush cells) occur rarely and may serve as receptor cells, although nerve fibers directly associated with these cells have not been identified (239).

Between all alveolar epithelial cells exist zonulae occludentes ("tight junctions"). These epithelial tight junctions are impermeable to macromolecules, including horseradish peroxidase (207). Pinocytotic

vesicular transport is the only means by which macromolecules may bypass the intercellular junctions of alveolar epithelium (207).

The pulmonary vascular endothelium forms a continuous lining in the arteries, capillaries and veins. Ultrastructurally the pulmonary capillary endothelium is continuous and nonfenestrated resembling that found in skeletal and cardiac muscle (207). Each endothelial cell consists of a nucleus and long cytoplasmic extensions. The luminal surface is specifically designed for degradation or transformation of several vasoactive substances that include the adenine nucleotides, bradykinin and angiotensin I. The anatomic site for these metabolic functions is the caveolae intracellulares which are localized invaginations of the luminal surface that communicate with the bloodstream through a single lamellar (i.e., diaphragm) membrane (170).

Relative to alveolar epithelium the vascular endothelium is "leaky". Schneeberger (207) has demonstrated that junctional slits between endothelial cells are sufficiently wide (4 nm) to allow passage of small protein molecules and horseradish peroxidase from plasma into the interstitial space.

In all mammals the pulmonary alveolar epithelial and capillary endothelial ultrastructure is essentially identical. This is not the case however, in the interstitium where species variation is great. The size and number of connective tissue fibers are directly proportional to the size of the animal. For example, the primate and canine lung has considerably more and coarser collagenous and elastic fibers than does the rat or mouse lung (238).

Elastic, collagenous, and reticular connective tissue fibers are present in the lung interstitium. These fibrous elements are the supporting lattice for the entire lung and constitutes the so-called "fibrous continuum of the lung" (138). There are three different constituents of this fibrous continuum, albeit they are all interconnected and act as one functional unit: 1) axial connective tissue, 2) peripheral connective tissue, and 3) parenchymatous connective tissue. The axial connective tissue, originating at the hilum, contains the airways, arteries and deep lymphatics. The peripheral connective tissue is essentially the visceral pleura connective tissue and has the superficial lymphatics embedded within it. The parenchymatous connective tissue lies inside alveolar walls and forms a loose basket around each and every alveolus, thus providing structural support for alveoli as well as capillaries (239).

In addition to connective tissue elements occupying the interstitium, there are cellular constituents (e.g., mesenchymal and mononuclear cells) and proteoglycan filaments. The latter are 98% hyaluronic acid and 2% protein and fill the spaces between connective tissue fibers and cells. The interstitial fluid normally present is entrapped within these proteoglycan filaments and together they are known as the tissue gel. Free fluid is also present but represents a very small compartment in normal lungs (104).

The alveolar-capillary membrane is subdivided into a thin portion and thick portion (170). The thin side is approximately 0.5 μm and is characterized by absence of a morphologic identifiable interstitial space between the fused alveolar and endothelial basement membranes, even

during pulmonary edema (239). This narrow membrane combined with a large surface area (approximately 70 m^2 in man) makes it an ideal location for diffusion of gases between blood and alveoli (104). In contrast, the thick side with a variable thickness up to several micrometers, contains a distinct interstitial space between the nonfused alveolar and endothelial basement membranes (178). The thick portion provides a supporting structure as well as the primary site for fluid and solute exchange (86). This portion of the interstitium connects without interruption to the interstitial fluid sumps associated with the connective tissue sheaths surrounding airways and blood vessels (239).

II. Pulmonary Hemodynamics

Interrelationship of Pressure, Flow, Volume, Distensibility and Resistance

The complexity of understanding pulmonary hemodynamics is perhaps best summarized in the following quote:

> The investigator seeking to understand the pulmonary circulation is confronted by awesome problems: a system of collapsible tubes, of variable number, parts of which narrow while others expand with lung inflation, suspended in an air-filled organ and perfused in a pulsatile fashion with a fluid whose viscosity changes with flow rate, the whole system being subjected to cyclical changes of pressure and volume during breathing (49).

Pressure

Relative to pressures in the systemic circulation, pressures in the pulmonary circulation are very low. Pulmonary artery systolic and diastolic pressures are about 25 and 8 mmHg, respectively, with a mean pressure of approximately 15 mmHg. Since the left atrial pressure is

about 5 mmHg, the vascular pressure gradient across the lung (i.e., pulmonary perfusion pressure) is approximately 10 mmHg (242). Pulmonary artery wedge pressure represents the pressure at the first postcapillary collateral venous vessel (82) and thus is slightly greater than left atrial pressure and less than capillary pressure. In isolated dog lungs the average isogravimetric capillary pressure is 7 (88) to 9 (1) mmHg. Vascular transmural (or distending) pressure, which represents the difference between the intravascular and extravascular pressure is an important concept in pulmonary hemodynamics because even small changes in transmural pressure greatly affect vascular caliber (82). The extravascular pressures are subject to continuous fluctuations in the lung due to changes in intrapleural pressure during ventilation (82). Under static conditions alveolar pressure is zero (i.e., atmospheric) and therefore the capillary transmural pressure is the intravascular pressure. Pressure surrounding the parenchymal pulmonary arteries and veins (i.e., extra-alveolar vessels) is considerably less than alveolar pressure. This occurs because as the lung expands the blood vessels are pulled open by radial traction of the lung parenchyma. Since the vessels are relatively more rigid than the surrounding elastic parenchyma, a substantial negative pressure may develop around these vessels thus increasing transmural pressure (185,242).

Flow

Blood flow through the pulmonary circulation is pulsatile (164) and, at least in man, is unevenly distributed. The latter occurs because the low pressure pulmonary circulation is operating in a gravitational field (170). In such a system a vertical distribution of flow exists because

of increasing transmural pressure and decreasing vascular resistance from the top to the bottom of the lung. Using radioactive xenon West (242) demonstrated this phenomenon and subsequently divided the lung into 3 zones according to the magnitude of pressures in the pulmonary artery, alveolus, and pulmonary vein. At the apex of the lung (dorsum in quadrapeds) is zone 1 where alveolar pressure exceeds arterial pressure, thus collapsing alveolar capillaries and precluding flow. This zone is thought not to exist under normal conditions. Furthermore, even if alveolar pressure exceeds pulmonary artery pressure, flow through zone 1 is possible through corner vessels. These vessels are located in the corners of 3 alveoli and are not subject to alveolar pressure. Because of surface tension forces at the alveolus, large retracting forces tend to pull these vessels open allowing blood to flow through zone 1 (239). In zone 2 pulmonary arterial pressure exceeds alveolar pressure and both of these exceed venous pressure. The alveolar vessels are essentially collapsible tubes surrounded by a chamber of higher pressure, analogous to a Starling resistor. Under zone 2 conditions blood flow is determined by the arterial-alveolar pressure gradient, rather than the classical arterial-venous pressure difference, and therefore flow is unaffected by the pressure distal to the collapse point until this exceeds alveolar pressure. This phenomenon is known as the sluice or waterfall effect because flow over a waterfall is unaffected by the height of the drop beyond (12). Vascular pressure increases about 1 cm water/cm vertical distance down the lung. Thus, the pressure gradient (i.e., pulmonary artery minus alveolar pressure) increases, resistance decreases, and flow increases down zone 2. The decreasing resistance is due to recruitment

and distension of vessels resulting from the increasing transmural pressure (242). In zone 3 venous pressure exceeds alveolar pressure causing distention of alveolar vessels and flow once again is determined by the arterial-venous pressure gradient. Flow increases down this zone, albeit less dramatically than in zone 2. This increased flow cannot be explained by an increased pressure gradient since all vascular pressures increase equally down zone 3. However, transmural pressure (across alveolar vessels) does increase and this distends and recruits vessels thus decreasing vascular resistance and increasing conductance (242). At the extreme base of the lung a zone 4 has been described (125) in which blood flow is reduced relative to zone 3. Zone 4 is small at high lung volumes and large at low lung volumes suggesting that vascular resistance is affected by lung retractive forces surrounding extra-alveolar vessels. Increased interstitial pressure has also been suggested as a cause for increased resistance and decreased flow in this zone (170).

Volume

The pulmonary vasculature is a distensible reservoir for blood with the veins holding about 50%, arteries 30%, and capillaries 20% of the pulmonary blood volume (251). The volume of blood within the lungs is determined passively by the balance between inflow from the right heart and outflow from the left heart. Normally pulmonary blood volume is approximately 10% of total blood volume while blood in the heart and lungs (i.e., central blood volume) is 20 to 25% of total blood volume (82).

Distensibility (Compliance)

Pulmonary vascular distensibility, expressed as the change in vascular volume per unit change in transmural pressure is determined by the elastic properties of the vasculature, smooth muscle tone, perivascular air and tissue pressures, alveolar surface tension forces, and mechanical distortions associated with surrounding elastic tissue that is rapidly expanding (82). Despite these complex considerations, several generalizations can be made regarding pulmonary vascular distensibility (12,82,127,140). 1) The pressure-volume characteristics of the entire pulmonary vascular tree resemble those of a large systemic vein (i.e., highly distensible at low transmural pressure but relatively indistensible at high transmural pressure). 2) The pulmonary veins are essentially rigid tubes when left atrial pressure exceeds 15 mmHg. 3) The vascular pressure at a given volume is higher when pulmonary vessels are being filled than when they are emptying. 4) The pulmonary venous-left atrial segment is less distensible than the systemic venous-right atrial segment. 5) Approximately 60% of the distensibility of the entire pulmonary vascular bed lies in the veins, 25% in arteries and 15% in capillaries. 6) In contrast to systemic arterioles (which are relatively rigid), pulmonary arterioles are thin-walled and easily distensible and therefore contribute to the pressure-volume characteristics of the pulmonary circulation.

Resistance

Poiseuille's Law states that resistance to fluid flowing through cylindrical tubes is inversely proportional to the fourth power of the tubes radius and directly proportional to fluid viscosity and tube length.

It assumes laminar flow of Newtonian fluid (i.e., constant viscosity) through rigid tubes. To varying degrees these assumptions are not met in the pulmonary circulation and therefore the relationship between pressure and flow is not a linear one (82,127). For example, blood flow through the pulmonary circulation is not laminar nor does blood maintain a constant viscosity as it passes through the microcirculation. With increasing flow or transmural pressure, pulmonary vascular resistance initially falls rapidly and then more slowly. This occurs because increasing transmural pressure easily distends all segments of the pulmonary vascular bed as well as recruiting previously collapsed segments. When all the vessels become recruited and maximally distended, pressure then increases linearly with flow and resistance remains constant (127). In contrast to the systemic circulation where resistance to flow is predominantly in the arterioles, resistance through the pulmonary circulation is more longitudinally distributed. Brody et al. (29) found that pulmonary arteries contributed 46%, capillaries 34% and veins 20% of the total lobar vascular resistance in the isolated dog lung.

III. Factors Controlling Pulmonary Vascular Resistance and Compliance

Passive Factors

Factors controlling pulmonary vascular resistance can be passive or active. Passive changes in resistance are secondary to changing mechanical conditions within the lung or systemic circulation. Control of resistance in the normal pulmonary circulation is dominated by mechanical factors, especially the effects of ventilation and gravity (12,85).

Active changes in pulmonary vascular resistance imply changes in vessel caliber due to contraction or relaxation of vascular smooth muscle in response to neural or humoral stimuli that are under local or remote control.

Pulmonary vascular resistance is least at functional residual capacity, vascular resistance increasing when lung volume increases or decreases. At very high lung volumes alveolar vessels are stretched longitudinally and at low lung volumes extra-alveolar vessels become kinked resulting in greater resistance to flow (170).

Anything which increases transmural pressure in pulmonary vessels decreases pulmonary vascular resistance. Elevation of left atrial and/or pulmonary artery pressures decreases pulmonary vascular resistance, an effect that is quantitatively greater when initial vascular pressures are low (24). Another consideration is interstitial pressure. At least 3 factors contribute to negative interstitial pressure: 1) pleural pressure, 2) tendency for alveoli to collapse thus pulling on corner vessels, and 3) retractive forces pulling open pulmonary vessels as the surrounding lung parenchyma expands (i.e., interdependence). Similarly, an increase in intravascular blood volume will distend other vessels and lung parenchyma causing a decrease in pulmonary vascular resistance. Decreased blood viscosity may also decrease pulmonary vascular resistance. Recognizing these passive components is important because interpretation of active vasoconstriction or vasodilation is difficult in the presence of passive changes in vessel caliber. The only exception is when the vasomotor responses are opposite in direction and predominate over concomitant passive changes (24,170).

Active Factors

Much of the active pulmonary vascular response to alveolar hypoxia or hypercapnia is mediated locally within the lungs (83). Local alveolar hypoxia (14,123,135,136,143), and to a lesser extent hypercapnia (14,23, 85), increase pulmonary vascular resistance by constricting primarily the small arteries (83). Pulmonary veins have also been reported to constrict in response to alveolar hypoxia (163,190). That these responses are mediated locally is supported by the fact that they occur in isolated lungs devoid of autonomic innervation, in sympathectomized animals, and in animals following administration of adrenergic blocking agents (82). Although the precise mechanism for this local response is unclear, it is thought that alveolar hypoxia or hypercapnia may directly interfere with excitation-contraction coupling of vascular smooth muscle or cause its effect indirectly through release of intrinsic chemical mediators (83). The most likely candidates for the latter are catecholamines, histamine, prostaglandins and angiotensin (83).

Nerve Stimulation

Although the pulmonary vasculature has an abundant sympathetic innervation (66,98,117,132), the functional role of the sympathetic nervous system in regulating the pulmonary vascular bed remains controversial (66,133). Evidence that pulmonary lobar arteries and veins (external diameter 0.8 to 1.4 mm) have the ability to contract is provided by Greenberg et al. (98). In this investigation, large contractile responses were elicited during vascular transmural nerve stimulation and this effect was attenuated in a dose-dependent manner by several

adrenergic blocking agents including phentolamine, tolazoline, quanethidine and bretylium. Cocaine, which blocks reuptake of norepinephrine, enhanced the contractile activity (98). Using intact preparations, Daly et al. (54) demonstrated that electrical stimulation of the sympathetic chain, stellate or middle cervical ganglions increased pulmonary artery pressure 10 to 15% during constant flow experiments. Furthermore, when pulmonary artery pressure was held constant, stimulations of similar magnitude produced a 30% decrease in flow. Since all passive factors affecting pulmonary vascular resistance were excluded, these investigators (54) concluded that active vasoconstriction caused pulmonary vascular resistance to increase. In more recent studies, electrical stimulation of the stellate ganglion at increasing frequencies caused a frequency-dependent increase in pulmonary vascular resistance in the open- (110,132) and closed- (133) chest dog and this effect was blocked by phentolamine. Using constant flow experiments, Kadowitz et al. (134) demonstrated that the postcapillary vessels contributed as much as 50% to the total increase in pulmonary vascular resistance with the remaining constriction occurring primarily in small arteries.

In contrast, other investigators have been unable to show increased pulmonary vascular resistance in response to stellate ganglion stimulation in the perfused canine lung, but found instead that nerve stimulation increased pulse wave velocity and elastic modulus and decreased distensibility of large pulmonary arteries. These effects were blocked by the alpha blocker, phenoxybenzamine (129,229). Ingram et al. (129) believe their results are more consistent with the functional anatomy of the pulmonary circulation since the larger pulmonary arteries (> 2 mm diameter)

have more abundant elastic tissue, a greater supply of adrenergic nerves, and contain more norepinephrine in their walls than do the small arteries (66,85). The functional significance of increased stiffness of large pulmonary arteries would be to help maintain equal stroke volume between the two ventricles which would be particularly useful during sudden increases in right ventricular cardiac output, as might occur at the start of exercise. Thus, in contrast to the effects of local alveolar hypoxia which acts on small resistance vessels to redistribute blood to better ventilated parts of the lung, reflex sympathetic stimulation acts on larger arteries to synchronize right and left cardiac output by adjusting vascular distensibility (229).

The absence of any change in pulmonary vascular resistance during stellate ganglion stimulation led Ingram et al. (129) and Szidon and Fishman (229) to conclude that the increased pulmonary vascular resistance demonstrated in earlier studies (54), was probably not due to vasoconstriction but rather due to viscosity changes. They argue that, because of the nonlinear behavior of blood at low shear rates (associated with low blood flow), such studies (54) would be expected to exaggerate the effects of viscosity on the pulmonary vascular bed (129,229). This explanation, however, is no longer tenable since more recent investigations demonstrating increased pulmonary vascular resistance during stellate ganglion stimulation have utilized normal pulsatile flows and cannulation techniques that are not likely to alter vascular innervation (110,132,133). Thus, it appears that sympathetic stimulation of pulmonary vessels is capable of both increasing vascular resistance and decreasing vascular compliance (66). Indeed, Daly and Daly (52) and Pace (177) electrically

stimulated the stellate ganglion in dogs and found that pulmonary vascular resistance and input impedance both increased. Input impedance, which is the ratio of peak pressure to peak flow, increases as vascular compliance decreases. The latter effect increases the fraction of total hydraulic power associated with pressure oscillations (117).

The numerous studies (52,54,110,129,132-134,177) involving nerve stimulation have firmly established the presence of efferent sympathetic pathways that may participate in neural regulation of pulmonary vessels. However, these studies do not establish the existence of afferent and/or central integrative pathways that are a prerequisite for reflex regulation of the pulmonary circulation (66). Reflex regulation of the pulmonary vasculature could be mediated through the peripheral baroreceptors, peripheral or central chemoreceptors, or through release of humoral agents.

Peripheral Baroreceptors and Chemoreceptors

Changes in systemic blood pressure may cause alterations in pulmonary vascular resistance that are reflexly mediated through the carotid and aortic sinuses (53). The hemodynamic effects of carotid or aortic body stimulation on the systemic circulation have been well documented (44,118, 180) but the role of the peripheral chemoreceptors in reflex control of the pulmonary circulation remains unsettled (66). Aviado et al. (10) and Wilcox et al. (246) reported that systemic hypoxemia stimulated the peripheral chemoreceptors to reflexly increase pulmonary vascular resistance. In contrast, while ventilating the left lower lobe with normoxic gases during systemic hypoxemia, Szidon and Flint (230) demonstrated a decrease in left lower lobe pulmonary vascular compliance but no change in

pulmonary vascular resistance as determined from pressure-volume and pressure-flow curves, respectively. None of these preparations, however, could distinguish between carotid and aortic body stimulation. In a complicated preparation Daly and Daly (53) reported increased pulmonary vascular resistance during hypoxemic perfusion of the carotid bodies but this effect was consistently found only in the absence of bronchial arterial blood flow. In another study, pharmacologic stimulation of the carotid bodies with nicotine failed to increase pulmonary vascular resistance but an increase in pulmonary vascular resistance was elicited during aortic body stimulation (225) and was later shown to be both pre- and post-capillary in origin (224). Whether the aortic bodies reflexly alter pulmonary vascular resistance or compliance in response to local physiologic stimulation (i.e., altered gas tensions and pH) is unknown (66). An interesting but deleterious effect of peripheral chemoreceptor stimulation was reported by Levitzky et al. (142). They reported that hypoxemic stimulation (P_aO_2 < 40 mmHg) of the peripheral chemoreceptors attenuated the local alveolar hypoxia response causing increased right to left shunting of blood, thus worsening systemic hypoxemia. Denervation of the peripheral chemoreceptors blocked this positive feedback mechanism.

Brain

That the brain not only integrates afferent impulses but may also initiate efferent impulses to the pulmonary vasculature is evidenced by decreased pulmonary vascular compliance during brain ischemia (96) or electrical stimulation of the hypothalamus (229). In other studies electrical stimulation of the hypothalamus (4) or increased intracranial pressure (120,151) increased pulmonary vascular resistance.

Humoral Agents

Humoral agents may be released from the adrenal glands (epinephrine and norepinephrine), from within the lungs themselves (histamine, serotonin and prostaglandins), or released elsewhere in the body and activated within the lungs (angiotensin 2). These agents have potent effects on the pulmonary circulation. In the isolated intact lung preparation, with constant blood flow and outflow pressures, these agents are generally vasoconstrictors; however, in the intact animal they cause variable responses because they also alter cardiac output, mean arterial and left atrial pressures which secondarily produce passive changes in the lung vasculature (17). While a large variety of factors may cause release of catecholamines from the adrenal glands or antidiuretic hormone from the posterior pituitary (104) it is particularly interesting that carotid body hypoxia also reflexly causes release of these humoral agents (7,209). Thus, it seems clear that sympathetic nerves and receptors supplying lung vessels are part of an extensive control system which can be stimulated centrally and reflexly, thereby modulating pulmonary hemodynamics.

IV. Lung Fluid Balance

Starling Forces

Transvascular movement of water in the lung is believed to be governed by hydrostatic and osmotic forces as described in the Starling equation (88,106,141,221):

$$\dot{Q}_f = K_f \left[(P_{mv} - P_{pmv}) - \sigma (\pi_{mv} - \pi_{pmv}) \right] ,$$

where $\dot{Q}_f$ is the rate of net transvascular fluid flow, K_f is the

microvascular filtration coefficient, P_{mv} is the microvascular hydrostatic pressure, P_{pmv} is the perimicrovascular hydrostatic (interstitial) pressure, σ is the weighted plasma protein reflection coefficient, π_{mv} is microvascular colloid osmotic pressure, and π_{pmv} is the perimicrovascular colloid osmotic pressure. When discussing these forces average values for the entire lung are usually used; however, large differences in the distribution of Starling forces exist at different levels in the lung due to the action of gravitational forces on blood flow and ventilation.

Until relatively recently it was believed that net reabsorption of fluid into the microcirculation occurred in the lung (105). However, it is now generally agreed that since lymph is continuously formed in normal lungs, the balance of the Starling forces must favor net filtration (26). While the magnitude of intravascular Starling forces (i.e., P_{mv} approximately 7 to 9 mmHg and π_{mv} approximately 25 to 28 mmHg) are generally well established, the magnitude of extravascular forces is intensely debated. Staub (221) believes P_{pmv} is atmospheric and π_{pmv} is very high (approximately 20 mmHg) whereas Guyton et al. (106) believe P_{pmv} is substantially subatmospheric (approximately - 8 mmHg) and π_{pmv} is only about 13 mmHg. Guyton et al. (106) maintain that pulmonary lymph protein may become concentrated by lymph nodes and therefore lung lymph overestimates the actual perimicrovascular protein concentration. Regardless of which theory is correct, both agree that the relative magnitude of these extravascular Starling forces are such that the lung normally has net filtration occurring from the microcirculation.

Pathways for Fluid Movement

Several pathways for fluid and protein transport are thought to exist across the pulmonary microvascular endothelium (20,218). These include the small pores (radii 34 angstroms) which allow complete protein sieving, intermediate pores (radii 34 to 300 angstroms) which allow partial sieving of protein, and infrequently occurring large pores (approximately 1000 angstroms) which allow no protein sieving (i.e., all proteins pass through). These pores are all in the intercellular junction and are hydraulically conductive as well as a diffusion pathway for lipid insoluble macromolecules. Their sizes arbitrarily signify their relative reflection coefficients for plasma proteins (i.e., σ = 1 for small pores, 0 for large pores, and variable for intermediate pores). In addition to pores in the intercellular junctions, extremely small intracellular pores (5 angstroms) also exist. These intracellular pores are thought to conduct water but are very restrictive to almost all solute molecules (218). Vesicular transport may also account for some protein conductance although this process is considered to be too slow to be physiologically significant (20,231).

V. Pulmonary Edema

Types and Etiologies

Pulmonary edema is a pathologic state in which there is abnormal extravascular water accumulation in the lung (234). According to the Starling equation pulmonary edema can be mediated by two possible mechanisms: 1) increase in pulmonary microvascular hydrostatic pressure or 2) increase in microvascular permeability. The former could be due

to an alteration in pulmonary hemodynamics (i.e., increased pulmonary blood volume, pulmonary vascular resistance or decreased pulmonary vascular compliance) and the latter mediated by mechanical, humoral or neural factors (86). Increased microvascular hydrostatic pressure causes increased fluid filtration from the microvasculature and this is manifested by a low protein concentration in pulmonary lymph. However, increased endothelial permeability results in an increase in both fluid and protein conductances causing pulmonary lymph to be high in protein (218). Although the latter may be reversible with time, it may be much more serious than conditions which only elevate capillary hydrostatic pressure (e.g., congestive heart failure) because of the marked reduction in the transmural colloid osmotic pressure gradient (222).

Sites of Fluid Leakage and Accumulation

Leakage of fluid from the pulmonary circulation is not limited to capillaries and venules (2,3,128,162). Using isolated dog lungs, Iliff (128) increased pulmonary artery or venous pressures while maintaining zone 1 conditions (thus compressing alveolar vessels). In either case lung weight increased substantially, with leakage primarily occurring from extra-alveolar veins. Under zone 3 conditions approximately 60% of transvascular fluid movement was through the extra-alveolar vessels. In similar studies Mitzner and Robotham (162) concluded that 50% of transvascular fluid movement was through alveolar vessels, 23% through extra-alveolar arteries and 27% through extra-alveolar veins. The principal Starling force contributing to leakage of fluid from extra-alveolar vessels is presumably the perivascular hydrostatic pressure, which may

become increasingly subatmospheric (< - 20 mmHg) as the surrounding lung parenchyma "pulls" on the relatively indistensible perivascular connective tissue.

The extravascular-extracellular space of the lung is composed of an interstitial and an alveolar gas space. The interstitial space has two components, the alveolar wall interstitium (thick septum) and the loose connective tissue space surrounding airways and blood vessels (222). The former site is where excess fluid is first detected by electron microscopy (45) whereas the latter is the first site detected by light microscopy (223). The alveolar-capillary barrier (i.e., thin septum) shows no evidence of fluid accumulation even during severe pulmonary edema resulting from high microvascular hydrostatic pressure (45).

The alveolar wall interstitium is continuous with the loose connective tissue space surrounding vessels and airways, and although this space is not large in the normal lung, it has a very large potential for expansion to a volume that is approximately equal to pulmonary blood volume (222,251). The alveolar gas space has an enormous potential for fluid accumulation that is an order of magnitude greater than the potential interstitial space; however, alveoli do not begin accumulating a significant fluid volume until interstitial edema is extensive (222).

Fluid filtered into the alveolar interstitium apparently moves by bulk flow to the perivascular and peribronchial regions. Since the interstitial pressure surrounding these structures is thought to be lower than it is around alveolar capillaries, fluid moves down a hydrostatic pressure gradient toward junctional tissues where arterioles, venules and lymphatic vessels lie (84,106).

Safety Factors

Safety factors that operate to prevent pulmonary edema when capillary filtration pressure is increased include (178): 1) a very low compliance of the interstitial space; 2) decreased interstitial colloid osmotic pressure because of protein washout; and 3) increased lymph flow. Because the interstitial space has an initial low compliance, interstitial pressure can increase from -7 to 0 mmHg without development of gross edema. However, when interstitial hydrostatic pressure increases above atmospheric pressure, compliance of the interstitial space dramatically increases resulting in rapid accumulation of water in the interstitial space and alveoli. Under chronic conditions of increased fluid filtration lymphatics may hypertrophy, thus facilitating rapid removal of lymph. During chronic pulmonary venous hypertension in dogs, lymph flow has been found to increase as much as 28-fold (115).

Quantitation of Lung Water

Quantitation of pulmonary edema is a difficult task, particularly in the intact animal (234). Lung auscultation, lung radiographs or measurements of lung compliance, and blood gases are all nonspecific and often show little evidence for increased lung water accumulation until pulmonary edema becomes severe (105,219). Attempts to quantitate pulmonary edema have primarily centered on three techniques: 1) measurement of transthoracic electrical impedance, 2) determination of radiation emission or absorption, and 3) double indicator-dilution studies (219). In the latter technique diffusible (e.g., heat, tritiated water) and nondiffusible (e.g., radiolabeled red blood cells, dye-tagged albumin,

sodium) substances are simultaneously injected into the right heart with measurement of these substances in the left heart or aorta. The diffusible indicator measures total tissue volume. For heat (which is extremely diffusible) this includes blood volume, lung water and solids. Tritiated water also measures blood volume but its extravascular volume of distribution is limited to approximately 70% of the lung water space. Thus, heat overestimates the lung water space while tritiated water underestimates this space. Since the nondiffusible indicator is confined to the intravascular space it only measures blood volume. Chinard et al. (41) has shown that even small ions such as sodium are confined to the normal pulmonary vascular space during their initial transit. In fact, sodium dilution curves are virtually superimposed onto dye-tagged albumin curves. By subtracting intravascular volume from total tissue volume one obtains extravascular volume and this is used as an index for lung water. Although double-indicator dilution techniques provide a quantitative assessment of pulmonary edema it is unlikely that changes less than 15% are detectable (219).

Gravimetric analysis provides the most accurate determination of lung water and is accomplished by weighing excised lungs, drying to constant weight and correcting for intravascular blood volume (183). The extravascular lung water can then be expressed as a function of the animals dry lung weight (219). Although this provides a reliable index to which in vivo techniques can be compared, it obviously cannot be used to make antemortem assessments of lung water.

IV. Brain and Pulmonary Edema

The brain's ability to alter pulmonary hemodynamics and cause pulmonary edema and alveolar hemorrhage is demonstrated in numerous experimental and clinical reports. Intracisternal injection of fibrin (34,204) or veratrin (130), blunt head trauma (15,36-38,147,159), electrical (91,149) or chemical (248) stimulation of the hypothalamus, saline induced hypertension of cerebral vessels (146), chemically induced convulsions (16), electrolytic destruction of the nucleus tractus solitarius (64), and increased intracranial pressure (35,74,151) all cause pulmonary edema and alveolar hemorrhage. Clinical disorders of the brain leading to pulmonary edema and alveolar hemorrhage include seizures (21,124), increased cerebrospinal fluid pressure (73), head trauma (79, 212), cerebral hemorrhage (240), apoplexy and tumors (33). In all of these experimental and clinical reports the following observations appear consistent: 1) the edema and hemorrhage are sudden in onset frequently leading to death of the animal, 2) the edema fluid is very high in protein content with numerous red blood cells suggesting large increases in vascular permeability, 3) massive central sympathetic outflow to the cardiovascular system occurs as evidenced by large increases in pulmonary and systemic arterial pressures, 4) pulmonary blood volume increases, and 5) vasodilator agents prevent pulmonary edema and alveolar hemorrhage by preventing large increases in left ventricular afterload, thus preventing left ventricular failure and subsequent pooling of blood in the pulmonary circulation.

It seems plausible that the brain might regulate pulmonary hemodynamics through the autonomic nervous system since the latter extensively

innervates the pulmonary vascular bed (117,245) with alpha, and to a lesser extent beta adrenergic receptors (17). The ability of the brain, through the autonomic nervous system, to control the pulmonary vasculature is suggested by several investigations. Pulmonary denervation protects the lungs from edema and alveolar hemorrhage during isolated cerebral hypoxemia (167) or hemorrhagic shock (226,227). By preventing large increases in pulmonary vascular pressures, phenoxybenzamine (an alpha blocker) prevents pulmonary edema associated with chemically induced convulsions (16), chemical hypothalamic stimulation (248), blunt head trauma (15,36) and increased intracranial pressure (151). Although a portion of this protective effect is due to less pulmonary vasoconstriction during various brain stimuli, a major portion is due to the fact that the normally large increase in left ventricular afterload (i.e., mean aortic pressure) is prevented. Since afterload is an important determinant of stroke volume (i.e., stroke volume transiently decreases as afterload increases), it follows that left ventricular stroke volume would remain closely matched with right ventricular stroke volume thereby preventing increases in pulmonary blood volume and vascular pressures. In other studies (129,229) sympathetic nerve stimulation, hypothalamic stimulation, or systemic hypoxia decreased pulmonary artery compliance, an effect that was blocked by phenoxybenzamine. Phentolamine (another alpha blocker) blocks the increased pulmonary vascular resistance that occurs during electrical stimulation of the stellate ganglion (132-134), alveolar hypoxia (123) or systemic hypoxia (13). Phentolamine (36,64,248) or cervical cord transection (38,149) prevents pulmonary edema associated with hypothalamic stimulation, blunt head trauma, or electrolytic

destruction of the nucleus tractus solitarius. Propranolol or practolol (both beta blockers) potentiate the increase in pulmonary vascular resistance during alveolar hypoxia (123). Propranolol also potentiates the increase in pulmonary vascular resistance during systemic hypoxia (13,233). In other studies propranolol attenuated the increase in pulmonary vascular resistance associated with increased intracranial pressure (151). This seems paradoxical since the effect of removing beta receptor activity should be vasoconstriction and therefore potentiation of any increase in pulmonary vascular resistance. However, propranolol also induced left ventricular failure causing pulmonary vascular pressures to rise. The effect of increasing vascular transmural pressure is to increase vessel diameter and thus passively decrease pulmonary vascular resistance. In contrast to considerable sympathetic control of the pulmonary circulation (18), parasympathetic control is virtually nonexistent (170). Bilateral cervical vagotomy has no effect on elevated pulmonary vascular resistance due to alveolar hypoxia (136); however, acetylcholine antagonizes this effect during alveolar hypoxia (123) or systemic hypoxia (65). Thus, there is considerable circumstantial evidence which suggests that the brain has the ability to alter pulmonary hemodynamics during systemic hypoxia and/or hypercapnia and that this response may be regulated by the sympathetic component of the autonomic nervous system.

VII. Adult Respiratory Distress Syndrome

Definition and Incidence

The adult respiratory distress syndrome is a severe pulmonary complication usually occurring within 72 hours of a wide variety of

extrapulmonary insults, the most common being hemorrhagic shock and trauma (19). In its most dramatic form, it is characterized by the acute and unexpected onset of severe, life-threatening respiratory distress in patients whose lungs were previously normal. The syndrome is synonymous with shock lung, congestive atelectasis, capillary leak syndrome, DaNang lung, wet lung and numerous other terms (19,113,122).

Despite the diverse nature of the adult respiratory distress syndrome, diffuse damage to the alveolar-capillary membrane is considered a common denominator and once this occurs the ensuing events are similar in most patients (122). It should be emphasized, however, that this may simply represent the limited manner in which the lung responds to injury (19,122). Indeed, this is the strongest argument against combining the many diverse but specific entities into a single diagnostic category of adult respiratory distress syndrome since this may detract from important distinctions that should be made concerning pathophysiology, treatment and prognosis (81,122).

The recent development of this syndrome is thought to reflect improved emergency treatment of severely traumatized patients who would have otherwise succumbed to the initial insult (81,167). Although the incidence of human adult respiratory distress syndrome is increasing, mortality has been slowly decreasing and is now approximately 50% (122, 241). In veterinary medicine the adult respiratory distress syndrome is not well documented (191). This may be due to lack of awareness, financial considerations, and/or death of the animal from the initial insult because of a relative lack of major trauma centers.

Etiologic Factors

The exact etiology of the adult respiratory distress syndrome is unknown, although a number of factors are known to be involved. The most frequently cited factors are (19,113,167): 1) direct injury to the lung secondary to hemorrhagic shock, 2) oxygen toxicity, 3) ventilator induced injury, 4) fluid overload, 5) central nervous system trauma, 6) thromboembolism, 7) sepsis, 8) release of humoral agents (e.g., histamine, serotonin, kinins, prostaglandins, complement activation, catecholamines), 9) lymphatic insufficiency, and 10) brain hypoxia. When considering etiology of the adult respiratory distress syndrome it becomes very difficult to distinguish between initiating and complicating events. For example, a patient in hemorrhagic shock may have some or all the above-mentioned etiologic factors as secondary complications. Therefore, I believe that adult respiratory distress syndrome should be thought of as having a multifactorial etiology rather than a distinct single etiology. That is, the more factors that are present in a clinical situation, the more likely that the adult respiratory distress syndrome will develop.

Pathophysiology

The gross pathologic changes associated with the adult respiratory distress syndrome are nonspecific. Within a few hours following the clinical insult scattered petechial hemorrhages are evident over the surface of the lungs. By approximately 24-48 hours the petechial hemorrhages have become confluent, especially in zone 3, causing the lungs to appear congested and hemorrhagic. However, inflation of the lungs during this phase results in clearing of much of the hemorrhagic appearance, indicating that the primary changes are those of congestion and atelectasis.

By 48 to 72 hours the lungs grossly resemble the liver and are hemorrhagic, as evidenced by persistance of a dark red color even when the lungs are inflated. Secondary infection is common causing formation of abscesses and purulent bronchial secretions which may ultimately lead to septicemia and death. When the thorax is opened, little or no collapse of the lungs is observed and the lungs may be several times their normal weight (19,81).

Early histologic features in the adult respiratory distress syndrome consist of interstitial and alveolar edema with hemorrhage and focal atelectasis. Pulmonary vessels develop thrombi while cellular debris and proteinaceous fluid accumulate in alveoli. Hyaline membranes, thought to be composed of high molecular weight proteins, are found lining alveoli and alveolar ducts. The damaged alveolar epithelium becomes lined with type 2 alveolar cells. Lesions in alveolar epithelium usually appear more severe than those of the vascular endothelium, however, this is thought to be because of the much more rapid repair capacity of the latter rather than a unique susceptibility of the alveolar epithelium (11). Eventually interstitial fibrosis may develop, although complete healing and repair may occur if the underlying factors causing the adult respiratory distress syndrome are brought under control (241).

Pulmonary function gradually deteriorates as evidenced by increased arterio-venous shunting and respiratory dead space and decreased functional residual capacity. By increasing surface tension forces, atelectasis and alveolar edema decrease lung compliance (242). Diffusion impairment and ventilation perfusion inequalities exist and shunt fraction may exceed 50%. These effects lead to severe hypoxemia and hypocapnia. The latter occurs because ventilation is increased secondary to hypoxemic

stimulation of peripheral chemoreceptors and stimulation of vagal afferents located in the lung interstitium. When alveolar flooding occurs carbon dioxide is retained leading to severe respiratory acidosis (241).

Centrineurogenic Hypothesis

Recently Moss and Stein (167) and Brown (30) proposed a centrineurogenic etiology for the adult respiratory distress syndrome. These investigators (30,167) believe that brain hypoxia impairs oxidative metabolism in the hypothalamus which increases sympathetic outflow to postcapillary vessels leading to increased pulmonary vascular resistance and microvascular hydrostatic pressure, congestion, surfactant inactivation, atelectasis, edema, and hemorrhage. In their preparation venous blood (PO_2 35 torr) is pumped from the right atrium to one common carotid artery for 2 hours at a perfusion pressure 20 mmHg greater than mean aortic pressure. They believe the brain is being perfused only with venous blood since all other arterial channels supplying the Circle of Willis should experience retrograde flow because perfusion pressure exceeds mean aortic pressure. Moss and Stein (167) and Brown (30) reported that pulmonary lesions observed at postmortem were similar to those observed in the adult respiratory distress syndrome. They believe the pulmonary lesions secondary to brain hypoxia are species independent since similar responses were obtained in all species studied including dog, calf, pig, goat, rabbit, sheep and monkey (168). These investigators (167) then repeated their experiments following chronic unilateral pulmonary denervation. The denervation procedure involved transection of all ipsilateral hilar lung tissue followed by reanastomoses of bronchi and vessels. Two months later they induced brain hypoxia in these dogs for

two hours. Based upon gross and histologic examination they found that the innervated lung developed lesions consistent with the adult respiratory distress syndrome whereas the denervated contralateral lung was normal. Moss and Stein (167) believe their experiments are prima-facie evidence that brain hypoxia results in lesions consistent with the adult respiratory distress syndrome and that these events are neurogenically mediated.

The centrineurogenic hypothesis is heavily dependent on circumstantial evidence since there are no reports in the literature describing the specific effects of local brain hypoxia and/or hypercapnia on pulmonary hemodynamics. A critical element to the centrineurogenic hypothesis is that pulmonary postcapillary vessels have the ability to constrict in response to sympathetic stimulation. That postcapillary vessels are capable of increasing pulmonary vascular resistance is evidenced by constriction of pulmonary veins during systemic hypoxia (163,190,195,216) electrical stimulation of the stellate ganglion (134), aortic body stimulation (224), brisket disease (139) or hemorrhagic shock (137,169,226). Increased postcapillary resistance increases microvascular hydrostatic pressure which may lead to pulmonary congestion, edema, and alveolar hemorrhage (167,169). It should be pointed out, however, that precapillary constriction could also produce similar pathology. Increased pulmonary vascular resistance due to precapillary constriction occurs during alveolar and systemic hypoxia and causes pulmonary edema (126,213,243). Leakage of fluid under these conditions could occur from extra-alveolar vessels (128,162). It has also been suggested that damage to arterial walls proximal to constricted arterioles results in transarterial leakage

of fluid (243). An alternative hypothesis is that precapillary constriction may be non-uniform in nature so that the increased pulmonary artery pressure is transmitted to pulmonary capillaries not served by constricted arterioles (235).

Additional circumstantial support for the centrineurogenic hypothesis is that electrical stimulation of the hypothalamus (4) increases pulmonary vascular resistance (albeit during nonsteady state measurements of pressure and flow) as does increased intracranial pressure (120,151). In other studies, however, pulmonary vascular resistance did not change during increased intracranial pressure (144,155) or brain ischemia (96), conditions which presumably cause brain hypoxia.

During hemorrhagic shock a larger proportion of the cardiac output is delivered to the brain because of excellent autoregulatory ability of the cerebral vasculature. However, this sparing effect is relatively short-lived during severe hemorrhagic shock (167). Considerable evidence suggests that brain hypoxia is an important manifestation of late hemorrhagic shock. A large reduction in cerebral blood flow (202,215), decreased cerebral cortical PO_2 (236), increased brain lactate (249) and increased cerebrospinal fluid potassium and pseudocholinesterase (210) all offer circumstantial evidence that brain hypoxia occurs during hemorrhagic shock in the dog. Since hemorrhagic shock may produce pulmonary edema and alveolar hemorrhage (76,119,137,169,201,208,226-228) similar to that observed following brain hypoxia (167), Moss and Stein (167) believe brain hypoxia during shock is what initiates the pathophysiological events that culminate into the adult respiratory distress syndrome. Consistent with this hypothesis is the fact that during hemorrhagic shock,

anemia (and therefore decreased oxygen carrying capacity) predisposes to development of the syndrome (166) while diphenylhydantoin, a neuropharmacologic agent that reduces brain excitability, is protective (165).

In summary, the centrineurogenic hypothesis for the adult respiratory distress syndrome is based on a large body of circumstantial evidence that has not been critically tested. For example, there are no descriptions in the literature of the specific effects (i.e., changes in pulmonary vascular resistance, central blood volume, and lung water) of local brain hypoxia and/or hypercapnia on pulmonary hemodynamics. However, there are numerous experimental and clinical reports suggesting that a wide variety of brain insults can exert profound effects on pulmonary hemodynamics and ultimately cause pulmonary edema and alveolar hemorrhage similar to that observed in the adult respiratory distress syndrome. The adult respiratory distress syndrome is currently a major clinical problem for which no clear etiology has emerged and research in this area has not been particularly rewarding primarily because a suitable animal model has not been developed (63a). Clearly, a better understanding of pulmonary vascular control by the brain is needed, particularly during pathophysiological states such as the adult respiratory distress syndrome.

Thromboembolism and Humoral Agents

Although there appear to be numerous factors responsible for the adult respiratory distress syndrome, Blaisdell and Lewis (19) believe that following hemorrhagic shock and trauma thromboembolism becomes the primary initiating factor and that other postulated causes are thromboplastic in nature. This leads to activation of the coagulation cascade

with formation of microemboli consisting of platelets, red and white blood cells, fibrin, cellular debris and neutral fat. These microemboli cause mechanical obstruction of vessels and cause release of histamine, serotonin, and prostaglandins as well as activation of complement and release of proteolytic enzymes from polymorphonucleocytes. These vaso-active agents not only cause vasoconstriction but also increase bronchial and/or pulmonary microvascular permeability (19,84). In this regard, histamine is a potent constrictor of pulmonary veins (92,93) and causes a large increase in bronchial vascular permeability (188). Wilson (247) found a progressive increase in number of mast cells in the lung following hemorrhagic shock and cardiopulmonary by-pass. Since the mast cells were frequently degranulated (suggesting massive release of histamine) and the lungs developed pathologic changes similar to the adult respiratory distress syndrome, he concluded that histamine was a likely mediator of these events. Other investigators also believe that histamine may play an important role in the pathogenesis of the adult respiratory distress syndrome (19,197). Release of histamine in this syndrome also provides an explanation for the characteristic bronchoconstriction that is known to occur (19).

Complement activation, especially C3a and C5a fraction, and degranulation of polymorphonucleocytes also cause large increases in vascular permeability (63a). The combination of high pulmonary vascular pressures (mediated primarily by vasoconstriction and thromboemboli) and increased vascular permeability all contribute to development of severe pulmonary edema and alveolar hemorrhage. According to Blaisdell and Lewis (19), iatrogenic factors such as oxygen toxicity, ventilator induced injury,

and fluid overload simply enhance the development and severity of the adult respiratory distress syndrome.

VIII. Histamine, Microvascular Permeability and Adrenergic Receptors

Local intra-arterial administration of histamine to the canine forelimb (102,108,152) and equine digit (198,199) causes massive edema through increases in capillary hydrostatic pressure, microvascular surface area, and microvascular permeability (107a). The increase in the latter parameter is clearly the dominant factor in the edema produced by histamine. In this regard histamine appears to affect both the large and small pore systems (108a), however, its action on the latter is small (2 to 3 fold increases in capillary filtration coefficient) and transient lasting only 10-20 minutes (137a). Thus the majority of peripheral edema produced by histamine results from increased microvascular permeability to macromolecules, i.e., plasma proteins (108a). Many investigators believe this effect occurs primarily in venules and is due to contraction of actomyosin fibrils within the endothelial cytoplasm leading to increased gap formation between endothelial cells (150,188).

The edemagenic effects of local intra-arterial histamine on the forelimb can be blocked by simultaneous intra-arterial infusion of the beta agonist, isoproterenol (152). In contrast, intravenous (i.e., systemic) administration of histamine fails to increase forelimb weight even when calculated blood concentrations of histamine equal or exceed the intra-arterial dose (153). However, in the presence of beta blockade (propranolol) intravenous histamine causes massive forelimb edema

comparable to that obtained during intra-arterial histamine alone (100). Thus, it appears that increased blood levels of beta agonists during intravenous histamine infusion antagonize the increased water efflux in the canine forelimb (100).

With regard to action of histamine on microvascular permeability in the lung, Goetzman and Visscher (94) found no increase in canine alveolocapillary membrane permeability to radiolabeled albumin when histamine was added to the lung perfusate while Grega et al. (103) reported no increase in lung weight when histamine was infused (2.1-10 µg base/min) into the pulmonary artery of isolated fetal, neo-natal and adult canine lungs. In anesthetized dogs, Pietra et al. (188) found that intravenous histamine (7 µg base/min) caused no leak of colloidal carbon from the pulmonary microcirculation but did find transient leakage from the bronchial vessels that resulted in small increases in lung water. A similar distribution of colloidal carbon following intravenous histamine was observed in the rat lung (89). Pietra et al. (189) found no increase in lung weight when histamine was infused into the isolated rabbit lung. More recently, Drake and Gabel (70) found that intravenous histamine failed to increase pulmonary lymph flow and concentration, capillary filtration coefficient, and the calculated permeability-surface area product in the dog lung.

On the other hand, Brigham and Owen (27) reported that histamine infused into sheep caused a two to six fold increase in pulmonary lymph flow (collected from the efferent duct of the caudal mediastinal lymph node) without a change in the lymph to plasma protein ratio. They also found that histamine increased permeability-surface area product for

eight protein fractions and concluded that histamine increased microvascular permeability and that its principal site of action was the pulmonary microvascular bed. More recently, Nakahara and co-workers (171) infused histamine into the bronchial or pulmonary circulation of sheep. Under both conditions lymph protein clearance increased in a dose-dependent manner and they concluded that histamine causes a mild increase in pulmonary microvascular permeability. In both investigations (27,171) pulmonary edema was minimal. Critical assumptions in these preparations (27,171) are that the collected lymph is void of systemic contamination, is not modified by lymph nodes and is representative of perimicrovascular interstitial fluid. Drake et al. (72a) recently reported that lymph collected from the efferent duct of the caudal mediastinal node contains significant nonpulmonary contamination, thus raising doubts on conclusions drawn from these studies (27,171). However, even if the assumptions are valid, the effects of histamine on microvascular permeability and lung water in sheep can only be considered mild at best. It should be mentioned that sheep pulmonary vessels have more sympathetic innervation than most mammals (117) as well as more mast cells in their lung. The mast cells have a particularly rich supply of dopamine (78), the latter being a precursor for norepinephrine synthesis. These factors could contribute to a pulmonary vascular bed more reactive to histamine and sympathetic stimulation in sheep. Differences among preparations could also contribute to variable responses to histamine.

Recent studies suggest that beta adrenergic receptors may regulate transvascular fluid and protein movement in lungs. In sheep, Hakim et al. (111) reported increased lymph protein clearance following beta blockade

with propranolol. Although they believe this effect is partly due to increased microvascular permeability, their data can be explained entirely by an increase in vascular surface area. Persson et al. (186) reported that the $beta_2$ agonist, terbutaline, prevented histamine induced (aerosol) pulmonary edema in the guinea-pig. In most (and possibly all) previous studies concerned with the effects of histamine on lung permeability the possibility exists that abnormally high plasma catecholamine levels partially or completely antagonized the permeability effects of histamine and thus prevented pulmonary edema. Increased levels of beta agonists during intravenous histamine administration would be expected to occur because histamine not only causes direct release of catecholamines from the adrenal glands (217) but also indirectly through reflex sympathoadrenal stimulation secondary to systemic hypotension (100,153).

In summary, local intra-arterial administration of histamine increases microvascular permeability and causes edema in the canine forelimb. During intravenous infusion of histamine these effects are not seen unless there is concomitant beta blockade suggesting that increased blood levels of beta agonists during intravenous histamine antagonize the increased water efflux. Whether a similar phenomenon occurs in the pulmonary microvasculature has not been specifically tested. I believe this is an important question to be answered because of the potential endogenous release of histamine during pathophysiological states and because of increased clinical use of beta blockade therapy.

STATEMENT OF OBJECTIVES

The first objective of this research was to determine the effects of local brain hypoxia or hypercapnia or both on pulmonary hemodynamics in systemically normoxemic and normocapnic dogs. I determined pulmonary vascular resistance, lung extravascular thermal volume, and central blood volume during brain hypoxia. Lung water was determined gravimetrically following brain hypoxia.

In the experimental preparation used by Moss and Stein (167), venous blood is pumped from the right atrium to one common carotid artery. This means that the carotid bodies and brain are perfused with hypoxemic blood. Therefore, any change in pulmonary hemodynamics could be caused by either brain hypoxia or by carotid body hypoxia. Thus the second objective of this research was to evaluate the effects of carotid body hypoxia and/or hypercapnia on pulmonary hemodynamics. Physiologic stimulation of the carotid bodies was achieved by altering gas tensions of blood perfusing the carotid bodies in systemically (including the brain) normoxemic and normocapnic dogs.

A third objective of this research was to evaluate the effects of one humoral agent (i.e., histamine) thought to be involved in the pathogenesis of the adult respiratory distress syndrome. Of particular interest was the effect of histamine on lung water before and after adrenergic blockade. Specifically, I tested the possibility that increased levels of beta agonists may account for the fact that intravenous

histamine causes little or no increase in microvascular permeability and water content of dog lungs. For completeness, I also examined the possibility that stimulation of alpha adrenergic receptors might alter the response to histamine.

I believe these investigations are of considerable significance for both the physiologist and clinician because the specific effects of local brain hypoxia on pulmonary hemodynamics have not been reported, the effects of carotid body hypoxia on pulmonary hemodynamics are controversial, and the effects of histamine on lung water following beta or alpha blockade have not been reported. Furthermore, these studies have important therapeutic implications because if it can be demonstrated that the brain (or carotid bodies) increases pulmonary vascular resistance or pulmonary blood volume during local brain (or carotid body) hypoxia and/or hypercapnia, then pharmacologic agents with actions on the brain (or carotid bodies) and vasculature may become an important modality in the prevention or treatment of pulmonary edema and alveolar hemorrhage during periods of systemic hypoxia and/or hypercapnia. In addition, since propranolol is used in certain clinical situations, it is important to determine whether beta blockade alters the effect of histamine on the pulmonary circulation.

In this dissertation the experiments involving "Brain Hypoxia and/or Hypercapnia", "Carotid Body Hypoxia and/or Hypercapnia", and "Histamine and Adrenergic Receptors" are each presented sequentially in the "METHODS", "RESULTS", and "DISCUSSION" sections. In the "SUMMARY and CONCLUSIONS" section I have attempted to bring together all aspects of this research. The final section of the text includes "RECOMMENDATIONS" for future research on the brain's role in causing pulmonary edema.

METHODS

I. General

One-hundred nineteen mongrel dogs of either sex weighing 22± 0.6 kg were used in these investigations. All dogs were anesthetized with sodium thiamylal (17.6 mg/kg, Bio-tal, Bio-Ceutic Laboratories, Inc., St. Joseph, MO) and anesthesia was maintained with a mixture of chloralose (75 mg/kg) and urethane (500 mg/kg, Sigma Chemical Company, St. Louis, MO). The dogs were intubated with a cuffed endotracheal tube and placed on positive pressure ventilation (Model 613, Harvard Apparatus Company, Millis, MS) with 5 cm water positive end-expiratory pressure. They were placed in a supine position and ventilated with room air supplemented with one to two liters O_2 per minute. Tidal volume and respiratory rate were 22 ml/kg and 14 breaths/min, respectively. Systemic pH, PaO_2, and $PaCO_2$ were maintained at 7.38 ± 0.01, 122 ± 4 torr, and 36 ± 1 torr, respectively. Sodium bicarbonate and lactated ringers solution (Cutter Laboratories, Berkeley, CA) were administered intravenously to correct for metabolic acidosis and fluid loss. A blood acid-base alignment nomogram was utilized to determine the base deficit and the estimated lost fluid volume (in open-chest preparations) was 4 ml/kg/hour. Pancuronium bromide (0.08 mg/kg, Pavulon, Organon, Inc., W. Orange, NJ) and heparin sodium (10 mg/kg, Lipo-Hepin, Riker Laboratories, Inc., Northridge, CA) were given intravenously to paralyze the muscles of respiration and for anticoagulation, respectively.

II. Brain and Carotid Body Studies

Polyethylene catheters were placed into the aorta via the femoral artery and following a median sternotomy, into the left atrial appendage. A 7F thermistor-tip Swan-Ganz catheter (Swan-Ganz Directed Monitoring Catheter, Edwards Laboratories, Inc., Santa Ana, CA) was floated into the pulmonary artery. Left atrial (as measured in its appendage), pulmonary artery, pulmonary artery wedge and aortic pressures were measured using Statham P23Gb pressure transducers (Gould Medical Products, Statham Industries, Oxnard, CA) referred to the level of the left atrium. In 30 dogs (brain perfusion experiments), a 20 gauge needle was inserted directly into the left ventricle and the needle hub sutured to the ventricular wall. A polyethylene catheter connected this needle to a pressure transducer. Left ventricular dP/dt was obtained by electrical differentiation of the ventricular pressure signal. All recordings were made continuously on a polygraph recorder (Model 7796A, Hewlett-Packard, Farmington Hills, MI).

Cardiac output was measured by the thermodilution-technique. Four ml normal saline (1-2°C) was injected into the right atrium via a side port (located 20 cm from the catheter tip) in the Swan-Ganz catheter. A thermistor positioned near the tip of the catheter detected changes in blood temperature and a computer (Cardiotherm 500, Columbus Instruments, Columbus, Ohio) calculated cardiac output. The mean of 3 to 5 determinations was computed as right ventricular output. A blood gas analyzer (Radiometer-blood micro system, Copenhagen, Denmark), which was calibrated daily, was used to determine pH, PO_2 and PCO_2 of systemic arterial blood and of blood from the extracorporeal lung (i.e., perfusate).

III. Brain Hypoxia and Hypercapnia

Brain hypoxia, hypercapnia, and hypoxia-hypercapnia were caused by pumping arterial autologous blood through an extracorporeal lung (Figure 1). Outflow from the extracorporeal lung was pumped to the external carotid arteries. The head was perfused via the external carotid arteries with flow to the Circle of Willis via the extensive anastomotic connections that exist in the dog (97). In order to minimize systemic blood flow to the brain the following vessels were initially bilaterally ligated: internal carotid, external carotid, occipital, lingual, ascending pharyngeal, cranial laryngeal and cranial thyroid arteries. It is unlikely that any of these ligations resulted in reduced brain blood flow since Green and Rapela (97) reported that, following bilateral common carotid artery ligation, vertebral artery perfusion pressure is approximately 90% of mean arterial pressure indicating an extensive collateral blood supply to the canine brain. The internal carotid and occipital arteries were ligated cephalad to the carotid sinuses and bodies, respectively (Figure 1). Thus the carotid sinuses were exposed to systemic arterial pressure and the carotid bodies received systemic blood in which gas tensions and pH were normal. Meticulous dissection preserved the carotid sinus nerves and their functional integrity was assumed if arterial pressure increased during temporary bilateral common carotid artery occlusion.

The vertebral, costocervical, and omocervical arteries were initially bilaterally tagged with silk suture at their origin from the subclavian artery (Figure 1) but were not ligated until after head perfusion had

Figure 1. Head perfusion preparation. Blood was pumped (Pump 1 = P1) from the femoral artery (fa) into the main pulmonary artery of the extracorporeal lung (ECL) at a rate sufficient to maintain its mean pulmonary venous pressure (P_{pv}) at 5 mmHg. The trachea was connected to a Harvard respirator (R). A second pump (P2) delivered the perfusate through a 38°C water bath (B) to the cannulated (polyethylene-280 catheters) external carotid arteries (eca); blood flow was initially adjusted to maintain head perfusion pressure (P_{HP}) $\geq$ mean aortic pressure; ligatures are shown placed around the internal carotid artery (ica) cephaled to the carotid sinus (cs), occipital artery (oa) cephaled to the carotid body (cb), vertebral artery (va), costocervical artery (ca), and omocervical artery (oa); cca, common carotid artery.

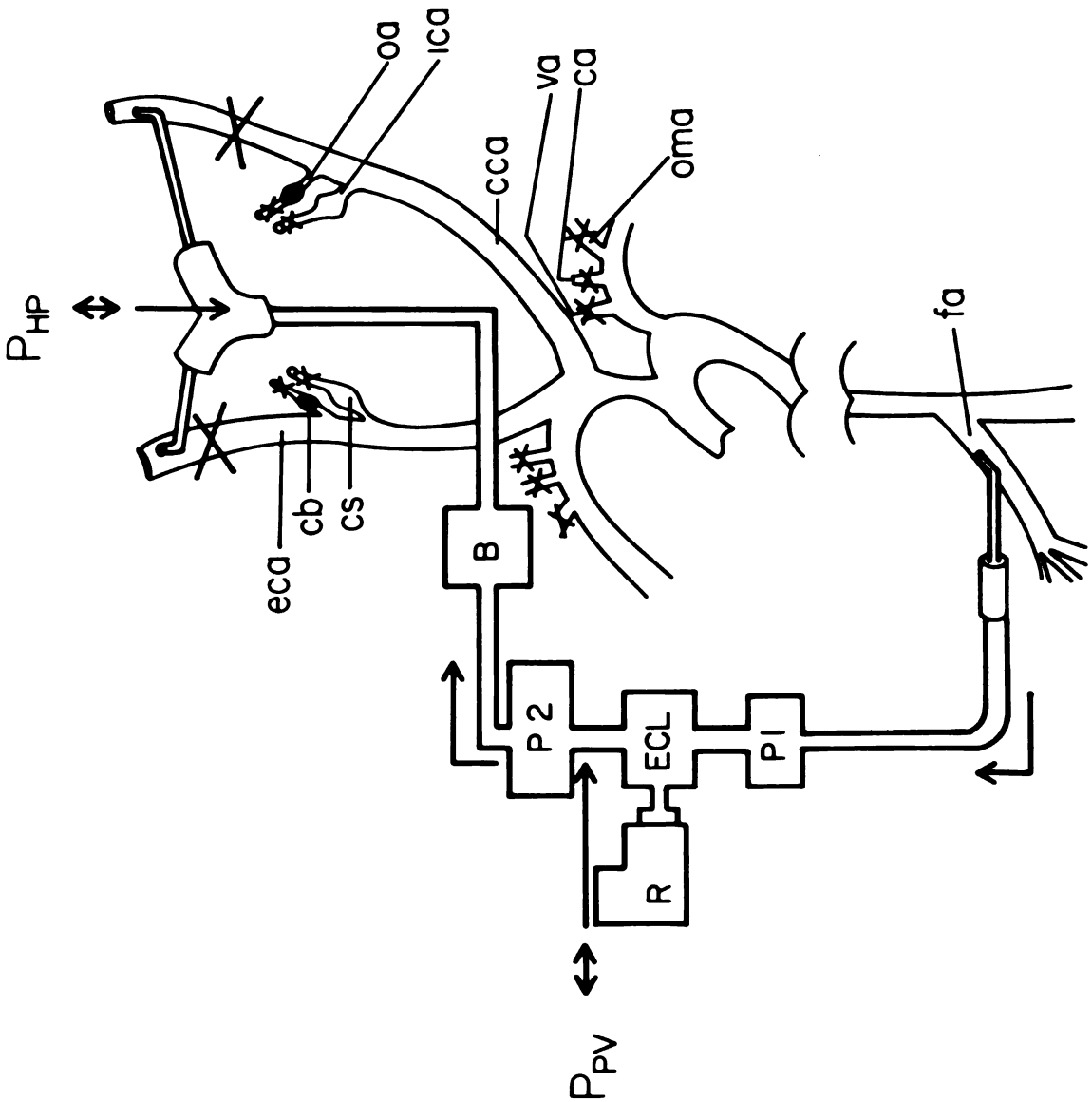


Figure 1

begun thus ensuring adequate brain perfusion at all times. It was necessary to ligate the costocervical and omocervical arteries because they frequently reanastamose with the vertebral artery as this vessel passes cephalad leading to a reconstitution of flow to the Circle of Willis (244). The ventral spinal artery is primarily supplied through branches from the vertebral arteries (160) and because these anastomoses occur cephalad to the ligatures, the ventral spinal artery was not ligated.

A lung was obtained from a donor dog weighing 9-12 kg. Approximately one hour prior to anesthesia the dog was given 300 mg aspirin intravenously to block prostaglandin synthesis that may occur in hypoxic lungs (203). The dog was anesthetized with sodium thiamylal (17.6 mg/kg) and given heparin sodium (10 mg/kg) for anticoagulation. Sufficient blood was removed from the donor dog to prime the extracorporeal system. The heart and lungs were removed and suspended from a large bore latex cannula inserted into the left atrium. Total lung ischemia time was less than 20 minutes.

Blood was pumped from the right femoral artery of the experimental animal into the pulmonary artery of the extracorporeal lung at a rate sufficient to maintain its mean pulmonary venous pressure at 5 mmHg. A second pump delivered this perfusate from the extracorporeal lung, through a 38°C water bath, and then to the cannulated external carotid arteries (Figure 1). Blood flow was initially adjusted to maintain head perfusion pressure $\geq$ mean aortic pressure during both constant pressure and constant flow experiments.

Since the head perfusion preparation used in this investigation has not been previously described, it is necessary to provide evidence that

blood delivered to the external carotid arteries reaches the brain, that other collateral sources of blood flow are virtually excluded, and that the preparation is viable. First, perfusing the head with hypercapnic blood caused slowing of heart rate and movement of respiratory muscles out of phase with mechanical ventilation (before neuromuscular blockade), suggesting that the medullary chemoreceptors were being perfused with this blood. Second, hypercapnic blood (PCO_2 75 to 85 torr) caused head perfusion pressure to decrease approximately 30%. This means that vascular resistance fell an equal amount because blood flow was constant. Since CO_2 is a potent dilator of cerebral vessels (97) and a weak dilator of vessels supplying skin and skeletal muscle (58), it is likely that a major portion of this fall in vascular resistance was due to dilation of cerebral vessels. Third, when flow into the external carotid arteries was stopped, head perfusion pressure fell to less than 20 mmHg and was nonpulsatile suggesting a virtual absence of collateral flow (Figure 2). Fourth, a central nervous system ischemic response was elicited when flow through the external carotid arteries was stopped (Figure 2). This response is characterized by massive sympathetic outflow to the cardiovascular system causing large increases in mean aortic pressure, thus attempting to relieve brain ischemia (104). Fifth, infusion of 5 ml of methylene blue dye into the external carotid arteries resulted in diffuse homogenous staining of the brain. When this dye was injected into the dog's left atrium little or no dye was observed in the brain providing head perfusion pressure was approximately equal to mean aortic pressure; however, dye was detectable in the cerebellum and pontomedullary area of some dogs when flow through the external carotid artery was zero. The latter conditions

Figure 2. Tracing of the cardiovascular response following cessation of flow through the external carotid arteries. Notice the large oscillations in vascular pressures that are characteristic of the central nervous system ischemic response. P_{LV}, left ventricular pressure; LV dP/dt, left ventricular contractility; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{LA}, left atrial pressure; P_{HP}, head perfusion pressure, P_{MA}, mean aortic pressure.

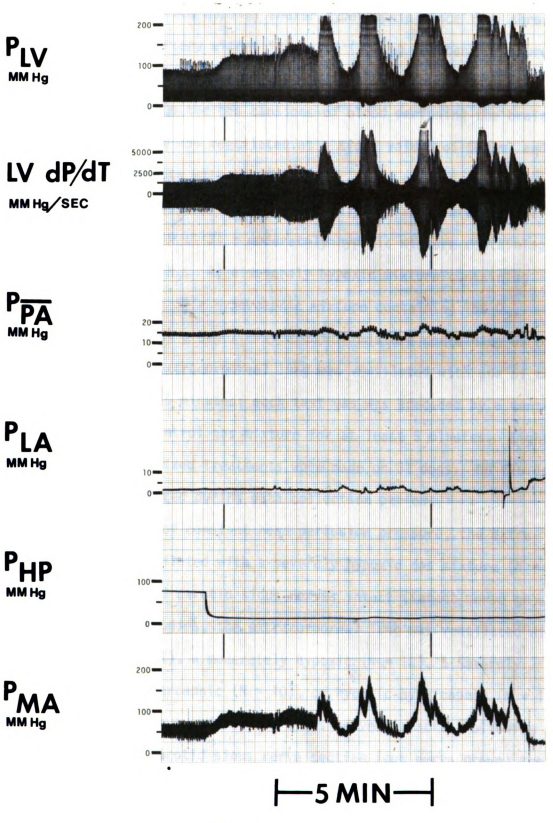

P_{LV}
MM Hg
200
100
0
LV dP/dT
MM Hg/SEC
5000
2500
0
$P_{\overline{PA}}$
MM Hg
20
10
0
P_{LA}
MM Hg
10
0
P_{HP}
MM Hg
100
0
P_{MA}
MM Hg
200
100
0
5 MIN

Figure 2

did not exist during brain hypoxia and/or hypercapnia since flow through the external carotid artery either increased (during constant pressure experiments) or was held constant.

In order to change the gas tensions of blood perfusing the brain, the extracorporeal lung was ventilated at a tidal volume of 500 ml and rate of 12 strokes/minute with the following: 1) a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2; 2) a mildly hypoxic mixture containing 5% O_2, 5% CO_2, 90% N_2; 3) a moderately hypoxic mixture containing 2.5% O_2, 5% CO_2, 92.5% N_2; 4) a severely hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2; 5) a hypercapnic mixture containing 15% O_2, 15% CO_2, 70% N_2; and 6) a hypoxic-hypercapnic mixture containing 0% O_2, 15% CO_2, 85% N_2. The extracorporeal lung was ventilated with one of the above gas mixtures for 5 minutes; each test gas was preceded by a ventilation period with the control gas mixture for at least 5 minutes. Eighty-seven paired and randomized treatments were made on 31 dogs. No fluids or drugs were administered during data collection periods.

Under conditions of constant head perfusion pressure, the extracorporeal lung was ventilated with a severely hypoxic gas mixture (N = 10) with the dogs' vagus and carotid sinus nerves intact (intact nerve group). During constant flow studies, the extracorporeal lung was ventilated with a mildly hypoxic (N = 11), a moderately hypoxic (N = 12), a severely hypoxic (N = 10), a hypercapnic (N = 10), or hypoxic-hypercapnic (N = 10) gas mixture with the vagus and carotid sinus nerves intact. Following cervical vagotomy and carotid sinus nerve section (cut nerve group) the extracorporeal lung was ventilated with a severely hypoxic (N = 10), a hypercapnic (N = 7) or a hypoxic-hypercapnic (N = 7) gas mixture.

Total pulmonary (PVR_T), pre-large venous (PVR_P) and large venous resistances (PVR_V) were calculated by dividing the appropriate pressure gradient by cardiac output as follows: $(P_{\overline{PA}} - P_{LA}) / \dot{Q} = PVR_T$, $(P_{\overline{PA}} - P_{PAW}) / \dot{Q} = PVR_P$ and $(P_{PAW} - P_{LA}) / \dot{Q} = PVR_V$; where $P_{\overline{PA}}$ equals mean pulmonary artery pressure, P_{LA} equals left atrial pressure, P_{PAW} equals pulmonary artery wedge pressure, $\dot{Q}$ equals cardiac output. The pulmonary artery wedge pressure represents downstream pressure at the point of the first post-capillary collateral venous vessel (82). Therefore, PVR_P represented resistance proximal to the point of the first collateral venous vessel and PVR_V represented resistance distal to the point of the first collateral venous vessel (Appendix A). Total peripheral resistance was calculated by dividing $P_{MA}/ \dot{Q}$, where P_{MA} equals mean aortic pressure.

Statistical analyses were performed using 2-way analysis of variance (ANOVA) with comparison between means based on Student-Newman-Keuls' test. Data are expressed as mean ± standard error (SE). Treatment means were considered significantly different at $P < 0.05$.

Thermal-Conductivity Method

Using the thermal-conductivity method, additional experiments were performed in order to determine lung extravascular thermal volume and central blood volume during brain hypoxia. A 5F polyethylene catheter (Edslab Thermodilution Catheter, Edwards Laboratories, Inc., Santa Ana, CA) was introduced into the femoral artery and advanced into the aorta such that its tip was within 5 cm of the aortic valve (determined by palpation). This catheter had a thermistor positioned 0.5 cm from the tip to detect changes in blood temperature. Two platinum ring electrodes

positioned 1.0 and 1.5 cm from the tip detected changes in blood conductivity. A 7F Swan-Ganz catheter was inserted into the jugular vein and advanced into the pulmonary artery. When the balloon near the catheter tip was inflated the pulmonary artery wedge pressure was obtained. A second Swan-Ganz angiography catheter (Swan-Ganz Flow Directed Pulmonary Angiography Catheter, Edwards Laboratories, Inc., Santa Ana, CA) was inserted through the same jugular vein and advanced into the right ventricle. This catheter had eight holes near its tip, thus facilitating rapid injection and mixing of indicator solution. Swan-Ganz catheter positions were verified by pressure recordings.

Cardiac output was measured by the thermodilution technique. Ten ml 3% saline (23-25°C) was rapidly injected into the right ventricle through the angiography catheter. A second cardiac output determination was made after blood temperature had returned to a stable baseline. The thermistor and platinum electrodes positioned near the tip of the aortic catheter detected changes in blood temperature and conductivity, respectively. The dilution curves were recorded on a polygraph recorder (Model 7784A, Hewlett-Packard, Farmington Hills, MI) (Figure 3). Using a data digitizer (graf/pen, Science Accessories Corporation, Southport, CT) these curves were sampled every 200 msec to the point where recirculation occurred, which was determined from a log-concentration time curve. These points were fit by a computer (Model PDP 11/34, Digital Equipment Corporation, Maynard, MS) to a single exponential decay to time infinity. Area under each curve was integrated and the following equation was used to calculate cardiac output ($\dot{Q}$):

$$\dot{Q} = \frac{[V_{inj} - V_{cath}]\ [\Delta T]\ [d_{inj} \times s_{inj}]}{\int_0^{\infty} C(t)\ dt \quad [d_b \times s_b]}$$

where V_{inj} equals volume of saline injected, V_{cath} equals volume of saline in catheter at time of injection, ΔT equals the difference between blood and injectate temperature in degrees centigrade, d_{inj} equals density of injectate, s_{inj} equals specific heat of injectate, d_b equals density of blood, s_b equals specific heat of blood, $\int_0^{\infty} C(t)\ dt$ equals the integral of blood temperature change in degrees centigrade multiplied by time (t). The product of $[d_{inj} \times s_{inj}]/[d_b \times s_b]$ and catheter heat loss was assumed to equal 1.0. Mean transit time ($\bar{t}$) for each curve was calculated as the first moment of the curve from initiation of injection using the following equation:

$$\bar{t} = \frac{\int_0^{\infty} txC(t)\ dt}{\int_0^{\infty} C(t)\ dt} \quad .$$

The product of cardiac output and heat mean transit time was taken as total tissue volume. The product of cardiac output and conductivity (Na^+) mean transit time was taken as intravascular volume (i.e., central blood volume). Lung extravascular thermal volume was obtained by subtracting intravascular volume from total lung volume. After normalization for body weight, central blood volume and lung extravascular thermal volume were expressed in ml/kg.

In using this technique I made two assumptions. First, I assumed the sodium in the injectate was confined to the vascular compartment during its initial passage through the lung and that all sodium injected was

recovered. In support of this assumption, Chinard et al. (41) reported mean transit time and shape of T-1824 and $^{22}Na^{+}$ dilution curves for the pulmonary vascular bed to be almost identical and concluded that both substances are essentially confined to the intravascular compartment during their initial passage. Furthermore, Pearce (181) reported virtually complete recovery of $^{24}Na^{+}$ in normal lungs and only 4.5% loss in high pressure pulmonary edema while Noble et al. (174) found no detectable loss of sodium during pulmonary edema. The second assumption I make is that there is no irreversible loss of heat into the lung. This has previously been shown to be the case even at low cardiac output (8). Furthermore, Pearce and Beazell (182) reported that lung extravascular thermal volume was unaffected by the air in the lungs presumably because of the great disparity in specific heat of alveolar air and lung tissue.

Although the thermal-conductivity method for measurement of lung water has been established as a valid technique (173,174), I felt it was necessary to verify the method in our laboratory prior to utilizing this technique during brain hypoxia experiments. In 11 dogs a 5F balloon-tip Foley catheter was inserted directly into the left atrium of open-chested dogs. The balloon was inflated sufficiently to raise left atrial pressure to approximately 30 mmHg for 1 to 2 hours. In most dogs this procedure caused various degrees of pulmonary edema and therefore increased lung extravascular thermal volume. At the completion of each experiment all lung tissue was rapidly excised at the hila. Analysis of lung composition was according to the method of Pearce et al. (183) as modified by Noble and Severinghaus (173). Briefly, the excised lungs were passively drained of blood, weighed and homogenized with 200 ml distilled water in

Figure 3. Tracing of thermal-dilution (top) and conductivity-dilution (bottom) curves. Ten ml 3% NaCl were injected into the right ventricle. A thermal and conductivity catheter in the proximal aorta detected changes in blood temperature and conductivity. °C, degrees centrigrade; Ω, ohmic resistance; $\overline{t}_H$, heat mean transit time; $\overline{t}_c$, conductivity (Na+) mean transit time; ETV_L, lung extravascular thermal volume. Dots represent an extrapolation of the single exponential decay. In this dog cardiac output = 2.24 L/min, $\overline{t}_H$ = 10.80 sec, $\overline{t}_c$ = 7.72 sec; therefore ETV_L = 115 ml.

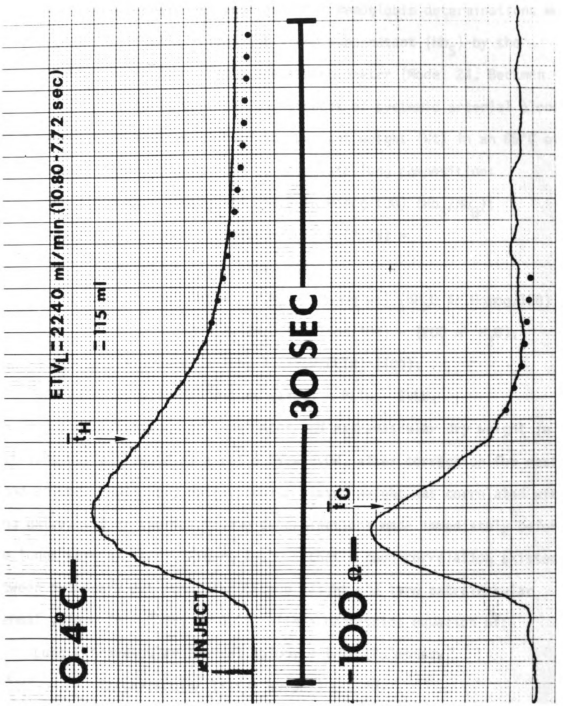

0.4°C
ETVL= 2240 ml/min (10.80-7.72 sec)
$\bar{t}_H$
= 115 ml
INJECT
30 SEC
100
$\bar{t}_C$

Figure 3

a blender. Aliquots of homogenate were centrifuged at 15,000 rpms for 30 min producing a clear red supernatant. Hemoglobin determinations were made on systemic arterial blood (Hb_B) and supernatant (Hb_S) by the cyanmethemoglobin method using a spectrophotometer (Model 24, Beckman Instruments Inc., Fullerton, CA). Aliquots of systemic arterial blood and homogenate (Homog) were dried to constant weight (Wt) in an 85°C oven. The following formulae were used to calculate lung composition:

lung blood wt = (Homog wt) (%H_2O in Homog/100) (Hb_S/Hb_B);

pulmonary extravascular tissue weight (PETW) =

(lung wt) - (lung blood wt);

extravascular lung water (EVLW) = (Homog wt) (%H_2O in Homog/100)

- (lung blood wt) (%H_2O in blood/100) - (200 ml H_2O);

% H_2O in extravascular lung = (EVLW/PETW) (100);

and extravascular dry weight (EVDW) = PETW - EVLW.

The amount of extravascular lung water and extravascular dry weight in each lung was expressed as a ratio EVLW/EVDW, after correction for residual blood volume. Pulmonary extravascular tissue weight was correlated with lung extravascular thermal volume determinations made immediately before the lungs were excised. Figure 4 shows that a good correlation existed between pulmonary extravascular tissue weight and lung extravascular thermal volume ($r = 0.88$; $P < 0.01$) with a regression equation of:

Lung Extravascular Thermal Volume = 1.07 (Pulmonary

Extravascular Tissue Weight) - 0.43.

Since the thermal-conductivity method proved to be a reliable technique in our laboratory, I utilized this technique in two additional groups of brain hypoxia experiments. In one group of dogs lung

Figure 4. Linear regression of lung extravascular thermal volume (ETV_L) versus pulmonary extravascular tissue weight (PETW) from dogs in which left atrial pressure was increased to produce various degrees of pulmonary edema. Broken line is the line of identity. Solid line is the line of best fit, based on the method of least squares, N = 11.

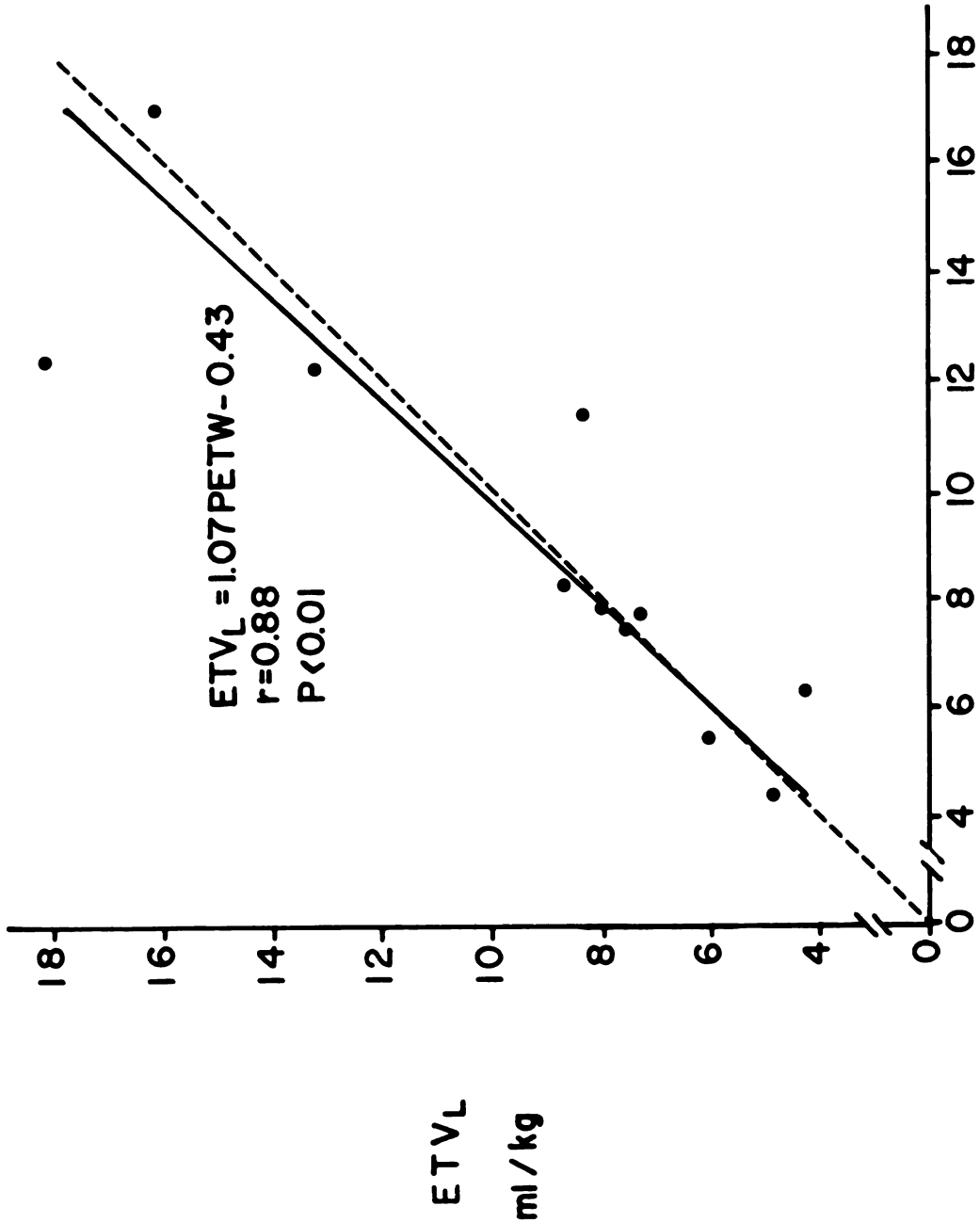

ETV_L =1.07PETW-0.43
r=0.88
P<0.01
ETV_L ml/kg
PETW ml/kg
0
4
6
8
10
12
14
16
18

Figure 4

extravascular thermal volume and central blood volume was determined at 0 and 5 minutes of severe brain hypoxia (N = 6). In a second group these parameters were measured at 0, 30, 60, 90, and 120 minutes of severe brain hypoxia (N = 6). In both groups the vagus and carotid sinus nerves were cut and flow through the external carotid arteries was constant. Following 5 minutes or 2 hours of brain hypoxia the lungs were excised at the hilum and lung composition was determined as described earlier.

IV. Carotid Body Hypoxia and Hypercapnia

Hypoxic, hypercapnic, and hypoxic-hypercapnic stimulation of the carotid bodies was achieved by pumping arterial autologous blood through the extracorporeal lung ventilated with appropriate gas mixtures (Figure 5). Outflow from the extracorporeal lung was pumped to the common carotid arteries at constant flow and pressure. In order to isolate and perfuse the carotid bodies, the following vessels were bilaterally ligated: internal carotid, occipital, lingual, ascending pharyngeal, and cranial laryngeal arteries. The internal carotid and occipital arteries were ligated cephalad to the carotid sinuses and bodies, respectively (Figure 5). Meticulous dissection preserved the carotid sinus nerves and their functional integrity was assumed if arterial pressure increased during temporary bilateral common carotid artery occlusion and if movement of respiratory muscles occurred (before neuromuscular blockade) out of phase with mechanical ventilation during hypoxemic perfusion of the carotid bodies. The preparation was assumed to be isolated when cessation of flow through the common carotid arteries caused perfusion pressure to decrease to < 20 mmHg without pulsations.

The extracorporeal lung preparation was identical to that described for the brain studies with the following exceptions. Perfusate from the extracorporeal lung was delivered to the cannulated common carotid arteries. Blood flow was maintained constant (100 to 125 ml/min) as was perfusion pressure. The latter was set equal to mean aortic pressure by adjusting outflow resistance with a screw clamp. The effluent perfusate was collected from the external carotid arteries and returned to the dog via the right femoral vein (Figure 5).

Ventilatory parameters for the extracorporeal lung and test gas mixtures were identical to those used in the brain hypoxia and/or hypercapnia experiments. Ninety paired treatments were made on 30 dogs. With the vagi intact the extracorporeal lung was ventilated with a severely hypoxic gas mixture (N = 12). Following vagotomy the extracorporeal lung was ventilated with a mildly hypoxic (N = 14), a moderately hypoxic (N = 14), a severely hypoxic (N = 10), a hypercapnic (N = 13) or a hypoxic-hypercapnic (N = 10) gas mixture. The purpose of vagotomy was to eliminate buffering effects of the aortic baroreceptors and cardiac stretch receptors on the cardiovascular system (180).

In a separate set of experiments, after vagotomy, phentolamine (1 mg/kg) was infused as a slow intravenous bolus to block alpha adrenergic receptors during severe carotid body hypoxia (N = 7) and hypoxia-hypercapnia (N = 10). An alpha agonist, phenylephrine (100 μg) or norepinephrine (10 μg), was given intravenously as a bolus both before and after phentolamine. Adequate blockade was assumed when the response (i.e., increased mean aortic and pulmonary artery pressures) to the agonist given before alpha blockade was abolished after alpha blockade. In all

Figure 5. Carotid body perfusion preparation. Blood was pumped (Pump 1 = P1) from the femoral artery (fa) into the main pulmonary artery of the extracorporeal lung (ECL) at a rate sufficient to maintain its mean pulmonary venous pressure (P_{pv}) at 5 mmHg. The trachea was connected to a Harvard respirator (R). A second pump (P2) delivered the perfusate through a 38°C water bath (B) to the cannulated common carotid arteries (cca). Blood flow and perfusion presure (P_p) were maintained constant. Perfusate was collected from the cannulated external carotid arteries (eca) and returned to the dog via the femoral vein (fv). A screw clamp adjusted outflow resistance. Ligatures are shown placed around the eca, internal carotid artery (ica) cephalad to the carotid sinus (cs), and the occipital artery (oa) cephalad to the carotid body (cb).

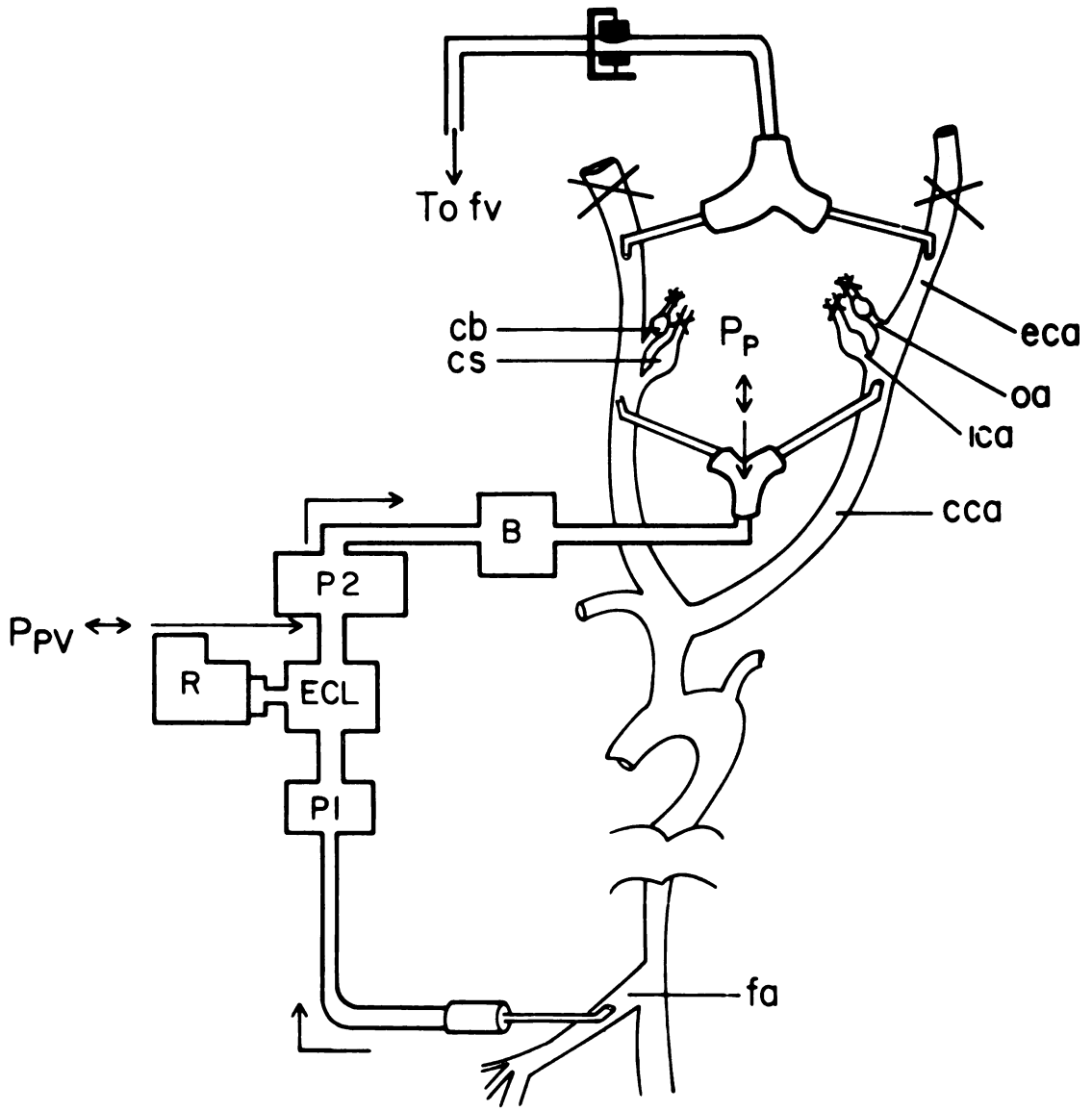


Figure 5

experiments carotid sinus perfusion and pulse pressures were constant between control and test gas period.

Statistical analysis and vascular resistance calculations were identical to those used for the brain perfusion studies.

V. Histamine and Adrenergic Receptors

In closed-chest dogs the thermal-conductivity method was used to determine cardiac output, lung extravascular thermal volume, and central blood volume. The theory, calculations, and methods applicable to this procedure were discussed earlier.

Aortic, mean pulmonary artery, and pulmonary artery wedge pressures were measured using Statham P23Gb pressure transducers referred to the level of the left atrium. All recordings were made continuously on a polygraph recorder (Model 7796A, Hewlett-Packard, Farmington Hills, MI).

A 20 gauge needle was inserted into the oral end of an endotracheal tube. A polyethylene catheter connected this needle to a Statham PM 131 pressure transducer (Gould Medical Products, Statham Industries, Oxnard, CA) for measurement of airway opening pressure.

Pre-large vein pulmonary vascular resistance was calculated as $(P_{\overline{PA}} - P_{PAW})/CI$, where $P_{\overline{PA}}$ equals mean pulmonary artery pressure, P_{PAW} equals pulmonary artery wedge pressure and CI equals cardiac index expressed in ml/sec/kg. Total peripheral resistance was calculated as P_{MA}/CI where P_{MA} equals mean aortic pressure.

Data collection was begun approximately 1 hour after the onset of anesthesia when all vascular pressures were in a steady state for at

least 20 min. Thermal and conductivity curves were obtained at -20, 0, 30, 60 and 90 minutes. In the time control group (N = 10) no vasoactive drugs were administered during the 110 min protocol. In the histamine group (N = 8), histamine base (10 μg/kg/min) was infused intravenously between 0 and 90 minutes. In the propranolol-histamine group (N = 11), propranolol (2 mg/kg) was infused intravenously between -20 and -15 min and then at 20 μg/kg/min for the remainder of the experiment (i.e., 105 min). A beta agonist, isoproterenol (10 μg), was given intravenously as a bolus both before and after infusion of 2 mg/kg propranolol. Adequate blockade was assumed when the response to the agonist (i.e., increased heart rate) given before beta blockade was abolished after beta blockade. In the phentolamine-histamine group (N = 6), phentolamine (1 mg/kg) was infused intravenously between -20 and -15 min and then at 10 μg/kg/min for the remainder of the experiment. An alpha agonist, phenylephrine (100 μg), was given intravenously as a bolus both before and after infusion of 1 mg/kg phentolamine. Adequate blockade was assumed when the response to the agonist (i.e., increased mean aortic and pulmonary artery pressures) given before alpha blockade was abolished after alpha blockade. In the propranolol-histamine and phentolamine-histamine groups, histamine base (10 μg/kg/min) was infused intravenously between 0 and 90 minutes.

At the completion of each experiment the dogs were euthanized by intravenous injection of 20 ml saturated KCl solution (6 dogs in time control and 6 in propranolol-histamine groups) or sodium pentobartital (all other dogs). The chest was immediately opened and all lung tissues

were rapidly excised at the hilum. Analysis of lung composition was as described earlier.

Statistical analysis over the 110 minute protocol was performed using 2-way analysis of variance (ANOVA) with comparison of means based on Student-Newman-Keuls' test. An unpaired Students t-test was used to compare the means between groups of dogs. Means were considered significantly different at $P < 0.05$.

RESULTS

I. Brain Hypoxia and Hypercapnia

Vagus and Carotid Sinus Nerves Intact

Table 1 shows the cardiovascular effects of perfusing the brain with severely hypoxemic blood under constant pressure conditions (perfusion pressure = 111 ± 2 mmHg). Perfusate PO_2 decreased from 96 to 27 torr, PCO_2 decreased from 31 to 29 torr and pH increased from 7.37 to 7.41. Flow through the external carotid arteries increased 66% from 104 to 173 ml/min. None of the other measured or calculated variables changed.

Tables 2-4 show the cardiovascular effects of perfusing the brain with mildly, moderately, and severely hypoxemic blood in which head flow was constant at 179 ± 22, 194 ± 22, and 238 ± 25 ml/min, respectively. During mild hypoxia perfusate PO_2 decreased from 112 to 54 torr, during moderate hypoxia from 122 to 40 torr, and during severe hypoxia from 125 to 29 torr. Perfusate pH increased from 7.37 to 7.39 during moderate hypoxia while systemic pH and PaO_2 decreased from 7.39 to 7.36 and 106 torr to 97 torr, respectively. During severe brain hypoxia systemic pH and PaO_2 decreased from 7.38 to 7.35 and 98 torr to 87 torr, respectively, while $PaCO_2$ increased from 35 to 39 torr. Head perfusion pressure decreased 6% (from 122 to 115 mmHg), 23% (from 127 to 98 mmHg), and 31% (from 143 to 99 mmHg) during perfusion of the brain with mildly, moderately, and severely hypoxemic blood, respectively. None of the other

measured or calculated variables changed during mild, moderate, or severe brain hypoxia.

The cardiovascular effects of perfusing the brain with hypercapnic blood under constant flow conditions (head flow = 218 ± 19 ml/min) are shown in Table 5. During this treatment perfusate PCO_2 increased from 33 to 79 torr and pH decreased from 7.39 to 7.15. Head perfusion pressure decreased 30% from 139 to 97 mmHg. Stroke volume increased 12% from 11.0 to 12.3 ml, heart rate decreased 6% from 156 to 147 beats/min, and mean aortic pressure increased 10% from 80 to 88 mmHg. Systemic pH decreased from 7.38 to 7.34. None of the other measured or calculated variables changed.

Table 6 shows the cardiovascular effects of hypoxic-hypercapnic blood perfusing the brain. In this series blood flow was constant (head flow = 271 ± 26 ml/min) and perfusate PO_2 and pH decreased from 121 torr to 33 torr and 7.43 to 7.18, respectively, while PCO_2 increased from 31 to 73 torr. Head perfusion pressure decreased 38% from 138 to 85 mmHg. Stroke volume increased 20% from 10.7 to 12.8 ml while heart rate decreased 8% from 162 to 149 beats/min. Systemic pH and PaO_2 decreased from 7.39 to 7.33 and 99 torr to 87 torr, respectively, while $PaCO_2$ increased from 34 to 40 torr. All other measured or calculated variables did not change.

Table 1. Cardiovascular effects of perfusing the brain with severely hypoxemic blood under constant pressure conditions (head perfusion pressure = 111 ± 2 mmHg) with the vagus and carotid sinus nerves intact. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA, N = 10. *, significantly different from control at $P < 0.05$; $\overline{P_{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 1

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	96	27	3.50*
Perfusate PCO_2 (torr)	31	29	0.40*
Perfusate pH	7.37	7.41	0.01*
Head Blood Flow (ml/min)	104	173	4.40*
$P_{\overline{PA}}$ (mmHg)	14.4	14.3	0.10
P_{PAW} (mmHg)	6.3	6.4	0.10
P_{LA} (mmHg)	3.7	3.7	0.10
P_{PAP} (mmHg)	8.4	8.1	0.10
PVR_T (mmHg/L/min)	4.40	4.41	0.10
PVR_P (mmHg/L/min)	3.28	3.24	0.10
PVR_V (mmHg/L/min)	1.12	1.17	0.04
$\dot{Q}$ (L/min)	2.71	2.72	0.04
HR (beats/min)	157	156	1.80
V_S (ml)	17.8	18.0	0.20
P_{MA} (mmHg)	106	105	0.40
TPR (mmHg/L/min)	42.3	41.6	0.40
P_aO_2 (torr)	102	95	2.20
P_aCO_2 (torr)	34	35	0.80
pH (systemic)	7.36	7.36	0.01

Table 2. Cardiovascular effects of perfusing the brain with mildly hypoxemic blood under constant flow conditions (head flow = 179 ± 22 ml/min) with the vagus and carotid sinus nerves intact. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 5% O_2, 5% CO_2, 90% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA. N = 11, unless otherwise indicated. *, significantly different from control at $P < 0.05$; P_{HP}, head perfusion pressure; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; dP/dt, left ventricular contractility (N = 6); P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 2

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	112	54	4.60*
Perfusate PCO_2 (torr)	35	35	1.00
Perfusate pH	7.37	7.38	0.01
P_{HP} (mmHg)	122	115	1.10*
$P_{\overline{PA}}$ (mmHg)	11.7	11.6	0.10
P_{PAW} (mmHg)	5.4	5.4	0.20
P_{LA} (mmHg)	2.7	2.5	0.10
P_{PAP} (mmHg)	11.1	10.8	0.20
PVR_T (mmHg/L/min)	5.63	5.81	0.10
PVR_P (mmHg/L/min)	3.89	4.02	0.10
PVR_V (mmHg/L/min)	1.74	1.79	0.10
$\dot{Q}$ (L/min)	1.72	1.69	0.03
HR (beats/min)	165	162	1.20
V_S (ml)	10.5	10.4	0.10
dP/dt (mmHg/sec)	2000	1833	62
P_{MA} (mmHg)	86	83	0.90
TPR (mmHg/L/min)	51.7	51.3	0.90
P_aO_2 (torr)	110	104	2.60
P_aCO_2 (torr)	33	33	1.10
pH (systemic)	7.39	7.38	0.01

Table 3. Cardiovascular effects of perfusing the brain with moderately hypoxemic blood under constant flow conditions (head flow = 194 ± 22 ml/min) with the vagus and carotid sinus nerves intact. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 2.5% O_2, 5% CO_2, 92.5% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA. N = 12, unless otherwise indicated. *, significantly different from control at $P < 0.05$; P_{HP}, head perfusion pressure; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; dP/dt, left ventricular contractility (N = 6); P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 3

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	122	40	3.60*
Perfusate PCO_2 (torr)	35	35	0.70
Perfusate pH	7.37	7.39	0.01*
P_{HP} (mmHg)	127	98	5.30*
$P_{\overline{PA}}$ (mmHg)	12.2	12.0	0.10
P_{PAW} (mmHg)	5.7	5.4	0.10
P_{LA} (mmHg)	2.8	2.6	0.10
P_{PAP} (mmHg)	10.7	10.3	0.20
PVR_T (mmHg/L/min)	5.79	5.80	0.10
PVR_P (mmHg/L/min)	4.01	4.08	0.10
PVR_V (mmHg/L/min)	1.78	1.72	0.10
$\dot{Q}$ (L/min)	1.72	1.70	0.03
HR (beats/min)	161	157	1.10
V_S (ml)	10.7	10.8	0.20
dP/dt (mmHg/sec)	1583	1521	21
P_{MA} (mmHg)	77	75	0.70
TPR (mmHg/L/min)	46.7	46.5	0.70
P_aO_2 (torr)	106	97	1.50*
P_aCO_2 (torr)	34	34	0.70
pH (systemic)	7.39	7.36	0.01*

Table 4. Cardiovascular effects of perfusing the brain with severely hypoxemic blood under constant flow conditions (head flow = 238 ± 25 ml/min) with the vagus and carotid sinus nerves intact. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA. N = 10, unless otherwise indicated. *, significantly different from control at $P < 0.05$; P_{HP}, head perfusion pressure; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; dP/dt, left ventricular contractility (N = 8); P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 4

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	125	29	4.70*
Perfusate PCO_2 (torr)	34	34	0.80
Perfusate pH	7.41	7.43	0.01
P_{HP} (mmHg)	143	99	4.30*
$\overline{P_{PA}}$ (mmHg)	12.0	12.2	0.20
P_{PAW} (mmHg)	5.8	5.8	0.10
P_{LA} (mmHg)	1.7	1.5	0.10
P_{PAP} (mmHg)	10.7	11.0	0.20
PVR_T (mmHg/L/min)	5.74	5.88	0.20
PVR_P (mmHg/L/min)	3.49	3.60	0.20
PVR_V (mmHg/L/min)	2.25	2.28	0.10
$\dot{Q}$ (L/min)	1.86	1.88	0.04
HR (beats/min)	176	180	3.20
V_S (ml)	10.7	10.6	0.20
dP/dt (mmHg/sec)	1813	1947	84
P_{MA} (mmHg)	79	84	2.30
TPR (mmHg/L/min)	43.8	45.8	2.00
P_aO_2 (torr)	98	87	1.40*
P_aCO_2 (torr)	35	39	0.70*
pH (systemic)	7.38	7.35	0.01*

Table 5. Cardiovascular effects of perfusing the brain with hypercapnic blood under constant flow conditions (head flow = 218 ± 19 ml/min) with the vagus and carotid sinus nerves intact. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypercapnic mixture containing 15% O_2, 15% CO_2, 70% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA. N = 10, unless otherwise indicated. *, significantly different from control at $P < 0.05$; P_{HP}, head perfusion pressure; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure, PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; dP/dt, left ventricular contractility (N = 8); P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 5

	Control	Hypercapnia	SE
Perfusate PO_2 (torr)	110	97	5.10
Perfusate PCO_2 (torr)	33	79	2.50*
Perfusate pH	7.39	7.15	0.01*
P_{HP} (mmHg)	139	97	3.50*
$P_{\overline{PA}}$ (mmHg)	11.2	11.6	0.20
P_{PAW} (mmHg)	4.4	4.5	0.10
P_{LA} (mmHg)	1.3	1.3	0.04
P_{PAP} (mmHg)	12.1	13.0	0.30
PVR_T (mmHg/L/min)	5.85	5.77	0.20
PVR_P (mmHg/L/min)	4.01	3.98	0.10
PVR_V (mmHg/L/min)	1.84	1.79	0.10
$\dot{Q}$ (L/min)	1.71	1.80	0.05
HR (beats/min)	156	147	2.20*
V_S (ml)	11.0	12.3	0.40*
dP/dt (mmHg/sec)	1866	1975	81
P_{MA} (mmHg)	80	88	2.20*
TPR (mmHg/L/min)	47.9	50.7	1.30
P_aO_2 (torr)	94	95	1.80
P_aCO_2 (torr)	35	38	1.10
pH (systemic)	7.38	7.34	0.01*

Table 6. Cardiovascular effects of perfusing the brain with hypoxemic-hypercapnic blood under constant flow conditions (head flow = 271 ± 26 ml/min) with the vagus and carotid sinus nerves intact. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic-hypercapnic mixture containing 0% O_2, 15% CO_2, 85% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA. N = 10, unless otherwise indicated, *, significantly different from control at $P < 0.05$; P_{HP}, head perfusion pressure; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; dP/dt, left ventricular contractility (N = 8); P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 6

	Control	Hypoxia-Hypercapnia	SE
Perfusate PO_2 (torr)	121	33	5.80*
Perfusate PCO_2 (torr)	31	73	1.90*
Perfusate pH	7.43	7.18	0.02*
P_{HP} (mmHg)	138	85	4.00*
$P_{\overline{PA}}$ (mmHg)	10.8	11.2	0.20
P_{PAW} (mmHg)	5.1	5.1	0.20
P_{LA} (mmHg)	2.0	2.0	0.10
P_{PAP} (mmHg)	10.6	11.0	0.20
PVR_T (mmHg/L/min)	5.42	5.34	0.20
PVR_P (mmHg/L/min)	3.45	3.54	0.10
PVR_V (mmHg/L/min)	1.97	1.80	0.10
$\dot{Q}$ (L/min)	1.70	1.87	0.07
HR (beats/min)	162	149	3.20*
V_S (ml)	10.7	12.8	0.50*
dP/dt (mmHg/sec)	1566	1750	87
P_{MA} (mmHg)	68	77	3.80
TPR (mmHg/L/min)	41.6	44.4	1.70
P_aO_2 (torr)	99	87	2.50*
P_aCO_2 (torr)	34	40	1.00*
pH (systemic)	7.39	7.33	0.01*

Vagus and Carotid Sinus Nerves Cut

Figures 6-9 show the cardiovascular effects of perfusing the brain with severely hypoxemic blood under constant flow conditions (head flow = 259 ± 16 ml/min) in which perfusate PO_2 was reduced from 101 to 22 torr (SE = 5.70) and pH increased from 7.39 to 7.42 (SE = 0.01). Head perfusion pressure decreased 19% from 106 to 86 mmHg (SE = 3.40). Mean pulmonary artery pressure increased 14% from 11.1 to 12.6 mmHg (SE = 0.20), left atrial pressure 65% from 1.7 to 2.8 mmHg (SE = 0.30), and pulmonary artery pulse pressure 17% from 10.1 to 11.8 mmHg (SE = 0.50). Pulmonary vascular resistance values (i.e., PVR_T, PVR_P, PVR_V) were not significantly different from control. Cardiac output increased 18% from 1.36 to 1.61 L/min (SE = 0.06), stroke volume 21% from 6.8 to 8.2 ml (SE = 0.30), dP/dt 41% from 1850 to 2600 mmHg/sec (SE = 126); mean aortic pressure increased 35% from 60 to 81 mmHg (SE = 3.30) and total peripheral resistance 13% from 46.2 to 52.1 mmHg/L/min (SE = 1.80). Systemic pH and P_aO_2 decreased from 7.38 to 7.34 (SE = 0.01) and 114 torr to 97 torr (SE = 4.00), respectively. None of the other measured or calculated variables changed.

In a separate set of experiments, 5 min brain hypoxia caused no significant change in lung extravascular thermal volume (i.e., control = 8.27 ml/kg, hypoxia = 8.23 ml/kg, SE = 0.20) but central blood volume increased 18% from 12.5 to 14.7 ml/kg (SE = 0.30) (Figure 10). In this group the hemodynamic changes were similar to that reported in Figures 6-9. Postmortem extravascular lung water to extravascular dry weight ratio was 3.56 ± 0.07, which is not significantly different from control values (3.64 ± 0.14; N = 10) in our laboratory.

Figure 6. Effect of ventilating the extracorporeal lung with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2 on perfusate gas tensions and pH and head perfusion pressure (P_{HP}). The vagus and carotid sinus nerves were cut. Head flow was maintained constant. Values are means ± standard error based on error mean square from ANOVA. N = 10; *, significantly different from control at $P < 0.05$.

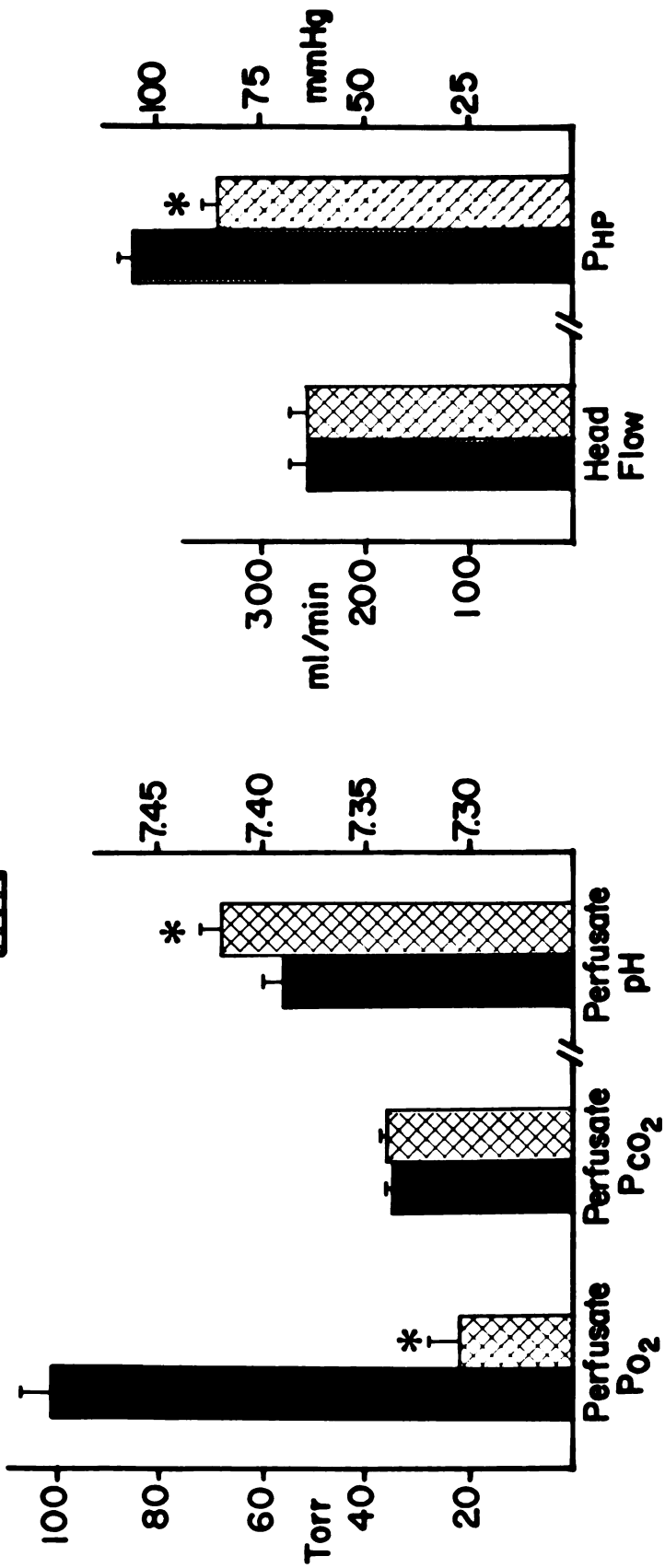
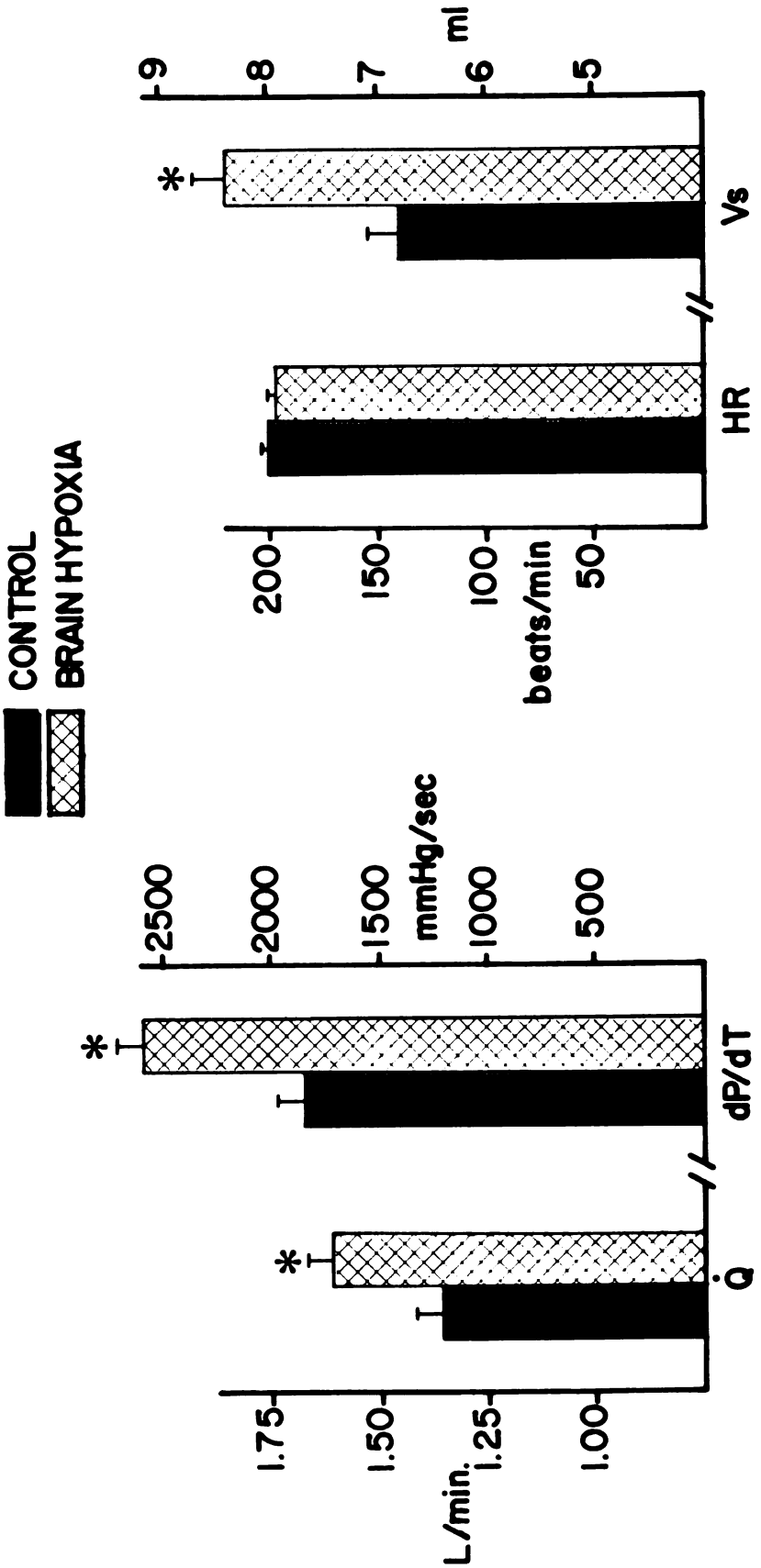

CONTROL
BRAIN HYPOXIA
Torr
100
80
60
40
20
Perfusate P_{O_2}
Perfusate P_{CO_2}
7.45
7.40
7.35
7.30
Perfusate pH
ml/min
300
200
100
Head Flow
mmHg
100
75
50
25
P_{HP}
*

Figure 6

Figure 7. Effect of perfusing the brain with severely hypoxemic blood on cardiac output ($\dot{Q}$), left ventricular contractility (dP/dt), heart rate (HR), and stroke volume (V_S). Flow to the head was constant (259 ± 16 ml/min) and the vagus and carotid sinus nerves were cut. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are means ± standard error based on error mean square from ANOVA. N = 10; *, significantly different from control at $P < 0.05$.


CONTROL
BRAIN HYPOXIA
L/min.
1.75
1.50
1.25
1.00
Q̇
*
mmHg/sec
2500
2000
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1000
500
dP/dT
*
beats/min
200
150
100
50
HR
*
ml
9
8
7
6
5
Vs

Figure 7

Figure 8. Effect of perfusing the brain with severely hypoxemic blood on left atrial pressure (P_{LA}), pulmonary artery wedge pressure (P_{PAW}), mean pulmonary artery pressure ($P_{\overline{PA}}$), pulmonary artery pulse pressure (P_{PAP}), and mean aortic pressure (P_{MA}). Flow to the head was constant (259 ± 16 ml/min) and the vagus and carotid sinus nerves were cut. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are means ± standard error based on error mean square from ANOVA. N = 10, except P_{PAW} where N = 9. *, significantly different from control at $P < 0.05$.

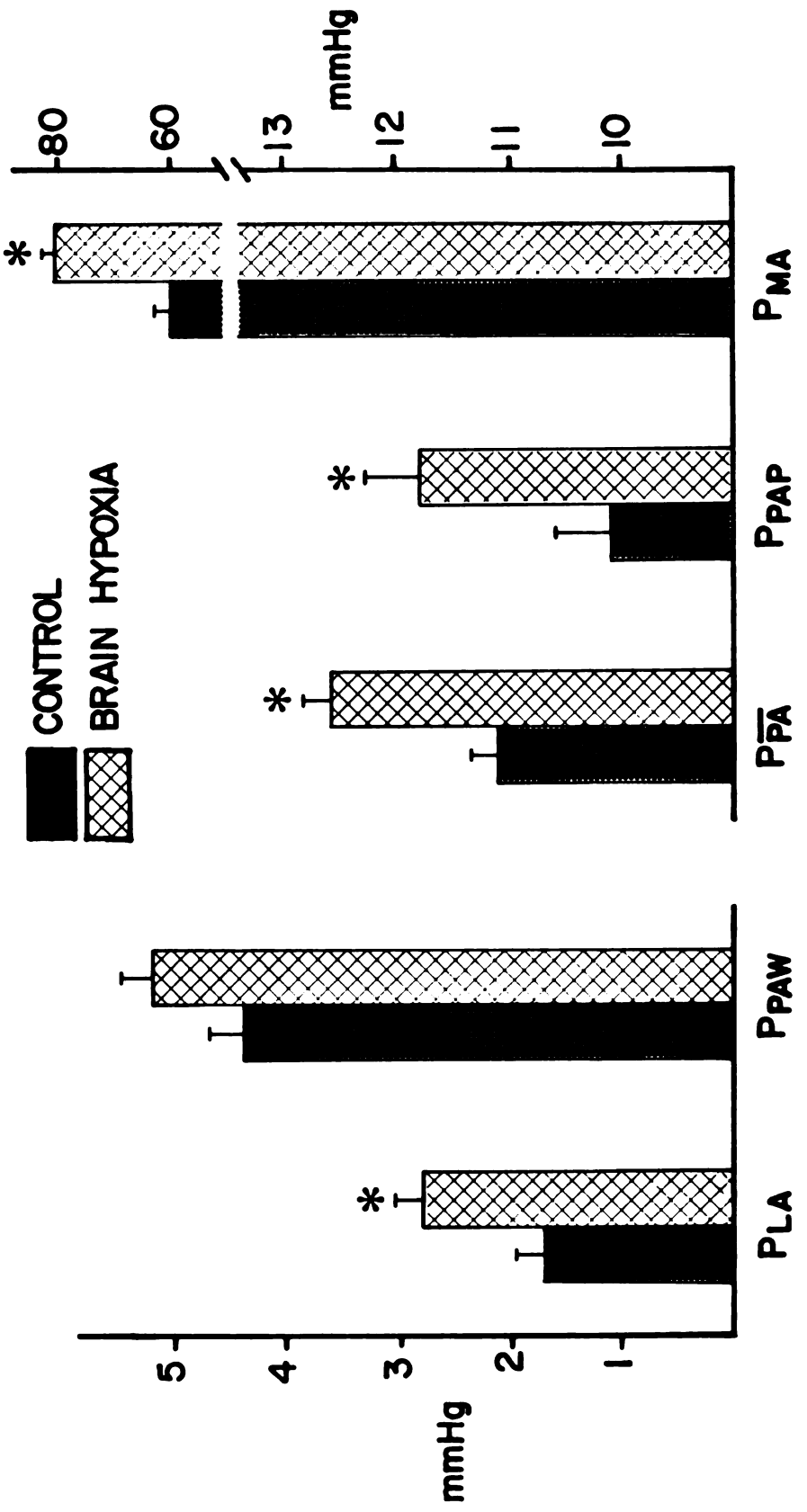

CONTROL
BRAIN HYPOXIA
mmHg
5
4
3
2
1
80
60
13
12
11
10
*
P_{LA}
P_{PAW}
$P_{\overline{PA}}$
P_{PAP}
P_{MA}

Figure 8

Figure 9. Effect of perfusing the brain with severely hypoxemic blood on total pulmonary vascular resistance (PVR_T), pre-large vein pulmonary vascular resistance (PVR_P), large vein pulmonary vascular resistance (PVR_V), and total peripheral resistance (TPR). Flow to the head was constant (259 ± 16 ml/min) and the vagus and carotid sinus nerves were cut. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are means ± standard error based on error mean square from ANOVA. N = 10, except PVR_P and PVR_V where N = 9. *, significantly different from control at $P < 0.05$.

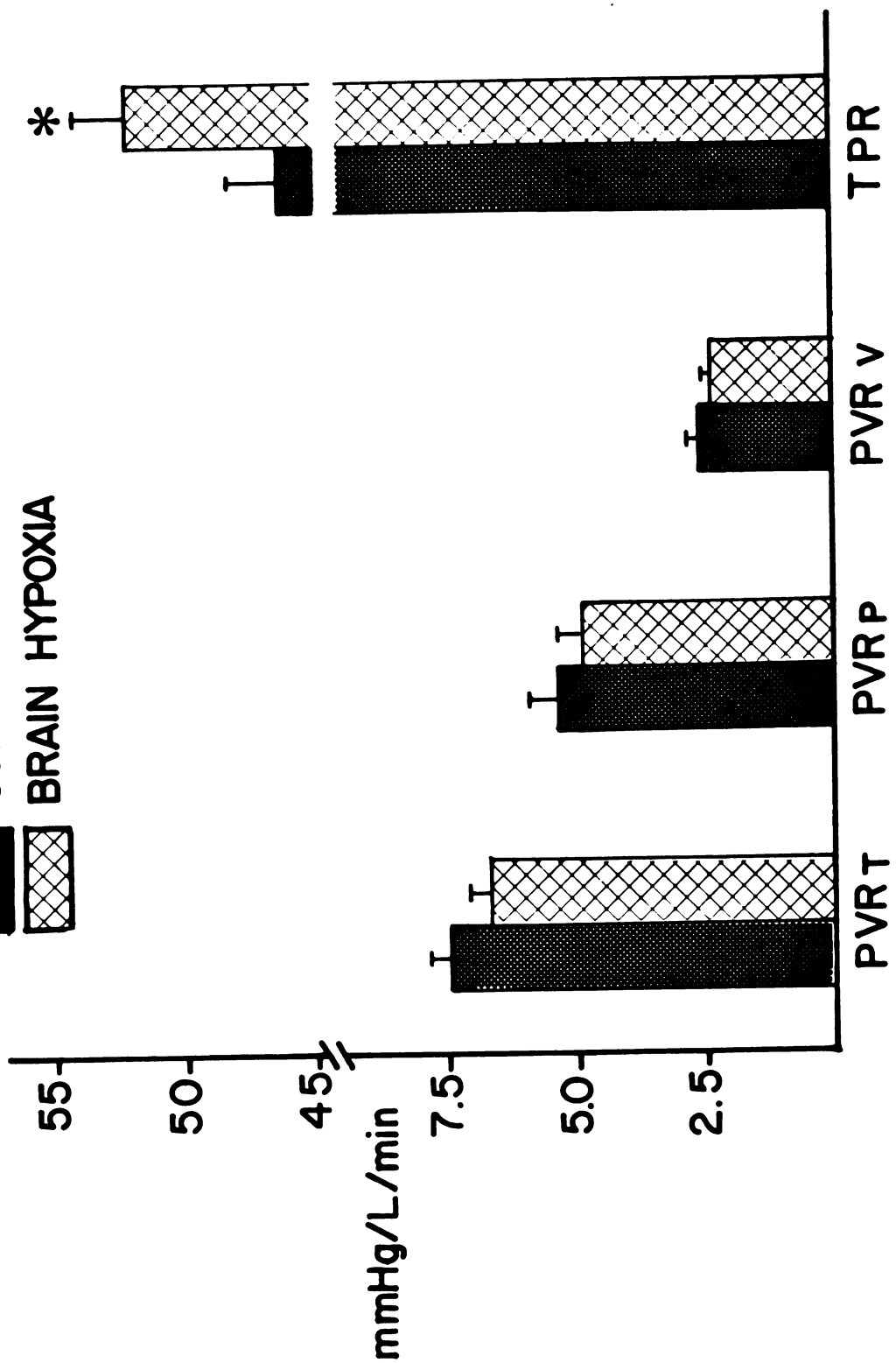

CONTROL
BRAIN HYPOXIA
mmHg/L/min
55
50
45
7.5
5.0
2.5
PVR T
PVR P
PVR V
TPR
*

Figure 9

Figure 10. Effect of perfusing the brain with severely hypoxemic blood on lung extravascular thermal volume (ETV_L), central blood volume (CBV), and extravascular lung water to extravascular dry weight ratio (EVLW/EVDW). Flow to the head was constant (259 ± 16 ml/min) and the vagus and carotid sinus nerves were cut. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are means ± standard error based on error mean square from ANOVA. N = 6, except EVLW/EVDW where N = 5. *, significantly different from control at $P < 0.05$.

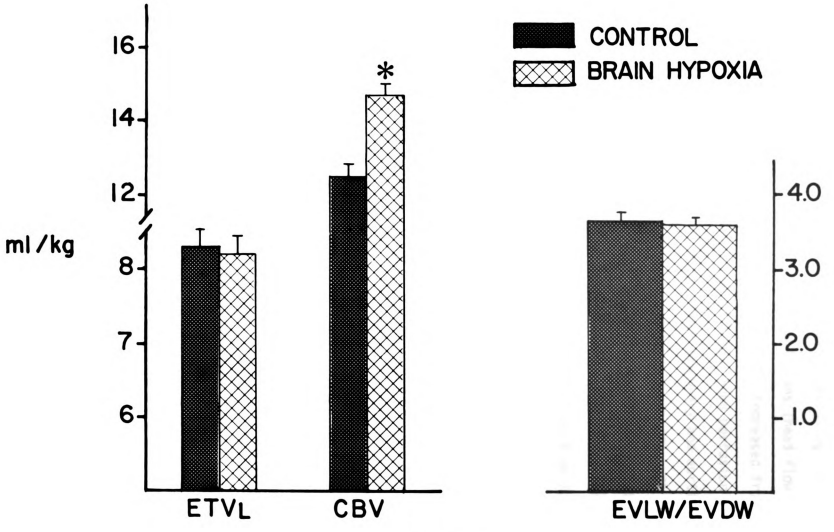

CONTROL
BRAIN HYPOXIA
ml/kg
16
14
12
8
7
6
*
4.0
3.0
2.0
1.0
ETVL
CBV
EVLW/EVDW

Figure 10

Table 7 shows the cardiovascular effects of perfusing the brain with hypercapnic blood under constant flow conditions (head flow = 275 ± 19 ml/min). During this treatment perfusate PCO_2 increased from 36 to 86 torr while pH decreased from 7.44 to 7.16. Head perfusion pressure decreased 22% from 110 to 86 mmHg. Mean pulmonary and aortic pressures increased 7% (from 11.7 to 12.5 mmHg) and 44% (from 61 to 88 mmHg), respectively. Left ventricular dP/dt and total peripheral resistance increased 31% (from 1750 to 2286 mmHg/sec) and 32% (from 50.3 to 66.4 mmHg/L/min), respectively. Systemic pH decreased from 7.41 to 7.33 while P_aCO_2 increased from 39 to 45 torr. None of the other measured or calculated variables changed.

The effects of perfusing the brain with hypoxic-hypercapnic blood on the pulmonary and systemic circulations are shown in Table 8. In this series blood flow was constant (head flow = 289 ± 19 ml/min) and perfusate PO_2 decreased from 113 to 27 torr, PCO_2 increased from 35 to 77 torr, and pH decreased from 7.41 to 7.17. Head perfusion pressure decreased 28% from 109 to 79 mmHg. Mean pulmonary and aortic pressures increased 15% (from 10.8 to 12.4 mmHg) and 51% (from 59 to 89 mmHg), respectively. Left atrial pressure increased 29% from 2.1 to 2.7 mmHg and pulmonary artery pulse pressure increased 24% from 9.7 to 12.0 mmHg. Large vein pulmonary vascular resistance decreased 32% (from 3.17 to 2.14 mmHg/L/min). Cardiac output increased 28% (from 1.22 to 1.56 L/min), stroke volume increased 25% (from 6.3 to 7.9 ml), dP/dt increased 70% (from 1679 to 2857 mmHg/sec), and total peripheral resistance increased 21% (from 48.4 to 58.5 mmHg/L/min). Systemic pH and P_aO_2 decreased from 7.39 to 7.32 and 139 torr to 115 torr, respectively, while P_aCO_2 increased from 38 to 46

torr. All other measured or calculated variables did not change.

The cardiovascular effects of perfusing the brain for two hours with severely hypoxemic blood are shown in Table 9. In this group head flow was constant (298 ± 18 ml/min) and the vagus and carotid sinus nerves were cut. Perfusate PO_2 decreased from 113 to approximately 32 torr for 120 min causing head perfusion pressure to decrease approximately 41%. Meanwhile, total peripheral resistance and mean aortic pressure progressively decreased throughout the perfusion period. All other measured or calculated hemodynamic variables did not change. Postmortem extravascular lung water to extravascular dry weight ratio was 3.76 ± 0.15, which is not significantly different from control values in our laboratory.

Table 7. Cardiovascular effects of perfusing the brain with hypercapnic blood under constant flow conditions (head flow = 275 ± 19 ml/min) with the vagus and carotid sinus nerves cut. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypercapnic mixture containing 15% O_2, 15% CO_2, 70% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA. N = 7, unless otherwise indicated. *, significantly different from control at $P < 0.05$; P_{HP}, head perfusion pressure, $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure (N = 6); P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance (N = 6); PVR_V, large vein pulmonary vascular resistance (N = 6); $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; dP/dt, left ventricular contractility; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 7

	Control	Hypercapnia	SE
Perfusate PO_2 (torr)	107	101	2.40
Perfusate PCO_2 (torr)	36	86	1.80*
Perfusate pH	7.44	7.16	0.01*
P_{HP} (mmHg)	110	86	2.00*
$P_{\overline{PA}}$ (mmHg)	11.7	12.5	0.20*
P_{PAW} (mmHg)	4.2	4.5	0.20
P_{LA} (mmHg)	2.1	2.6	0.20
P_{PAP} (mmHg)	10.4	12.3	0.30
PVR_T (mmHg/L/min)	8.07	7.65	0.30
PVR_P (mmHg/L/min)	6.08	5.83	0.30
PVR_V (mmHg/L/min)	2.70	2.53	0.10
$\dot{Q}$ (L/min)	1.24	1.35	0.03
HR (beats/min)	199	201	2.10
V_S (ml)	6.3	6.8	0.20
dP/dt (mmHg/sec)	1750	2286	151*
P_{MA} (mmHg)	61	88	3.60*
TPR (mmHg/L/min)	50.3	66.4	3.00*
P_aO_2 (torr)	129	132	1.90
P_aCO_2 (torr)	39	45	1.50*
pH (systemic)	7.41	7.33	0.01*

Table 8. Cardiovascular effects of perfusing the brain with hypoxemic-hypercapnic blood under constant flow conditions (head flow = 289 ± 19 ml/min) with the vagus and carotid sinus nerves cut. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic-hypercapnic mixture containing 0% O_2, 15% CO_2, 85% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA. N = 7, unless otherwise indicated. *, significantly different from control at $P < 0.05$; P_{HP}, head perfusion pressure; $\overline{P_{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure (N = 6); P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance (N = 6); PVR_V, large vein pulmonary vascular resistance (N = 6); $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; dP/dt, left ventricular contractility; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 8

	Control	Hypoxia-Hypercapnia	SE
Perfusate PO_2 (torr)	113	27	4.90*
Perfusate PCO_2 (torr)	35	77	2.00*
Perfusate pH	7.41	7.17	0.01*
P_{HP} (mmHg)	109	79	2.70*
$P_{\overline{PA}}$ (mmHg)	10.8	12.4	0.30*
P_{PAW} (mmHg)	4.8	4.8	0.20
P_{LA} (mmHg)	2.1	2.7	0.10*
P_{PAP} (mmHg)	9.7	12.0	0.30*
PVR_T (mmHg/L/min)	7.38	6.51	0.30
PVR_P (mmHg/L/min)	4.61	4.85	0.20
PVR_V (mmHg/L/min)	3.17	2.14	0.20*
$\dot{Q}$ (L/min)	1.22	1.56	0.06*
HR (beats/min)	195	199	1.60
V_S (ml)	6.3	7.9	0.30*
dP/dt (mmHg/sec)	1679	2857	74.0*
P_{MA} (mmHg)	59	89	2.00*
TPR (mmHg/L/min)	48.4	58.5	2.00*
P_aO_2 (torr)	139	115	5.40*
P_aCO_2 (torr)	38	46	1.40*
pH (systemic)	7.39	7.32	0.02*

Table 9. Cardiovascular effects of perfusing the brain for two hours with severely hypoxemic blood under constant flow conditions (head flow = 298 ± 18 ml/min) with the vagus and carotid sinus nerves cut. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 15% CO_2, 85% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA. N = 6; *, significantly different from control (0 min) at $P < 0.05$; P_{HP}, head perfusion pressure; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; dP/dt, left ventricular contractility; P_{MA}, mean aortic pressure; TPR, total peripheral resistance; CBV, central blood volume; $\overline{t}_c$, conductivity (NA^+) mean transit time; ETV_L, lung extravascular thermal volume.

Table 9

	Time (min)					
	(0)	(30)	(60)	(90)	(120)	SE
Perfusate PO_2 (torr)	113	29*	31*	33*	34*	2.00
Perfusate PCO_2 (torr)	33	33	35	34	33	1.00
Perfusate pH	7.39	7.38	7.42	7.38	7.34	0.02
P_{HP} (mmHg)	152	97*	88*	88*	83*	5.00
$P_{\overline{PA}}$ (mmHg)	12.6	13.3	12.7	13.2	13.4	0.30
P_{PAW} (mmHg)	6.1	6.1	6.3	6.3	6.8	0.40
P_{LA} (mmHg)	3.5	3.3	3.5	4.1	4.6	0.50
PVR_T (mmHg/L/min)	4.40	5.43	4.88	4.83	4.95	0.40
PVR_P (mmHg/L/min)	3.15	3.91	3.38	3.68	3.78	0.30
PVR_V (mmHg/L/min)	1.25	1.52	1.50	1.15	1.17	0.10
$\dot{Q}$ (L/min)	2.13	1.98	2.16	1.97	2.01	0.16
dP/dt (mmHg/sec)	2667	2708	2667	2459	2292	118
P_{MA} (mmHg)	89	78*	64*	60*	53*	2.00
TPR (mmHg/L/min)	43.5	41.7	33.6*	32.2*	29.6*	2.30
CBV (ml/kg)	14.2	12.0	12.7	12.8	12.2	0.60
$\overline{t}_C$ (sec)	9.47	8.64	8.85	9.37	9.06	0.50
ETV_L (ml/kg)	7.67	7.86	6.96	7.20	7.63	0.20

II. Carotid Body Hypoxia and Hypercapnia

Vagus Nerves Intact

Table 10 shows the effects of severe carotid body hypoxia on the pulmonary and systemic circulations. In this group perfusate PO_2 decreased from 96 to 23 torr, cardiac output decreased 10% from 2.09 to 1.89 L/min, and total peripheral resistance increased 12% from 54.9 to 61.7 mmHg/L/min. None of the other measured or calculated variables changed.

Vagus Nerves Cut

Tables 11-13 show the cardiovascular effects of perfusing the carotid bodies with mildly, moderately, and severely hypoxemic blood. During mild hypoxia perfusate PO_2 decreased from 98 to 49 torr, during moderate hypoxia from 103 to 36 torr, and during severe hypoxia from 100 to 22 torr. Perfusing the carotid bodies with mildly hypoxemic blood increased total peripheral resistance 12% (from 43.9 to 49.2 mmHg/L/min), moderately hypoxemic blood increased total peripheral resistance 28% (from 37.8 to 48.3 mmHg/L/min), and severely hypoxemic blood increased total peripheral resistance 40% (from 48.3 to 67.8 mmHg/L/min). Mean aortic pressure increased 21% during moderate (from 75 to 91 mmHg) and severe (from 102 to 123 mmHg) carotid body hypoxia. During severe carotid body hypoxia PVR_T and PVR_P increased 21% (from 4.66 to 5.63 mmHg/L/min) and 26% (from 3.27 to 4.13 mmHg/L/min), respectively, while cardiac output decreased 12% (from 2.19 to 1.93 L/min) and heart rate 6% (from 172 to 161 beats/min). All other measured or calculated variables during mild, moderate or severe hypoxia did not change.

The cardiovascular effects of hypercapnic and hypoxic-hypercapnic perfusion of the carotid bodies are shown in Tables 14-15. During hypercapnia perfusate PCO_2 increased from 38 to 83 torr and pH decreased from 7.36 to 7.10. Meanwhile systemic pH decreased from 7.36 to 7.33 and P_aCO_2 increased from 37 to 40 torr. During hypoxia-hypercapnia perfusate PO_2 and pH decreased from 112 torr to 20 torr and 7.38 to 7.20, respectively, while PCO_2 increased from 38 to 72 torr. Perfusing the carotid bodies with hypercapnic and hypoxic-hypercapnic blood increased total peripheral resistance 21% (from 40.9 to 49.5 mmHg/L/min) and 42% (from 35.8 to 50.9 mmHg/L/min), respectively, while mean aortic pressure increased 14% (from 79 to 90 mmHg) and 46% (from 74 to 108 mmHg), respectively. During hypoxic-hypercapnic perfusion of the carotid bodies mean pulmonary artery pressure increased 10% (from 12.6 to 13.9 mmHg) and pulmonary artery pulse pressure 17% (from 9.8 to 11.5 mmHg). Both PVR_T (from 5.09 to 5.78 mmHg/L/min) and PVR_p (from 3.83 to 4.36 mmHg/L/min) increased 14%. None of the other measured or calculated variables changed during hypercapnia or hypoxia-hypercapnia.

The cardiovascular effects of perfusing the carotid bodies with severely hypoxemic and hypoxic-hypercapnic blood, following alpha blockade, are shown in Tables 16-17. During severe hypoxemia, perfusate PO_2 was reduced from 104 to 25 torr and during hypoxia-hypercapnia perfusate PO_2 was reduced from 101 to 29 torr. Also during hypoxia-hypercapnia, perfusate pH decreased from 7.37 to 7.11 and PCO_2 increased from 38 to 76 torr while systemic pH decreased from 7.33 to 7.25 and P_aCO_2 increased from 40 to 48 torr. Despite alpha blockade, severely hypoxemic perfusion of the carotid bodies increased mean aortic pressure from

50 to 81 mmHg and during hypoxia-hypercapnia from 54 to 87 mmHg; in the latter total peripheral resistance increased from 40.0 to 53.7 mmHg/L/min, cardiac output from 1.45 to 1.76 L/min, and stroke volume from 7.1 to 9.1 ml. All other measured or calculated variables during alpha blockade did not change.

Table 10. Cardiovascular effects of perfusing the carotid bodies with severely hypoxemic blood, before vagotomy, under constant flow and pressure conditions. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2. 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA, N = 12. *, significantly different from control at $P < 0.05$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure, TPR, total peripheral resistance.

Table 10

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	96	23	3.30*
Perfusate PCO_2 (torr)	33	33	0.90
Perfusate pH	7.37	7.39	0.01
$P_{\overline{PA}}$ (mmHg)	12.3	11.9	0.10
P_{PAW} (mmHg)	4.9	4.8	0.10
P_{LA} (mmHg)	2.7	2.7	0.10
P_{PAP} (mmHg)	9.1	8.6	0.30
PVR_T (mmHg/L/min)	4.70	5.04	0.20
PVR_P (mmHg/L/min)	3.63	3.88	0.10
PVR_V (mmHg/L/min)	1.07	1.16	0.10
$\dot{Q}$ (L/min)	2.09	1.89	0.06*
HR (beats/min)	159	154	4.10
V_S (ml)	13.3	12.4	0.60
P_{MA} (mmHg)	110	112	2.20
TPR (mmHg/L/min)	54.9	61.7	1.90*
P_aO_2 (torr)	111	104	2.60
P_aCO_2 (torr)	32	30	0.80
pH (systemic)	7.37	7.36	0.01

Table 11. Cardiovascular effects of perfusing the carotid bodies with mildly hypoxemic blood, following vagotomy, under constant flow and pressure conditions. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 5% O_2, 5% CO_2, 90% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA, N = 14. *, significantly different from control at $P < 0.05$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 11

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	98	49	2.60*
Perfusate PCO_2 (torr)	36	35	0.60
Perfusate pH	7.38	7.39	0.01
$P_{\overline{PA}}$ (mmHg)	13.2	13.3	0.10
P_{PAW} (mmHg)	5.9	5.8	0.10
P_{LA} (mmHg)	2.4	2.3	0.10
P_{PAP} (mmHg)	9.9	10.1	0.20
PVR_T (mmHg/L/min)	5.68	5.99	0.10
PVR_P (mmHg/L/min)	3.78	4.10	0.10
PVR_V (mmHg/L/min)	1.90	1.89	0.10
$\dot{Q}$ (L/min)	2.06	2.01	0.03
HR (beats/min)	177	177	2.40
V_S (ml)	11.8	11.4	0.30
P_{MA} (mmHg)	82	90	2.70
TPR (mmHg/L/min)	43.9	49.2	1.60*
P_aO_2 (torr)	113	108	1.90
P_aCO_2 (torr)	36	35	0.50
pH (systemic)	7.36	7.36	0.01

Table 12. Cardiovascular effects of perfusing the carotid bodies with moderately hypoxemic blood, following vagotomy, under constant flow and pressure conditions. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 2.5% O_2, 5% CO_2, 92.5% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA, N = 14. *, significantly different from control at $P < 0.05$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 12

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	103	36	2.30*
Perfusate PCO_2 (torr)	37	37	1.00
Perfusate pH	7.39	7.39	0.01
$P_{\overline{PA}}$ (mmHg)	13.1	13.4	0.20
P_{PAW} (mmHg)	5.0	4.9	0.10
P_{LA} (mmHg)	1.6	1.5	0.10
P_{PAP} (mmHg)	9.1	9.4	0.10
PVR_T (mmHg/L/min)	5.88	6.41	0.20
PVR_P (mmHg/L/min)	4.15	4.56	0.20
PVR_V (mmHg/L/min)	1.73	1.85	0.10
$\dot{Q}$ (L/min)	2.05	1.96	0.03
HR (beats/min)	180	179	1.60
V_S (ml)	11.5	11.1	0.20
P_{MA} (mmHg)	75	91	2.10*
TPR (mmHg/L/min)	37.8	48.3	1.80*
P_aO_2 (torr)	108	104	2.00
P_aCO_2 (torr)	37	36	0.50
pH (systemic)	7.37	7.37	0.01

Table 13. Cardiovascular effects of perfusing the carotid bodies with severely hypoxemic blood, following vagotomy, under constant flow and pressure conditions. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA, N = 10. *, significantly different from control at $P < 0.05$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 13

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	100	22	4.60*
Perfusate PCO_2 (torr)	35	36	1.00
Perfusate pH	7.35	7.37	0.01
$P_{\overline{PA}}$ (mmHg)	11.7	12.1	0.20
P_{PAW} (mmHg)	5.0	4.8	0.10
P_{LA} (mmHg)	2.2	2.1	0.10
P_{PAP} (mmHg)	9.4	9.5	0.30
PVR_T (mmHg/L/min)	4.66	5.63	0.20*
PVR_P (mmHg/L/min)	3.27	4.13	0.20*
PVR_V (mmHg/L/min)	1.39	1.50	0.10
$\dot{Q}$ (L/min)	2.19	1.93	0.04*
HR (beats/min)	172	161	2.90*
V_S (ml)	12.7	12.1	0.30
P_{MA} (mmHg)	102	123	3.70*
TPR (mmHg/L/min)	48.3	67.8	3.40*
P_aO_2 (torr)	106	105	2.40
P_aCO_2 (torr)	36	35	0.70
pH (systemic)	7.34	7.33	0.01

Table 14. Cardiovascular effects of perfusing the carotid bodies with hypercapnic blood, following vagotomy, under constant flow and pressure conditions. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypercapnic mixture containing 15% O_2, 15% CO_2, 70% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA, N = 13. *, significantly different from control at $P < 0.05$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 14

	Control	Hypercapnia	SE
Perfusate PO_2 (torr)	100	99	2.40
Perfusate PCO_2 (torr)	38	83	2.30*
Perfusate pH	7.36	7.10	0.01*
$P_{\overline{PA}}$ (mmHg)	12.8	13.1	0.10
P_{PAW} (mmHg)	5.1	4.6	0.20
P_{LA} (mmHg)	1.7	1.7	0.10
P_{PAP} (mmHg)	9.2	9.1	0.20
PVR_T (mmHg/L/min)	5.76	6.28	0.20
PVR_P (mmHg/L/min)	3.88	4.57	0.20
PVR_V (mmHg/L/min)	1.88	1.71	0.10
$\dot{Q}$ (L/min)	2.04	1.97	0.04
HR (beats/min)	178	177	3.50
V_S (ml)	11.6	11.3	0.20
P_{MA} (mmHg)	79	90	1.90*
TPR (mmHg/L/min)	40.9	49.5	1.50*
P_aO_2 (torr)	113	113	1.80
P_aCO_2 (torr)	37	40	0.70*
pH (systemic)	7.36	7.33	0.01*

Table 15. Cardiovascular effects of perfusing the carotid bodies with hypoxemic-hypercapnic blood, following vagotomy, under constant flow and pressure conditions. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2 80% N_2 and a hypoxic-hypercapnic mixture containing 0% O_2, 15% CO_2, 85% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA, N = 10. *, significantly different from control at $P < 0.05$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure, P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 15

	Control	Hypoxia-Hypercapnia	SE
Perfusate PO_2 (torr)	112	20	4.90*
Perfusate PCO_2 (torr)	38	72	2.90*
Perfusate pH	7.38	7.20	0.01*
$P_{\overline{PA}}$ (mmHg)	12.6	13.9	0.20*
P_{PAW} (mmHg)	4.5	4.5	0.20
P_{LA} (mmHg)	1.9	1.7	0.10
P_{PAP} (mmHg)	9.8	11.5	0.20*
PVR_T (mmHg/L/min)	5.09	5.78	0.20*
PVR_P (mmHg/L/min)	3.83	4.36	0.10*
PVR_V (mmHg/L/min)	1.26	1.42	0.20
$\dot{Q}$ (L/min)	2.22	2.33	0.07
HR (beats/min)	177	168	4.00
V_S (ml)	13.0	14.1	0.50
P_{MA} (mmHg)	74	108	4.50*
TPR (mmHg/L/min)	35.8	50.9	2.30*
P_aO_2 (torr)	113	112	2.20
P_aCO_2 (torr)	36	37	1.00
pH (systemic)	7.38	7.35	0.01

Table 16. Cardiovascular effects of perfusing the carotid bodies with severely hypoxemic blood, following vagotomy and alpha blockade, under constant flow and pressure conditions. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic mixture containing 0% O_2, 5% CO_2, 95% N_2. Values are mean ± standard error (SE) based on error mean square from ANOVA, N = 7. *, significantly different from control at $P < 0.05$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 16

	Control	Hypoxia	SE
Perfusate PO_2 (torr)	104	25	3.30*
Perfusate PCO_2 (torr)	43	40	1.60
Perfusate pH	7.40	7.40	0.01
$P_{\overline{PA}}$ (mmHg)	13.0	14.1	0.40
P_{PAW} (mmHg)	6.0	6.4	0.20
P_{LA} (mmHg)	2.8	2.9	0.30
P_{PAP} (mmHg)	11.0	12.1	0.50
PVR_T (mmHg/L/min)	7.91	7.36	0.30
PVR_P (mmHg/L/min)	5.38	4.98	0.20
PVR_V (mmHg/L/min)	2.53	2.38	0.20
$\dot{Q}$ (L/min)	1.41	1.82	0.14
HR (beats/min)	213	209	1.80
V_S (ml)	6.4	8.7	0.70
P_{MA} (mmHg)	50	81	6.20*
TPR (mmHg/L/min)	37.6	50.3	4.20
P_aO_2 (torr)	111	110	2.30
P_aCO_2 (torr)	46	40	2.30
pH (systemic)	7.36	7.34	0.01

Table 17. Cardiovascular effects of perfusing the carotid bodies with hypoxemic-hypercapnic blood, following vagotomy and alpha blockade, under constant flow and pressure conditions. The extracorporeal lung was ventilated with a control gas mixture containing 15% O_2, 5% CO_2, 80% N_2 and a hypoxic-hypercapnic mixture containing 0% O_2, 15% CO_2, 85% N_2. Values are means ± standard error (SE) based on error mean square from ANOVA, N = 10. *, significantly different from control at $P < 0.05$; $\overline{P_{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_T, total pulmonary vascular resistance; PVR_P, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance; $\dot{Q}$, cardiac output; HR, heart rate; V_S, stroke volume; P_{MA}, mean aortic pressure; TPR, total peripheral resistance.

Table 17

	Control	Hypoxia-Hypercapnia	SE
Perfusate PO_2 (torr)	101	29	3.50*
Perfusate PCO_2 (torr)	38	76	1.50*
Perfusate pH	7.37	7.11	0.01*
$P_{\overline{PA}}$ (mmHg)	13.7	14.8	0.40
P_{PAW} (mmHg)	5.4	5.4	0.10
P_{LA} (mmHg)	2.0	2.1	0.20
P_{PAP} (mmHg)	11.8	12.2	0.30
PVR_T (mmHg/L/min)	8.67	8.18	0.20
PVR_P (mmHg/L/min)	6.14	5.95	0.20
PVR_V (mmHg/L/min)	2.53	2.23	0.10
$\dot{Q}$ (L/min)	1.45	1.76	0.09*
HR (beats/min)	205	194	3.00
V_S (ml)	7.1	9.1	0.40*
P_{MA} (mmHg)	54	87	6.30*
TPR (mmHg/L/min)	40.0	53.7	2.90*
P_aO_2 (torr)	124	124	4.20
P_aCO_2 (torr)	40	48	1.40*
pH (systemic)	7.33	7.25	0.01*

III. Histamine and Adrenergic Receptors

Time Control Group

Table 18 shows that none of the measured or calculated variables changed with time except cardiac index, which increased (at 30 min) from 2.16 to 2.53 ml/sec/kg (SE = 0.10; $P < 0.05$) and conductivity mean transit time, which decreased from 8.97 to 7.88 sec (SE = 0.23; $P < 0.05$). In both cases comparable values obtained at 0, 60 and 90 min were not different from -20 min.

Histamine Group

The effects of intravenous histamine infusion (between 0 and 90 min) on the pulmonary and systemic circulations are shown in Table 19. Values obtained prior to histamine infusion (i.e., -20 and 0 min) were not significantly different. Cardiac index decreased at 30 min but was not significantly reduced at 60 and 90 min. Pulmonary artery wedge and pulse pressures, stroke volume, mean aortic pressure, total peripheral resistance and central blood volume were reduced throughout the histamine infusion period. Heart rate, PVR_p, and airway opening pressure increased during histamine infusion whereas mean pulmonary artery pressure, conductivity mean transit time and lung extravascular thermal volume did not change. Systemic pH and P_aO_2 decreased during histamine infusion, although the latter returned to control levels at 90 min. Meanwhile, P_aCO_2 increased at 60 and 90 min.

Propranolol-Histamine Group

The cardiovascular effects of intravenous infusion of propranolol and histamine with propranolol are shown in Table 20. Propranolol (0 min)

increased mean pulmonary artery and pulmonary artery wedge pressures; total peripheral resistance, central blood volume and conductivity mean transit time while decreasing cardiac index, stroke volume, and pH. The other parameters were not affected. Histamine administration during beta blockade (30, 60 and 90 min) resulted in a rise in PVR_p and airway opening pressure and these increases were significantly greater ($P < 0.05$) than with histamine alone. Cardiac index and stroke volume decreased further when histamine was infused during beta blockade whereas conductivity mean transit time was not different from beta blockade alone. Histamine with beta blockade also caused significant reductions in pulmonary artery pulse and mean aortic pressures, total peripheral resistance, and central blood volume. Mean pulmonary artery and wedge pressures returned to pre-beta blockade levels while heart rate and lung extravascular thermal volume remained unaffected. The decreases in cardiac index, stroke volume and mean aortic pressure were significantly greater ($P < 0.05$) than the decreases with histamine alone. Systemic pH and P_aO_2 were reduced throughout histamine infusion while P_aCO_2 was increased at 90 min.

Phentolamine-Histamine Group

Table 21 shows the effects of alpha blockade and alpha blockade plus histamine infusion on the cardiovascular system. Infusion of the alpha blocker, phentolamine, was associated with an elevation in heart rate and reductions in mean pulmonary artery, pulmonary artery wedge and pulse pressures, stroke volume, mean aortic pressure, total peripheral resistance, conductivity mean transit time, central blood volume, and P_aO_2. None of the other parameters were affected. Histamine infusion

during alpha blockade increased PVR_p and airway opening pressure; however, these increases were significantly ($P < 0.05$) less than during beta blockade with histamine. Mean aortic pressure and total peripheral resistance decreased further when histamine was infused during alpha blockade; the latter decreased significantly more ($P < 0.05$) compared to beta blockade with histamine. Pulmonary artery wedge and pulse pressures, stroke volume, heart rate, central blood volume and conductivity mean transit time did not change from levels obtained during alpha blockade alone. Mean pulmonary artery pressure did not change at 30 min but returned to pre-alpha blockade level at 60 and 90 min while cardiac index and lung extravascular thermal volume remained unaffected. Systemic pH and P_aO_2 were reduced throughout histamine infusion whereas P_aCO_2 increased at 90 min.

Table 18. Time control group in which no vasoactive drugs were administered. Values are means ± standard error (SE) based on error mean square from ANOVA; N = 10; , significantly different from (-20) min at $P < 0.01$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{PAP}, pulmonary artery pulse pressure, PVR_P, pre-large vein pulmonary vascular resistance; CI, cardiac index; V_S, stroke volume; HR, heart rate; P_{MA}, mean aortic pressure; TPR, total peripheral resistance; CBV, central blood volume; $\overline{t}_C$, conductivity (Na^+) mean transit time; ETV_L, lung extravascular thermal volume.

Table 18

	Time (min)					
	(-20)	(0)	(30)	(60)	(90)	SE
$P_{\overline{PA}}$ (mmHg)	14.2	14.7	15.1	15.6	15.7	0.40
P_{PAW} (mmHg)	5.7	5.9	6.1	6.3	6.3	0.20
P_{PAP} (mmHg)	10.8	11.4	11.2	11.0	11.4	0.20
PVR_P[mmHg·sec(kg·ml)$^{-1}$]	3.99	3.89	3.65	3.98	4.34	0.20
CI (ml/sec/kg)	2.16	2.28	2.53†	2.37	2.19	0.10
V_S (ml)	22.5	23.2	25.8	21.2	19.7	1.60
HR (beats/min)	153	150	151	166	166	6.10
P_{MA} (mmHg)	148	153	151	152	148	3.30
TPR[mmHg·sec(kg·ml)$^{-1}$]	69.4	70.1	61.7	65.1	68.5	2.30
CBV (ml/kg)	19.0	19.3	19.7	19.6	19.4	0.40
$\overline{t}_C$ (sec)	8.97	8.63	7.88†	8.31	8.96	0.20
ETV_L (ml/kg)	6.96	7.13	7.61	7.64	7.51	0.20
P_aO_2 (torr)	144	127	126	120	129	5.00
P_aCO_2 (torr)	35	36	36	36	37	1.00
pH	7.39	7.36	7.35	7.37	7.37	0.01

Table 19. Effects of intravenous histamine on the cardiovascular system. Histamine base infused at 10 μg/kg/min between (0) and (90) min. Values are means ± standard error (SE) based on error mean square from ANOVA; N = 8; †, significantly different from control [(-20) min] at $P < 0.01$; *, significantly different from (0) min at $P < 0.01$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{PAP}, pulmonary artery pulse pressure; PVR_P, pre-large vein pulmonary vascular resistance; CI, cardiac index; V_S, stroke volume; HR, heart rate; P_{MA}, mean aortic pressure; TPR, total peripheral resistance; CBV, central blood volume; $\overline{t}_C$, conductivity (Na^+) mean transit time; ETV_L, lung extravascular thermal volume; P_{ao}, airway opening pressure.

Table 19

	Time (min)					
	(-20) Control	(0) Control	(30) Histamine	(60) Histamine	(90) Histamine	SE
$\overline{P_{PA}}$ (mmHg)	14.4	14.3	13.4	14.6	14.4	0.50
P_{PAW} (mmHg)	5.9	5.8	$3.3^{\dagger}$*	$4.1^{\dagger}$*	$4.3^{\dagger}$*	0.40
P_{PAP} (mmHg)	13.8	13.6	$10.9^{\dagger}$*	$10.3^{\dagger}$*	$10.4^{\dagger}$*	0.50
PVR_p[mmHg·sec(kg·ml)$^{-1}$]	3.81	3.66	$7.12^{\dagger}$*	$6.34^{\dagger}$*	$6.37^{\dagger}$*	0.60
CI (ml/sec/kg)	2.53	2.48	$1.67^{\dagger}$*	2.15	2.11	0.20
V_S (ml)	27.5	25.9	$13.6^{\dagger}$*	$15.1^{\dagger}$*	$14.3^{\dagger}$*	2.50
HR (beats/min)	125	133	$162^{\dagger}$*	$181^{\dagger}$*	$188^{\dagger}$*	8.20
P_{MA} (mmHg)	159	161	$69^{\dagger}$*	$72^{\dagger}$*	$64^{\dagger}$*	4.60
TPR[mmHg·sec(kg·ml)$^{-1}$]	74.2	71.7	$45.1^{\dagger}$*	$41.8^{\dagger}$*	$36.5^{\dagger}$*	4.20
CBV (ml/kg)	17.1	17.0	$11.9^{\dagger}$*	$13.2^{\dagger}$*	$13.2^{\dagger}$*	0.70
$\overline{t}_C$ (sec)	7.34	7.17	7.59	7.11	7.28	0.30
ETV_L (ml/kg)	7.19	7.48	7.37	7.39	7.26	0.20
P_{ao} (cm H_2O)	9.6	9.6	$12.1^{\dagger}$*	$11.6^{\dagger}$*	$11.7^{\dagger}$*	0.20
P_aO_2 (torr)	132	134	$99^{\dagger}$*	$96^{\dagger}$*	117	8.00
P_aCO_2 (torr)	39	41	44	$48^{\dagger}$*	$50^{\dagger}$*	2.00
pH	7.35	7.32	$7.24^{\dagger}$*	$7.21^{\dagger}$*	$7.18^{\dagger}$*	0.02

Table 20. Effects of intravenous propranolol and histamine on the cardiovascular system. Propranolol infused at 2 mg/kg between (-20) and (-15) min, then at 20 μg/kg/min for remainder of experiment. Histamine base infused at 10 μg/kg/min between (0) and (90) min. Values are means ± standard error (SE) based on error mean square from ANOVA; N = 11; †, significantly different from control [(-20) min] at $P < 0.01$; *, significantly different from (0) min at $P < 0.01$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure, P_{PAP}, pulmonary artery pulse pressure; PVR_P, pre-large vein pulmonary vascular resistance; CI, cardiac index; V_S, stroke volume; HR, heart rate; P_{MA}, mean aortic pressure; TPR, total peripheral resistance; CBV, central blood volume; $\overline{t}_C$, conductivity (Na^+) mean transit time; ETV_L, lung extravascular thermal volume; P_{ao}, airway opening pressure.

Table 20

	Time (min)					
	(-20)	(0)	(30)	(60)	(90)	SE
	Control	Propranolol	Histamine + Propranolol			
$P_{\overline{PA}}$ (mmHg)	15.3	17.9†	14.1*	13.9*	14.5*	0.50
P_{PAW} (mmHg)	6.8	11.0†	6.0*	5.6*	5.2*	0.50
P_{PAP} (mmHg)	16.1	14.4	11.8†*	10.4†*	10.7†*	0.70
PVR_P[mmHg·sec(kg·ml)$^{-1}$]	3.85	4.00	8.83†*	8.96†*	10.11†*	0.60
CI (ml/sec/kg)	2.39	1.90†	1.02†*	0.99†*	1.01†*	0.10
V_S (ml)	22.9	17.9†	9.1†*	8.2†*	8.1†*	1.20
HR (beats/min)	137	142	145	153	157	6.90
P_{MA} (mmHg)	163	159	39†*	43†*	42†*	3.50
TPR[mmHg·sec(kg·ml)$^{-1}$]	73.1	94.6†	41.0†*	45.7†*	44.1†*	4.30
CBV (ml/kg)	22.4	28.4†	16.8†*	15.5†*	15.4†*	1.50
$\overline{t}_C$ (sec)	9.45	15.35†	17.50†	16.41†	16.23†	0.80
ETV_L (ml/kg)	7.94	7.69	8.31	7.94	8.28	0.30
P_{ao} (cm H_2O)	10.2	10.4	15.0†*	14.8†*	14.9†*	0.30
P_aO_2 (torr)	138	124	90†*	85†*	90†*	5.00
P_aCO_2 (torr)	36	35	35	38	41†*	1.00
pH	7.39	7.36†	7.32†	7.28†*	7.28†*	0.01

Table 21. Effects of intravenous phentolamine and histamine on the cardiovascular system. Phentolamine infused at 1 mg/kg between (-20) and (-15) min, then at 10 μg/kg/min for remainder of experiment. Histamine base infused at 10 μg/kg/min between (0) and (90) min. Values are means ± standard error (SE) based on error mean square from ANOVA; N = 6; †, significantly different from control [(-20) min] at $P < 0.01$; *, significantly different from (0) min at $P < 0.01$; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure, P_{PAP}, pulmonary artery pulse pressure; PVR_P, pre-large vein pulmonary vascular resistance; CI, cardiac index; V_S, stroke volume; HR, heart rate, P_{MA}, mean aortic pressure; TPR, total peripheral resistance; CBV, central blood volume; $\overline{t}_C$, conductivity (Na^+) mean transit time; ETV_L, lung extravascular thermal volume; P_{ao}, airway opening pressure.

Table 21

	Time (min)					
	(-20) Control	(0) Phentol-amine	(30) Histamine + Phentolamine	(60) Histamine + Phentolamine	(90) Histamine + Phentolamine	SE
$P_{\overline{PA}}$ (mmHg)	14.2	12.3†	13.3	14.2*	14.3*	0.40
P_{PAW} (mmHg)	6.6	4.2†	3.3†	3.7†	3.8†	0.40
P_{PAP} (mmHg)	14.8	12.0†	9.7†	10.8†	10.7†	0.70
PVR_P[mmHg·sec(kg·ml)$^{-1}$]	2.64	2.86	4.05†*	3.87†*	4.32†*	0.20
CI (ml/sec/kg)	3.05	2.94	2.66	2.97	2.66	0.30
V_S (ml)	36.6	15.9†	17.2†	16.8†	14.7†	1.20
HR (beats/min)	103	231†	195†	223†	225†	6.10
P_{MA} (mmHg)	164	124†	58†*	57†*	55†*	5.40
TPR [mmHg·sec(kg·ml)$^{-1}$]	56.5	43.5†	22.2†*	19.7†*	20.7†*	2.40
CBV (ml/kg)	21.4	17.8†	15.5†	16.7†	15.5†	0.90
$\overline{t}_C$ (sec)	7.25	6.16†	6.08†	5.91†	6.15†	0.20
ETV_L (ml/kg)	6.73	7.61	7.36	7.15	7.32	0.30
P_{ao} (cm H_2O)	9.8	9.8	11.8†*	11.8†*	12.1†*	0.30
P_aO_2 (torr)	140	123†	101†*	90†*	120†	5.00
P_aCO_2 (torr)	33	38	39	43	45†	3.00
pH	7.39	7.34	7.27†	7.28†	7.27†	0.02

Pulmonary Extravascular Tissue Weight and Lung Extravascular Thermal Volume

Pulmonary extravascular tissue weight in time control, histamine, propranolol-histamine and phentolamine-histamine groups were 6.41 ± 0.34, 6.10 ± 0.38, 7.06 ± 0.46 and 6.48 ± 0.38 ml/kg, respectively. Lung extravascular thermal volume overestimated pulmonary extravascular tissue weight 17.2% ($P < 0.01$) in the time control group, 19.0% ($P < 0.05$) in the histamine group, 17.3% ($P < 0.01$) in the propranolol-histamine group and 13.0% ($P < 0.05$) in the phentolamine-histamine group. However, the difference in the amount of overestimate between groups is not significant. Figure 11 shows that a significant correlation existed between pulmonary extravascular tissue weight and lung extravascular thermal volume for the time control group ($r = 0.81$; $P < 0.01$), with a regression equation of:

Lung extravascular thermal volume = 0.87
(pulmonary extravascular tissue weight) + 1.92.

Among the histamine, propranolol-histamine, and phentolamine-histamine groups there were no significant differences in pulmonary extravascular tissue weight, lung extravascular thermal volume, or the regression slopes correlating pulmonary extravascular tissue weight with lung extravascular thermal volume. Thus, for purposes of regression analysis all dogs receiving histamine were combined resulting in a correlation coefficient of 0.84 ($P < 0.01$; Figure 12). The regression equation for all dogs receiving histamine is:

Lung extravascular thermal volume = 0.84
(pulmonary extravascular tissue weight) + 2.15.

The slopes for time control dogs (Figure 11) and all dogs receiving histamine (Figure 12) are not different ($P > 0.50$).

Figure 11. Linear regression of lung extravascular thermal volume (ETV_L) versus pulmonary extravascular tissue weight (PETW) from dogs in the time control group. Broken line is the line of identity. Solid line is the line of best fit, based on the method of least squares.

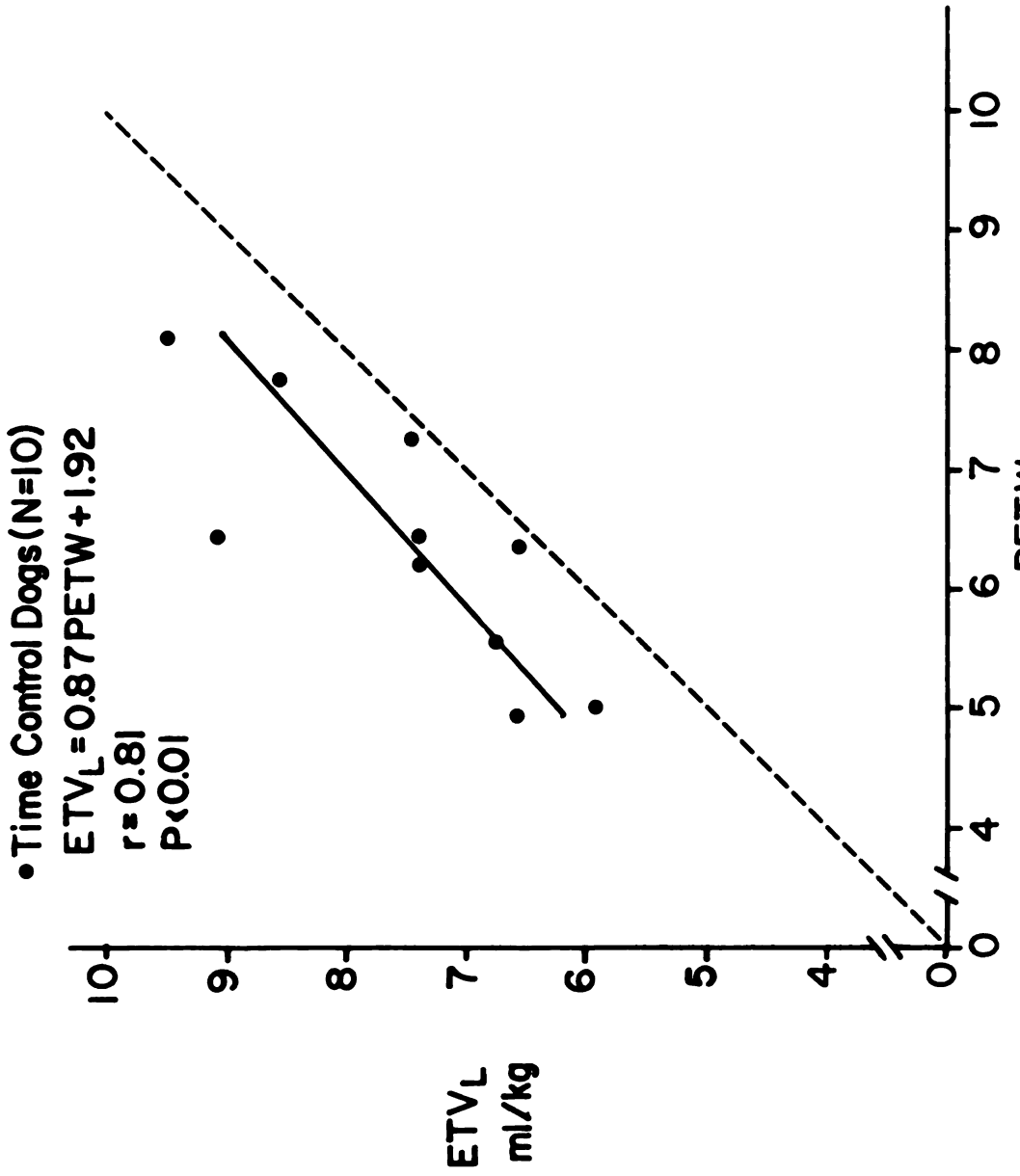

• Time Control Dogs (N=10)
ETV_L=0.87PETW+1.92
r=0.81
P<0.01
ETV_L ml/kg
PETW ml/kg
0
4
5
6
7
8
9
10

Figure 11

Figure 12. Linear regression of lung extravascular thermal volume (ETV_L) versus pulmonary extravascular tissue weight (PETW) in dogs for the combined histamine, propranolol-histamine, and phentolamine-histamine groups. Broken line is the line of identity. Solid line is the line of best fit, based on the method of least squares.

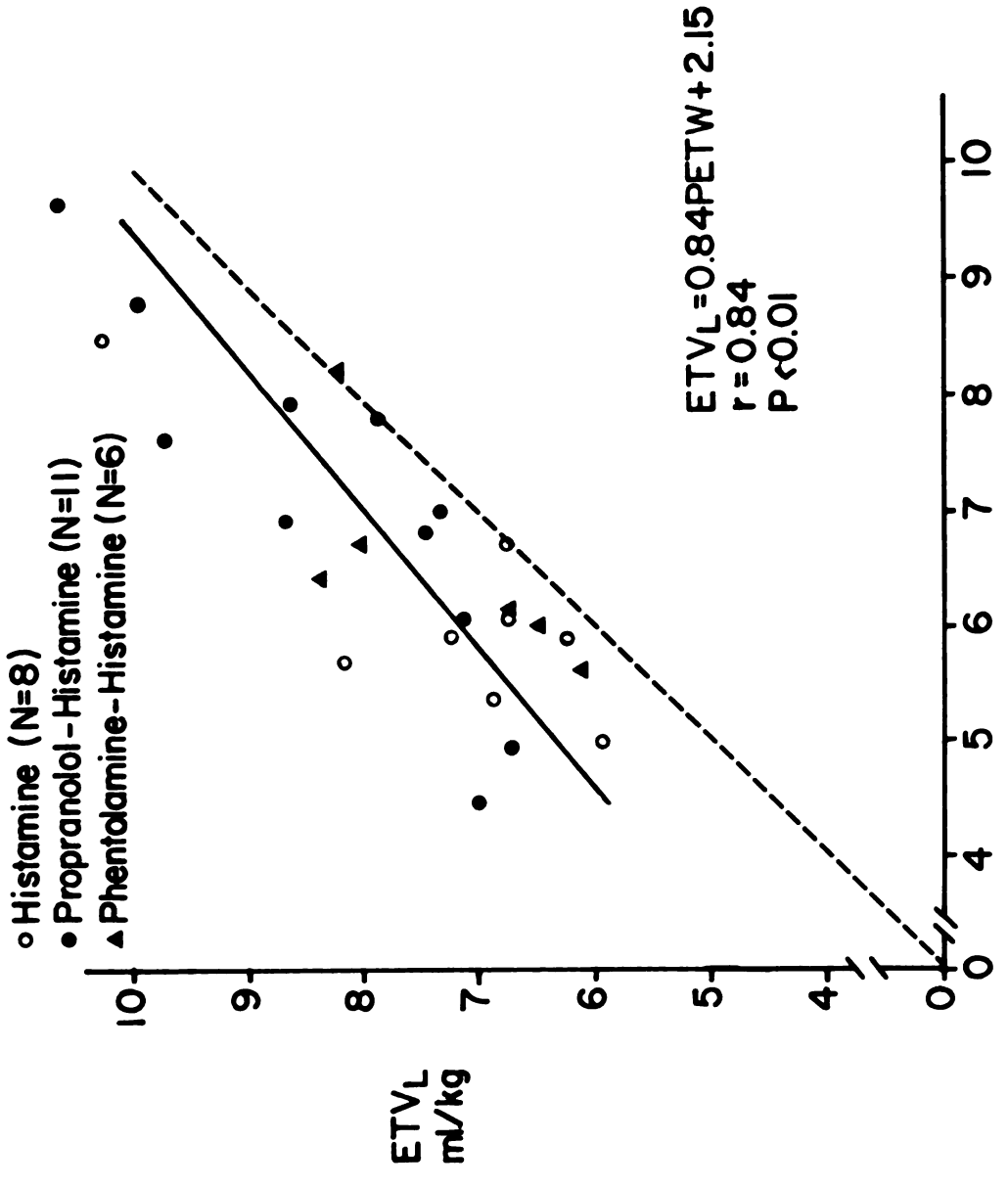

○ Histamine (N=8)
● Propranolol-Histamine (N=11)
▲ Phentolamine-Histamine (N=6)
ETV_L=0.84PETW+2.15
r=0.84
P<0.01
ETV_L ml/kg
PET W ml/kg
0
4
5
6
7
8
9
10

Figure 12

Extravascular Lung Water to Extravascular Dry Weight Ratio

No significant difference was found in extravascular lung water to extravascular dry weight ratio between time control and propranolol-histamine groups receiving the same euthanasia solution; however, a significant difference did exist depending on the type of euthanasia solution used. Time control dogs euthanized with KCl had an extravascular lung water to extravascular dry weight ratio of 2.87 ± 0.17 whereas propranolol-histamine dogs had a ratio of 2.66 ± 0.19. Because these ratios are lower than reported values (183), I began euthanizing subsequent dogs with sodium pentobarbital. Dogs in the time control group euthanized with sodium pentobarbital had an extravascular lung water to extravascular dry weight ratio of 3.97 ± 0.17 whereas dogs in the propranolol-histamine group had a ratio of 3.88 ± 0.12, dogs in the phentolamine-histamine group 3.98 ± 0.09 and dogs in the histamine group 3.75 ± 0.04. The extravascular lung water to extravascular dry weight ratio for dogs euthanized with KCl (i.e., 6 dogs in time control and 6 in propranolol-histamine groups) was 2.76 ± 0.13 and with sodium pentobarbital (i.e., all other dogs) was 3.88 ± 0.05 ($P < 0.01$). Because lung dry weight should not be affected by the type of euthanasia solution used, the most likely cause for this difference was reabsorption of extravascular lung water as the extremely hypertonic bolus of KCl passed through the lung suggesting that saturated KCl should be avoided for euthanasia purposes when performing investigations involving lung water determinations.

DISCUSSION

I. Brain Hypoxia and Hypercapnia

Experimental Preparation

In the experimental preparation of this investigation it was imperative that collateral (i.e., systemic) blood flow to the brain be negligible. Bilateral ligation of the common carotid and vertebral arteries often does not eliminate blood flow to the dog brain because of the extensive collateral blood supply (56,97,175,244). Daly et al. (56) reported that even following bilateral ligation of the vertebral and common carotid arteries, backflow pressure (from the Circle of Willis) in the common carotid artery could not be lowered below 60 mmHg suggesting maintenance of considerable collateral flow to the brain. Whisnant et al. (244), demonstrated that the costocervical and omocervical arteries are the main source of this collateral circulation because these vessels frequently reanastomose with the vertebral artery as the latter vessel courses cephalad. In my preparation these vessels were ligated. With zero flow through the external carotid arteries, head perfusion pressure decreased to < 20 mmHg and was nonpulsatile. This suggests that if any collateral flow remained it was minimal since normally when vertebral arteries and collateral vessels are intact, approximately 70% of the mean arterial pressure is transmitted back from the Circle of Willis to the common carotid artery (175).

In some of the cut nerve experiments, it was not possible under constant flow to maintain head perfusion pressure above mean aortic pressure since the former always decreased while the latter always increased during brain hypoxia and/or hypercapnia. This group nevertheless had the greatest systemic responses to brain hypoxia and/or hypercapnia. Such systemic responses would not be expected if collateral circulation was of any consequence.

When the extracorporeal lung was ventilated with a hypoxic or hypoxic-hypercapnic gas mixture P_aO_2 and systemic pH decreased and P_aCO_2 increased. Ventilation of the extracorporeal lung with a hypercapnic gas mixture caused no change in P_aO_2 while P_aCO_2 increased and systemic pH decreased. Thus, changes in systemic gas tensions and pH tended to follow changes in perfusate PO_2, PCO_2 and pH, but were of much lesser magnitude. Previous work (77) using a similar extracorporeal system reported no changes in systemic gas tensions and pH. However, flow through the extracorporeal lung in my experiments was approximately two-fold greater and represented approximately 15% of the cardiac output. In the cut nerve group these small changes in systemic gas tensions and pH were of no consequence because the peripheral chemoreceptors were denervated. In the intact nerve group these changes are unlikely to have affected my results or interpretation since the reflex vascular effects of increased P_aCO_2 on the peripheral chemoreceptors is considerably attenuated without a concomitant large decrease in pH (184) or ineffective when P_aO_2 is approximately 100 torr (57). Although pH did decrease, the change was of small magnitude and P_aO_2 was 94 ± 3 torr (Tables 1-6) during brain hypoxia and/or hypercapnia.

Intact Nerve Group

In all experiments in which the vagus and carotid sinus nerves were intact, head perfusion pressure decreased during constant flow perfusion. Hypoxia-hypercapnia caused a 38%, hypoxia a 31%, and hypercapnia a 30% decrease in head perfusion pressure. During constant head perfusion pressure experiments hypoxia caused a 66% increase in flow to the head. These responses can be attributed to the local vasodilator effect of hypoxia and hypercapnia (58,97).

All systemic and pulmonary hemodynamic parameters measured were unchanged from control during hypoxia. Similar results were obtained during hypercapnia and hypoxia-hypercapnia except that the addition of CO_2 to the perfusate caused a slowing of heart rate. This cardiac effect of perfusing the brain with hypercapnic blood has been previously reported (56) and was attributed to stimulation of vagal nuclei in the medulla leading to increased vagal tone to the heart. Stroke volume increased during hypercapnia and hypoxia-hypercapnia probably because of a slower heart rate. The latter effect would increase filling time resulting in increased end-diastolic volume. The tendency of both cardiac output and total peripheral resistance to increase contributed to an overall increase in mean aortic pressure during hypercapnia.

Cut Nerve Group (5 Minutes Brain Hypoxia)

As in the intact nerve group hypoxic, hypercapnic, and hypoxic-hypercapnic blood caused local dilation of vessels supplying the head resulting in decreased head perfusion pressure. The increase in left ventricular dP/dt, cardiac output, total peripheral resistance, and mean aortic pressure observed during brain hypoxia and hypoxia-hypercapnia are

consistent with other studies (62,68) that demonstrate the effect of brain hypoxia on the systemic vasculature. Although brain hypoxia has also been reported to increase heart rate (68), I did not observe this probably because control heart rates were high. While brain hypercapnia did not increase cardiac output, it increased dP/dt, total peripheral resistance, and mean aortic pressure, effects previously demonstrated in dogs (68) and more recently, in the monkey (157).

Total pulmonary vascular resistance was unaffected by any of the treatments despite increases in mean pulmonary artery and left atrial pressures. The net effect of these changes in pressure is to increase vascular transmural pressure, the passive effects of which would decrease PVR_T. Therefore, it is possible that some active vasoconstriction occurred and prevented a significant decrease in PVR_T.

These data do not support the hypothesis that brain hypoxia increases PVR_T (30,167) but are consistent with other investigations involving brain ischemia (96) or increased intracranial pressure (144, 155); conditions which presumably cause brain hypoxia and also do not elevate PVR_T (96,144,155).

Data from the cut nerve groups demonstrate that the major effect of brain hypoxia or hypoxia-hypercapnia on the pulmonary circulation is to increase pulmonary blood volume and secondarily increase microvascular hydrostatic pressure. The increase in central blood volume probably occurred as a result of increased left ventricular afterload as evidenced by an abrupt increase in mean aortic pressure. Under these conditions right ventricular cardiac output may transiently exceed left ventricular cardiac output causing a shift in blood volume from the systemic

vasculature to the pulmonary vasculature. Further evidence for this is the rise in mean pulmonary artery and left atrial pressures. It is possible that decreased left ventricular and pulmonary vascular compliance also contributed to increased mean pulmonary artery and left atrial pressures. Decreased vascular compliance may have also contributed to the increased pulmonary artery pulse pressure; though this was in part due to increased right ventricular stroke volume. Stellate ganglion stimulation (129) and brain ischemia (96) have been reported to decrease pulmonary vascular compliance resulting in an increased pulmonary artery pulse pressure without a change in PVR_T.

Differences Between Intact Nerve and Cut Nerve Groups

Differences in response to brain hypoxia and/or hypercapnia were obtained between the intact nerve and cut nerve groups. In the intact nerve group no changes were observed in dP/dt, total peripheral resistance, mean aortic pressure or pulmonary artery pulse pressure but in the cut nerve group these parameters increased. The vagus and carotid sinus nerves (i.e., intact nerve group) apparently buffered out the primary response observed in the cut nerve group. The primary response to brain hypoxia and/or hypercapnia is an increased sympathetic discharge to the cardiovascular system that results in increased ventricular contractility (67), heart rate and total peripheral resistance (68). The vagus and carotid sinus nerves increase their afferent nerve activity when the baroreceptors are stimulated by increased mean aortic pressure. Stimulation of cardiac stretch receptors also increases afferent vagal activity. Because these afferent impulses are inhibitory to medullary sympathetic

outflow, they are the likely explanation for the lack of responses in the intact nerve group compared to the cut nerve groups. Similar buffering effects on the cardiovascular system have been reported previously (62,67,184).

Perfusion of the brain with hypercapnic or hypoxic-hypercapnic blood decreased heart rate when the vagus nerves were intact. The likely explanation for this is that vagal tone to the heart increased during CO_2 stimulation of vagal nuclei in the medulla (56). This is further supported by the observation that after the vagus nerves were cut heart rate did not change during hypercapnia or hypoxia-hypercapnia.

The lower head perfusion pressures observed in the cut nerve group, despite higher blood flows to the head, probably occurred because in the dog cervical vagotomy eliminates sympathetic innervation to blood vessels supplying the head. This lack of sympathetic tone was also probably responsible for the smaller change in head perfusion pressure from control values during hypoxia, hypercapnia, and hypoxia-hypercapnia.

Brain Hypoxia and Pulmonary Edema

The hemodynamic results in the cut nerve group are consistent with those found in neurogenic pulmonary edema (albeit of lesser magnitude) which develops following a variety of brain disorders in the absence of primary cardiac and pulmonary disease (232). In this disorder massive sympathetic outflow occurs; a situation more analogous to the cut nerve than the intact nerve group of this investigation since in the latter sympathetic outflow was inhibited by the peripheral baroreceptors as discussed earlier.

The key factor in the development of neurogenic pulmonary edema appears to be a large increase in left ventricular alterload resulting in increased left atrial and pulmonary vascular pressures and volume (36-38,64,74,159,204). The increase in left ventricular afterload is caused by intense peripheral vasoconstriction and is mediated by alpha adrenergic receptors (204,232). Indeed, neurogenic pulmonary edema caused by chemically induced convulsions (16), chemical hypothalamic stimulation (248), blunt head trauma (15,36) and increased intracranial pressure (151) can be prevented by phenoxybenzamine (an alpha blocker). This has important clinical implications because in order to prevent a shift in blood volume from the systemic to the pulmonary circulation (and high microvascular pressure), alpha adrenergic blockade must be directed primarily with systemic arterial pressure in mind. It should also be kept in mind that there are two distinct phases to neurogenic pulmonary edema (232). First, a transient systemic hypertension and second, a return to normal vascular pressures accompanied by increased pulmonary microvascular permeability. The latter probably is induced by the transient capillary hypertension (196). Obviously for alpha blockade therapy to be effective it must be given prior to or during systemic hypertension to prevent a large shift in blood volume to the pulmonary circulation.

The increase in left atrial, mean pulmonary artery and aortic pressures during 5 min hypoxia (cut nerve group) suggest increased pulmonary blood volume. Indeed, central blood volume increased and although some of this may reflect increased left heart volume, it is likely that pulmonary blood volume increased as well and this certainly would

contribute to the increased pulmonary vascular pressures observed. In contrast, these increases in vascular pressures and central blood volume were not detected during 2 hours hypoxia. Although this might suggest that the effects of brain hypoxia on pulmonary hemodynamics is a transient phenomenon, I believe a more likely explanation is a progressive deterioration of my preparation as evidenced by falling total peripheral resistance and mean aortic pressure.

The lack of any change in lung extravascular thermal volume and postmortem lung water content is not surprising in view of the small hemodynamic changes elicited during brain hypoxia. The increase in plasma filtrate (i.e., lymph) caused by 1 to 2 mmHg increase in left atrial pressure would easily be removed by the lymphatics and therefore prevent any accumulation of extravascular lung water. In fact, Guyton and Lindsey (105) found that left atrial pressure had to increase to approximately 24 mmHg before lymphatics failed to drain the excess filtered fluid and thus prevent pulmonary edema. Although the results of this investigation could be interpreted to mean that brain hypoxia does not cause neurogenic pulmonary edema, I believe such a conclusion is inappropriate. In a clinical situation acute systemic hypoxia would cause direct and reflex (through stimulation of the peripheral chemoreceptors) stimulation of the brain as well as release of catecholamines from the adrenal glands. It is conceivable that these events, occurring in an unanesthetized and previously healthy individual, could lead to a dramatic increase in mean aortic pressure and secondarily cause large increases in left atrial and pulmonary vascular pressures. The latter being mediated by a massive shift in blood volume to the pulmonary

circulation causing capillary hypertension, and hence, neurogenic pulmonary edema. Indeed, a large increase in pulmonary blood volume is the likely explanation for development of pulmonary edema and alveolar hemorrhage during such clinical disorders as seizures (21,124), increased cerebrospinal fluid pressure (73), head trauma (79,212), cerebral hemorrhage (240), apoplexy and brain tumors (33).

With regard to the effects of anesthesia on the development of neurogenic pulmonary edema, Bean and Beckman (15) found that unanesthetized rats subjected to mechanical head injury developed severe pulmonary edema and alveolar hemorrhage. In contrast, rats pretreated with anesthetic agents (similar to those used in this investigation) prior to head trauma developed little or no pulmonary pathology presumably because excitability of the central nervous system was depressed. Thus it is not unreasonable to suggest that in the present investigation anesthesia may have attenuated the pulmonary hemodynamic effects of brain hypoxia.

Adult Respiratory Distress Syndrome

Recently Moss and Stein (167) and Brown (30) proposed a centrineurogenic etiology for the adult respiratory distress syndrome ("shock lung"). In their preparation venous blood (PO_2 35 torr) is pumped from the right atrium to a common carotid artery for two hours at a perfusion pressure that is 20 mmHg greater than mean aortic pressure thus ensuring hemodynamic isolation of the Circle of Willis. Moss and Stein (167) reported that the pulmonary lesions observed at postmortem are similar to those observed in the adult respiratory distress syndrome (i.e., congestion, edema, atelectasis and hemorrhage). They then repeated these

experiments following chronic unilateral pulmonary denervation. Based upon gross and histologic examination they found that the innervated lung developed lesions similar to the adult respiratory distress syndrome whereas the denervated contralateral lung was normal. Based on their work and a large body of circumstantial evidence (95,137,169,202,206,210-212,215,226-228,236,249) they hypothesized that brain hypoxia impairs oxidative metabolism in the hypothalamus which increases sympathetic outflow to the pulmonary postcapillary vessels leading to increased pulmonary vascular resistance and microvascular hydrostatic pressure, congestion, surfactant inactivation, atelectasis, edema, and hemorrhage. My findings support an increased microvascular hydrostatic pressure (volume mediated) during 5 min brain hypoxia but are not tenable with the hypothesis that this increase is secondary to increased postcapillary resistance because PVR_T, PVR_P, and PVR_V did not increase in either the intact nerve or cut nerve groups. I propose that brain hypoxia elevates microvascular hydrostatic pressure secondary to increased pulmonary blood volume and is therefore a form of neurogenic pulmonary edema.

Comparison of data between investigators is admittedly difficult when considerable differences exist between experimental preparations. However, I believe the pulmonary lesions reported by Moss and Stein (167) could also be explained by increased pulmonary blood volume. One of the intriguing aspects of Moss' work is that unilateral pulmonary denervation during brain hypoxia is protective. However, this should not be construed as prima-facie evidence that pulmonary nerves are responsible for the lesions observed in innervated lungs. Since the denervation procedure involved transection of all ipsilateral hilar lung tissue it is possible

that post-surgical fibrous tissue reduced the diameter of the reanastomosed pulmonary artery and veins. The former would increase upstream vascular resistance and preferentially direct more flow to the "innervated" lung. Furthermore, increased downstream (i.e., venous) resistance in the denervated lung would preferentially cause blood to "dam-up" in the "innervated" lung thus increasing microvascular hydrostatic pressure and possibly causing the pulmonary pathology reported by Moss and Stein (167).

Although the findings of this investigation during 5 min brain hypoxia are significant and the preparation was obviously viable, the findings during 2 hours hypoxia raise some questions about preparation viability inasmuch as it was difficult to keep the animals alive. There appeared to be a progressive deterioration of the cardiovascular system as evidenced by decreasing total peripheral resistance and mean aortic pressure despite intravenous fluids (to correct for fluid loss). This problem, however, is not unique to my preparation. I have had personal communication with 3 independent physiologists (Drs. M. Maron, B. Petersen, J. Reeves) who have used the experimental preparation described by Moss et al. (167,168). In all cases they were not able to maintain survival long enough to duplicate the studies of Moss and Stein (167). Crockard et al. (46) perfused the brain of monkeys using the Moss preparation and all animals died of brain edema approximately 95 minutes after the onset of hypoxemic perfusion. An interesting feature of their study was that the monkeys allowed to breathe spontaneously developed incidental pulmonary congestion and edema but those with positive pressure ventilation did not. This raises the possibility that much of the atelectasis and

systemic hypoxemia described by Moss and Stein (167) was exaggerated by the effects of spontaneous breathing.

II. Carotid Body Hypoxia and Hypercapnia

The second objective of this research was to evaluate the effects of carotid body hypoxia, hypercapnia, and hypoxia-hypercapnia on pulmonary hemodynamics. The data demonstrate that hypoxic and hypoxic-hypercapnic blood perfusing the carotid bodies can reflexly cause a small increase in PVR_T in vagotomized dogs. Increased PVR_T observed with hypoxia or hypoxia-hypercapnia was pre-large vein in origin [i.e., $(\overline{P_{PA}} - P_{PAW})/\dot{Q} = PVR_p$] and although precapillary vessels are the most likely sites of increased resistance, venules and small pulmonary veins cannot be ruled out because PVR_p includes the resistance of all vessels upstream from the first post-capillary collateral venous vessel. The increases in resistance must have resulted from active vasoconstriction because they cannot be explained by the passive effects of vascular transmural pressure. During hypoxia average prevenous vascular transmural pressure [i.e., $(\overline{P_{PA}} + P_{PAW}/2$] was unchanged from control (8.3 to 8.4 mmHg) despite decreased cardiac output and during hypoxia-hypercapnia it increased above control (8.5 to 9.2 mmHg) without a change in cardiac output. The passive effects of increased transmural pressure would act to increase vessel diameter and decrease PVR_T (82) and this is the likely explanation for a lesser increase in PVR_T during hypoxia-hypercapnia than during hypoxia.

Increased PVR_T during carotid body hypoxia and hypoxia-hypercapnia agree with the findings of other investigators (10,53,246). However,

Daly and Daly (53) reported that increased PVR_T during carotid body hypoxia in a non-vagotomized preparation only occurred consistently in the absence of bronchial flow. They concluded the primary effect of carotid body hypoxia on the pulmonary circulation was to increase PVR_T but that this effect was masked by hemodynamic events associated with the bronchial circulation. Despite an intact bronchial circulation in my preparation PVR_T increased during hypoxia and hypoxia-hypercapnia but only after bilateral cervical vagotomy. Thus, it appears that a vagotomized preparation (which eliminates vagal afferent inhibition of central sympathetic outflow) might be a more important factor in eliciting increased PVR_T during carotid body hypoxia and hypoxia-hypercapnia than is exclusion of the bronchial circulation.

I consider the presence of an intact bronchial circulation in my experiments to have negligible effects on the data or its interpretation for several reasons. First, Bruner and Schmidt (32) reported that approximately 1% of the cardiac output drains into the pulmonary veins from the bronchial circulation. This small amount of flow negligibly affects the pulmonary vascular resistance values. Second, if substantial transfer of blood from the bronchial arteries to the pulmonary veins occurred I would have expected left atrial and/or pulmonary artery wedge pressures to increase and these were unchanged. Third, results of more recent investigations involving changes in pulmonary vascular resistance (132) or vascular compliance (129) during electrical stimulation of stellate ganglion were not significantly different whether the bronchial circulation was intact or not. Thus, I believe an intact bronchial circulation in this study was of little or no consequence.

It is well known that changes in lung volume and active movement of respiratory muscles may passively influence pulmonary vascular resistance (53,82). In my preparation these factors were minimized by: 1) ventilating at constant volume, rate and end-expiratory pressure; 2) paralyzing the dogs respiratory muscles; 3) opening the thorax. It is unlikely local alveolar hypoxia caused the observed increases in pulmonary vascular resistance since P_aO_2 was unchanged from control values during carotid body stimulation (both > 100 torr).

Stern et al. (225) reported nicotine stimulation of aortic bodies reflexly increased PVR_T approximately 31% and with the carotid sinus nerves cut approximately 49%. Stern and Braun (224) reported nicotine stimulation of the carotid bodies caused no change in PVR_T either before or after vagotomy and concluded that carotid body stimulation does not reflexly increase PVR_T. This conclusion is at variance with those of others (10,53,246) and the results of the present study. While it is difficult to compare the responses to physiologic and pharmacologic stimulation it should be kept in mind that the pulmonary vascular response to severe hypoxic or hypoxic-hypercapnic carotid body stimulation was not of large magnitude. It may be that stimulation of the aortic bodies is more effective in elevating PVR_T than stimulation of the carotid bodies. Comroe (44) has emphasized this point with regard to the systemic circulation in the dog. Since sympathetic innervation to the pulmonary vasculature has been clearly demonstrated (117), with alpha receptors predominating (17), it is likely that the increased PVR_T and PVR_P observed before alpha blockade was due to activation of alpha adrenergic receptors either through stimulation of sympathetic nerves to

the pulmonary circulation or release of catecholamines from the adrenal glands (7). This conclusion is supported by the fact that following alpha blockade with phentolamine, carotid body hypoxia and hypoxia-hypercapnia failed to increase PVR_T and PVR_P. However, it must be recognized that baseline PVR_T was greater in the alpha-block compared to the non alpha-block control groups and this could have masked any further vasoconstriction during carotid body hypoxia and hypoxia-hypercapnia.

During hypoxic-hypercapnic stimulation of the carotid bodies an increased pulmonary artery pulse pressure was observed (without a significant change in stroke volume). This effect was also blocked by phentolamine suggesting that carotid body stimulation is capable of reflexly decreasing compliance of pulmonary vessels, an effect that has been previously reported (230).

Despite complete alpha blockade (as determined from blood pressure recordings) to an alpha agonist administered intravenously, an attenuated increase ($P < 0.05$) in total peripheral resistance still occurred during hypoxia-hypercapnia. This is consistent with the concept that alpha adrenergic antagonists are generally more effective in blocking responses to circulating alpha agonists than those resulting from adrenergic nerve activity (172).

The decreased cardiac output during carotid body hypoxia, under conditions of controlled ventilation and intact vagus nerves, has also been reported by other investigators (55,69). This investigation demonstrates a similar decrease following vagotomy and suggests that the decrease in cardiac output during carotid body hypoxia is due to withdrawal of sympathetic tone to the heart rather than increased vagal

outflow. Although hypothesizing sympathetic withdrawal from the heart while the vasculature receives increased sympathetic tone is difficult to reconcile teleologically, this has been previously reported. In vagotomized dogs, Downing et al. (69) found a general sympathetic withdrawal from the heart and increased sympathetic tone to the vasculature during carotid body stimulation with hypoxic blood. Their evidence for this was increased total peripheral resistance, decreased atrial and ventricular contractility, and decreased heart rate; the latter effect was abolished by the ganglionic blocker hexamethonium.

During hypercapnic and hypoxic-hypercapnic perfusion (before alpha blockade) of the carotid bodies, cardiac output was unchanged. Following alpha blockade cardiac output increased ($P < 0.05$) during hypoxia-hypercapnia and tended to increase during hypoxia ($P < 0.10$). These findings seem inconsistent with those reported during carotid body hypoxia before alpha blockade (i.e., cardiac output decreased), however, I believe the explanation lies in the fact that control mean aortic pressure during hypoxia was 110 mmHg (vagi intact) and 102 mmHg (vagi cut), during hypercapnia 79 mmHg, and during hypoxia-hypercapnia 74 mmHg. Following alpha blockade control mean aortic pressure was 50 mmHg during hypoxia and 54 mmHg during hypoxia-hypercapnia. It seems likely that baseline sympathetic outflow to the heart was greater in those groups with the lower carotid sinus perfusion pressures (set equal to mean aortic pressure). Downing et al. (69) reported that carotid body hypoxia in the presence of high carotid sinus pressure caused decreased ventricular contractility and increased vascular resistance but in the presence of low carotid sinus pressure both of these parameters increased.

Thus, it appears that the sympathetic activity to the heart during carotid body stimulation is somewhat dependent on the degree of afferent activity from the carotid sinus and perhaps aortic baroreceptors. During carotid body stimulation at high carotid sinus pressures, sympathetic withdrawal from the heart might occur but at low carotid sinus pressures cardiac sympathetic stimulation may occur. It seems likely that the interaction of these reflexes would occur within the central nervous system. Central interaction of baroreceptor and chemoreceptor reflexes has been previously suggested (118).

Adult Respiratory Distress Syndrome

In the experimental preparation of Moss and Stein (167), brain hypoxia is induced by pumping venous blood from the right atrium to one common carotid artery. This means that the ipsilateral carotid bodies (and probably the contralateral as well) are also being perfused with hypoxemic blood. The results of this investigation suggest that carotid body stimulation alone is not likely to produce the adult respiratory distress syndrome or neurogenic pulmonary edema because left atrial pressure was unaffected and only small increases in PVR_p and pulmonary vascular pressures were observed. Furthermore, although I did not determine water content in these lungs, no gross evidence of edema was present.

It seems likely, however, that carotid body hypoxia would contribute to the pulmonary lesions and hypoxemia obtained by Moss and Stein (167) for three reasons. First, carotid body hypoxia does reflexly increase PVR_p and this would increase fluid filtration from alveolar and/or extra-alveolar vessels. Second, peripheral chemoreceptor stimulation with hypoxemic blood (P_aO_2 < 40 torr) may attenuate the local alveolar hypoxia

response and cause increased right to left shunting of blood, thus worsening systemic hypoxemia (142). Third, a substantial increase in left ventricular afterload does occur during carotid body hypoxia and/or hypercapnia. The latter effect appears to be the precipitating factor that causes neurogenic pulmonary edema as discussed earlier.

Systemic hypoxemia would obviously stimulate the brain both directly and reflexly through primary stimulation of the aortic and carotid bodies. In this regard aortic body stimulation constricts pulmonary arteries and veins (224) and, compared to carotid body stimulation, is more effective in elevating mean aortic pressure (44). Thus the combined effects of acute hypoxic stimulation of the brain and peripheral chemoreceptors could result in pulmonary edema and alveolar hemorrhage similar to that observed in the adult respiratory distress syndrome.

III. Histamine and Adrenergic Receptors

The third objective of this research was to evaluate the effect of histamine on lung water and hemodynamics before and after adrenergic blockade and attempt to relate these findings to the adult respiratory distress syndrome as well as vascular permeability in general. Ninety minutes of histamine infusion (10 μg/kg/min) failed to increase lung extravascular thermal volume and postmortem extravascular lung water/extravascular dry weight ratio. These results are consistent with previous reports emphasizing the lack of ability of histamine to increase lung water (70,103). During simultaneous histamine and propranolol or phentolamine infusion, lung extravascular thermal volume was again unchanged as was the extravascular lung water/extravascular dry weight

ratio (compared to time control dogs receiving the same euthanasia solutions). Thus, it appears that the inability of histamine to markedly increase lung water in the dog is not due to enhanced beta (or alpha) receptor stimulation on the lung microvascular membrane. It should be emphasized that in the canine forelimb intravenous histamine with beta blockade causes massive edema (100). Indeed, in the systemic circulation beta agonists antagonize the action of histamine on both the large (100, 152,153) and small (194a) pore systems and prevent edema formation. Thus, if similar mechanisms were operative in the lung, I believe edema should have been detectable under the conditions of the present investigation. Therefore these results suggest a fundamental difference in response of the lung and systemic microvasculature to administration of histamine in the presence of beta blockade.

These results do not rule out the possibility that vascular permeability increased since I did not measure pulmonary lymph flow and protein concentration; however, if increased microvascular permeability had occurred it would have increased volume of distribution for Na^+. This would have increased central blood volume values and decreased lung extravascular thermal volume values (relative to control values), neither of which occurred with histamine alone or in the presence of alpha or beta blockade. Furthermore, lung extravascular thermal volume overestimated pulmonary extravascular tissue weight a similar amount (approximately 17%) in dogs receiving and not receiving histamine. Increased volume distribution for Na^+ would have caused a lesser overestimation of pulmonary extravascular tissue weight (or possibly an underestimation) in dogs receiving histamine. In addition, the fact that the slope for the

regression line and correlation coefficient between pulmonary extravascular tissue weight and lung extravascular thermal volume were not significantly different between time control dogs and dogs receiving histamine further suggests that histamine did not markedly alter the volume of distribution for Na^+ and therefore significant increases in microvascular permeability seem unlikely.

Investigations (89,188) using colloidal carbon as a tracer molecule suggest that histamine does not affect pulmonary microvascular permeability but does cause increased permeability in the bronchial microcirculation (especially in the venules) that is rapid and brief in duration. This observation is consistent with histamine's effect on forelimb microvasculature (102,108,152) and is not surprising since the bronchial circulation is part of the systemic circulation (188). Ultrastructurally Pietra et al. (188) observed that bronchial venules differed from corresponding vessels in the pulmonary microcirculation. Bronchial venules had a thicker endothelium, a greater number of pericytes, and a greater supply of cytoplasmic filaments within endothelial cells. Cytoplasmic filaments in endothelial cells of pulmonary veins were either absent or in very small amounts and they (188) concluded that the bronchial venular endothelium has a much greater potential for contraction than does the pulmonary venular endothelium. Therefore, it is possible that there was a transient increase in lung extravascular thermal volume because of peribronchial edema and that this effect disappeared prior to my first measurement (i.e., 30 minutes). However, since flow through the bronchial circulation is approximately 1% of the pulmonary circulation (32) any increase in total lung water would likely be of small magnitude

and in all likelihood undetectable by double-indicator dilution techniques. Furthermore, since there was no difference in postmortem lung water content between beta or alpha blocked and unblocked dogs any transient effect would have little physiological significance.

Hemodynamics

Histamine

The large decreases in mean aortic pressure, total peripheral resistance, cardiac index (at 30 min) and stroke volume caused by histamine are consistent with previously reported actions of histamine on the systemic circulation (107,193). Decreased mean aortic pressure was caused by both a fall in total peripheral resistance and cardiac index. The fall in total peripheral resistance is primarily due to arteriolar dilatation (107). Because histamine may cause venous constriction (107), pooling of blood occurs peripherally leading to decreased central venous pressure, venous return and cardiac index (193). Stroke volume decreases presumably because of decreased end-diastolic volume secondary to decreased filling pressure and time. The latter occurs because of the baroreceptor-induced tachycardia secondary to systemic hypotension as well as release of catecholamines from the adrenal glands (100,153, 217).

Although some of the increase in PVR_p caused by histamine can be attributed to passive mechanisms (due to decreased vascular transmural pressure), it is likely that some of the increase was also due to active vasoconstriction. Histamine is a potent postcapillary constrictor in the dog lung (28,92,93). Gilbert et al. (92) reported the predominant site of this heightened resistance to be distal to the first post-capillary

collateral venous vessel (i.e., pulmonary artery wedge position) but proximal to the large veins. Increased resistance at this site would tend to increase pulmonary artery wedge pressure; however, in the present investigation pulmonary artery wedge pressure decreased. It is unlikely increased venous compliance caused pulmonary artery wedge pressure to decrease since, if anything, compliance would have decreased because of increased sympathetic outflow secondary to systemic hypotension. Thus, in order to explain the fall in pulmonary artery wedge pressure a proportionately greater decrease in venous volume than an increased in venous resistance must have occurred. Indeed, central blood volume (which in this investigation represents the volume of blood between the right ventricle and proximal aorta) decreased and although it is likely that a portion of this reduction was secondary to decreased left heart volume, the change was too large not to involve a substantial reduction in pulmonary blood volume. Furthermore, a decrease in cardiac index (at 30 min) was not associated with an increase in conductivity mean transit time, which suggests a concomitant decrease in vascular cross-sectional area. Previous investigations using excised dog (28) and cat (61) lungs reported that histamine decreased post-capillary blood volume but was without effect on pre-capillary blood volume. Although decreased venous volume seems the most likely site for reduced pulmonary blood volume, the present data do not exclude a change in volume in the capillaries and pre-capillaries.

The decrease in central blood volume caused by histamine probably resulted from decreased left ventricular afterload (as evidenced by an abrupt decrease in mean aortic pressure) and decreased venous return

secondary to peripheral pooling of blood. Under these conditions left ventricular stroke volume may transiently exceed right ventricular stroke volume causing a shift in blood from the pulmonary vasculature to the systemic vasculature. When both ventricles regain equal stroke volumes central blood volume would remain in a steady state. Indeed, central blood volume did not change between 30 and 90 minutes of histamine.

Propranolol and Histamine

Infusion of the beta blocker, propranolol, decreased cardiac index and stroke volume, presumably because of decreased ventricular contractility. Mean aortic pressure was maintained by an increase in total peripheral resistance. Following beta blockade, PVR_p did not increase as might be expected when a vasodilating effect is removed (13,17,18). However, in the present investigation vascular transmural pressure increased, as evidenced by increased mean pulmonary artery and pulmonary artery wedge pressures. The passive effects of increased transmural pressure would act to increase vessel diameter and decrease PVR_p (22,82). Indeed, the fact that PVR_p did not decrease in the presence of rather large increases in transmural pressure is evidence that pulmonary vasoconstriction occurred following beta blockade.

Since central blood volume increased it is likely that the increase in pulmonary artery wedge pressure was volume mediated, albeit venous constriction and decreased venous compliance cannot be excluded as contributing factors. The negative inotropic effect of propranolol decreased stroke volume. The decrease in left ventricular stroke volume presumably exceeded the decrease in right ventricular stroke volume (at least transiently), thus shifting blood from the systemic vasculature to

the pulmonary vasculature and left heart (i.e., central blood volume). Increased central blood volume probably increased vascular cross-sectional area. This effect, as well as decreased cardiac output, caused a 62% increase in conductivity mean transit time.

The hemodynamic effects of histamine following beta blockade were qualitatively similar to those observed for histamine infusion except for heart rate and conductivity mean transit time. In the presence of beta blockade and histamine, heart rate did not change and conductivity mean transit time increased. This probably occurred because beta receptor blockade also eliminates any sympathetically mediated chronotropic response that would result secondary to systemic hypotension. Increased conductivity mean transit time was most likely due to a very low cardiac output. Cardiac index was significantly lower than during histamine infusion resulting also in a significantly lower mean aortic pressure. During histamine infusion cardiac index (60-90 min) returned to control values but during propranolol-histamine infusion this effect was abolished. Presumably catecholamines released from the adrenal gland (217) were responsible for maintaining not only a higher cardiac index but also increasing cardiac index (at 60 and 90 min) towards control values.

Histamine with beta blockade significantly potentiated ($P < 0.05$) the increase in PVR_p observed during histamine alone. Bergofsky (18) reported beta blockade with histamine more than doubled the pulmonary vasoconstrictor response to histamine, possibly by unmasking previously antagonized alpha receptors.

Phentolamine and Histamine

Alpha blockade with phentolamine decreased total peripheral resistance which decreased mean aortic pressure. Stroke volume decreased but cardiac index was maintained by an increased heart rate.

Following alpha blockade PVR_p did not decrease as is frequently reported (13,17,18). However, as with beta blockade, the passive effects of vascular transmural pressure apparently predominated. In contrast to increased vascular transmural pressure with beta blockade, alpha blockade decreased vascular transmural pressure. This should have increased PVR_p and since PVR_p did not change it suggests that alpha blockade caused pulmonary vasodilation. Pulmonary artery pulse pressure decreased and although decreased stroke volume was a contributing factor, it is possible that blockade of alpha receptors decreased vascular compliance.

Following alpha blockade mean aortic pressure, pulmonary artery wedge pressure, and central blood volume decreased in a manner similar to infusion of histamine only. The mechanism discussed for decreased central blood volume with histamine is also the likely explanation for decreased central blood volume with phentolamine. Decreased pulmonary vascular cross-sectional area probably occurred during alpha blockade because conductivity mean transit time decreased without a change in cardiac output.

Infusion of histamine following alpha blockade caused no further change in any hemodynamic parameter measured except for increased PVR_p, decreased mean aortic pressure and total peripheral resistance, and a gradual return of mean pulmonary artery pressure to control values. These results are consistent with the ability of histamine to cause

pulmonary vasoconstriction and peripheral vasodilation independent of alpha adrenergic receptors. However, this does not mean that alpha receptors are not utilized by histamine. Attenuation of histamine-induced increase in PVR_p by alpha blockade has been reported (18).

Lung Mechanics

Histamine, propranolol with histamine, and phentolamine with histamine increased airway opening pressure approximately 23%, 46%, and 21%, respectively. Since tidal volume and respiratory rate were held constant, this represents a decrease in dynamic compliance and can best be explained by airway constriction (241). These findings are consistent with previous reports that emphasize the ability of histamine to cause constriction of alveolar ducts and airways (42,63). Histamine with beta blockade significantly potentiated the decrease in dynamic compliance compared to the decrease observed with histamine or alpha blockade with histamine. Histamine induced release of catecholamines from the adrenal gland (217) presumably accounts for the lesser increase in airway opening pressure during histamine or histamine with alpha blockade. This is consistent with previous reports (42,63) that catecholamines released from the adrenal gland primarily affect beta adrenergic receptors (in airways) to antagonize the constricting effect of histamine.

Adult Respiratory Distress Syndrome

Histamine has been implicated as a possible mediator of the adult respiratory distress syndrome (19,247). In the present investigation, large doses of histamine failed to increase lung extravascular thermal volume and postmortem lung water and this response was unaffected by

alpha or beta blockade. Thus, it appears unlikely that histamine is an important contributing factor to the large increases in microvascular permeability and lung water that occur in the adult respiratory distress syndrome. However, histamine is a potent postcapillary constrictor (92, 93) in the lung and this would contribute to increased microvascular hydrostatic pressure, which in the presence of increased vascular permeability, could contribute substantially to development of pulmonary edema (84). On the other hand, the results of this investigation show that histamine decreases pulmonary artery wedge pressure by decreasing pulmonary blood volume. The effect of this would be to attenuate any increase in microvascular hydrostatic pressure brought about by venous constriction. Thus, histamine has considerable hemodynamic effects on the pulmonary circulation that include changes in vascular resistance, volume, blood flow, and probably vascular compliance. If the net effect of these changes is to increase microvascular hydrostatic pressure then histamine would obviously contribute to edema formation and in this way could play a role in mediating the adult respiratory distress syndrome.

In dogs of this investigation, histamine caused impairment of gas exchange as evidenced by decreased P_aO_2 and increased P_aCO_2 (at 90 min). This effect can best be explained by peripheral airway constriction resulting in greater ventilation-perfusion inequalities. Therefore, if endogenous release of histamine occurs in the adult respiratory distress syndrome (247), it would likely worsen the clinical malady by potentiating the hypoxemia and decreasing dynamic compliance. Thus the deleterious effects of histamine on lung mechanics and gas exchange may be a more important factor in mediating the adult respiratory distress syndrome than are histamines' effects on pulmonary hemodynamics.

SUMMARY AND CONCLUSIONS

Following ligation of collateral vessels (supplying blood to the brain) brain hypoxia, hypercapnia, and hypoxia-hypercapnia were induced by pumping arterial autologous blood through an extracorporeal lung to the external carotid arteries for 5 min or 2 hours. When the vagus and carotid sinus nerves were intact, hypoxia and hypoxia-hypercapnia caused no change in any pulmonary or systemic parameter measured or calculated. Hypercapnia increased mean aortic pressure and stroke volume and decreased heart rate. Following vagotomy and carotid sinus nerve section (which eliminated vagal and carotid sinus nerve afferent inhibition of central sympathetic outflow), 5 min hypoxia and hypoxia-hypercapnia increased cardiac output, dP/dt, total peripheral resistance, mean pulmonary artery, left atrial, pulmonary artery pulse, and mean aortic pressures. However, these effects were not maintained during 2 hours hypoxia. Central blood volume increased during 5 min hypoxia but pulmonary vascular resistance and lung extravascular thermal volume were unchanged during 5 min and 2 hours of brain hypoxia. Postmortem extravascular lung water to extravascular dry weight ratio was not altered following 5 min or 2 hours of brain hypoxia. I conclude that 5 min of brain hypoxia and/or hypercapnia does not increase pulmonary vascular resistance but may increase microvascular pressure secondary to increased pulmonary blood volume and in this way could cause pulmonary edema and alveolar hemorrhage similar to that observed in the adult

respiratory distress syndrome. Failure of these effects to be maintained for 2 hours may reflect deterioration of the preparation.

The carotid bodies were perfused bilaterally with hypoxic and/or hypercapnic blood by pumping arterial autologous blood through an extracorporeal lung to the common carotid arteries. Before vagotomy, carotid body hypoxia decreased cardiac output and increased total peripheral resistance but did not alter any pulmonary parameter measured or calculated. After vagotomy, carotid body hypoxia decreased cardiac output while pulmonary vascular resistance, mean aortic pressure and total peripheral resistance increased. During hypoxia-hypercapnia mean pulmonary artery, pulmonary artery pulse, and mean aortic pressures increased as did pulmonary vascular and total peripheral resistances. Hypercapnia increased mean aortic pressure and total peripheral resistance but did not change pulmonary vascular resistance. Following alpha blockade with phentolamine pulmonary vascular resistance failed to increase during carotid body hypoxia or hypoxia-hypercapnia. I conclude that carotid body hypoxia and hypoxia-hypercapnia reflexly increase pulmonary vascular resistance and left ventricular afterload, that these effects are mediated by alpha adrenergic receptors, and that carotid body stimulation could potentiate the effects of brain hypoxia on pulmonary hemodynamics and contribute to increased lung water.

The effects of 90 min intravenous histamine with and without alpha (phentolamine) or beta (propranolol) receptor blockade on lung water and hemodynamics were also studied. Histamine with and without alpha blockade decreased central blood volume, pulmonary artery wedge, and mean aortic pressures; pulmonary vascular resistance increased while lung

extravascular thermal volume was unchanged. Histamine with propranolol decreased mean aortic pressure, cardiac index, and central blood volume. Pulmonary vascular resistance increased and lung extravascular thermal volume was unchanged. In all experiments postmortem extravascular lung water to extravascular dry weight ratio was unchanged from control values. I conclude that histamine has little or no effect on lung microvascular permeability, does not increase lung water, and that these responses are not modified by reflex beta or alpha receptor stimulation on the microvascular membrane. Thus, histamine cannot be considered a likely mediator of the massive increase in lung water and permeability that occur in the adult respiratory distress syndrome.

RECOMMENDATIONS

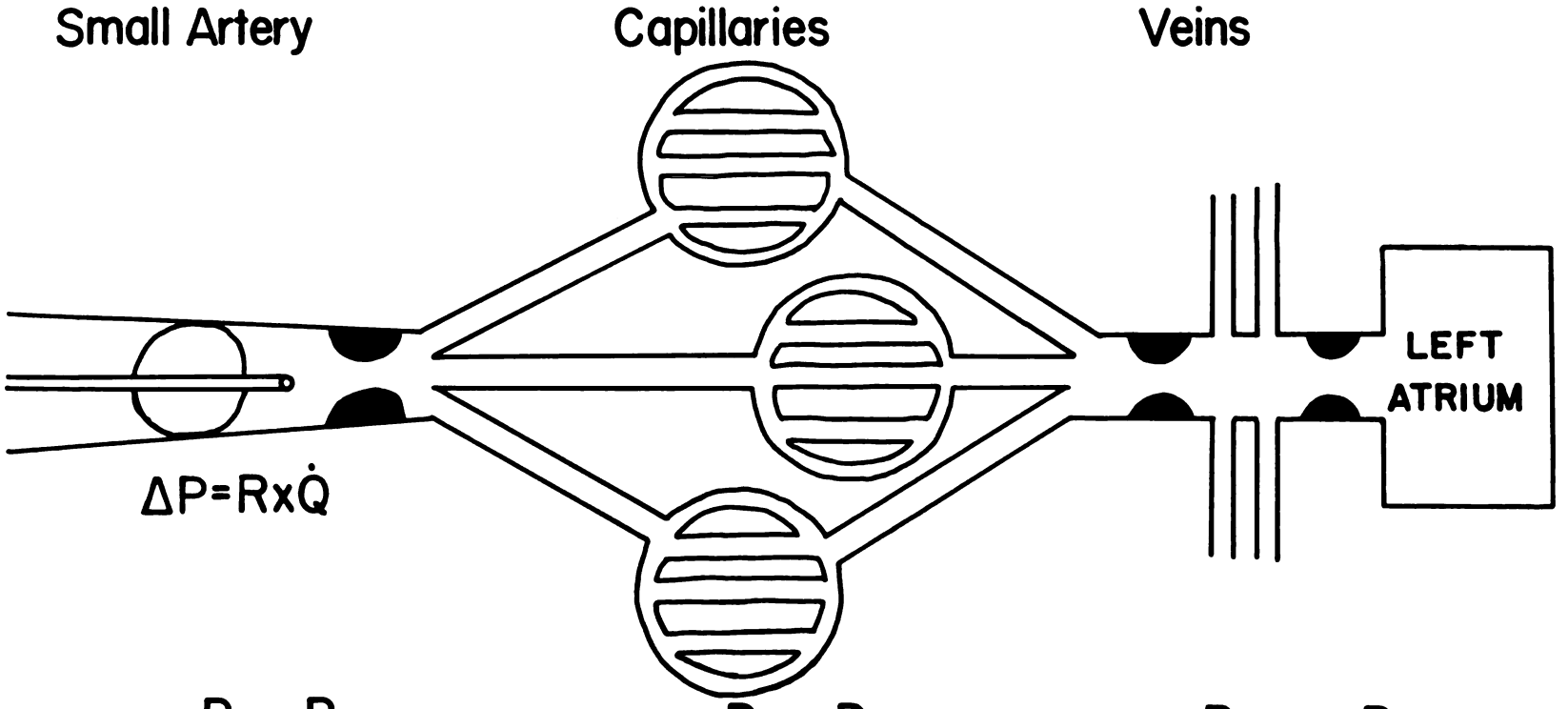
A major limitation of these studies is that the dog requires extensive surgical intervention to eliminate collateral blood flow to the brain, thus making the preparation a difficult one to study and maintain. A further complicating factor is that these experiments must be done in open-chested animals. In contrast, surgical manipulation required to induce local brain hypoxia in sheep should be minimal because practically the entire brain is supplied by blood through the external carotid arteries. The internal carotid artery is absent in the adult and the vertebral artery supplies only the cervical spinal cord to the level of the obex (11a). In addition, utilizing sheep would make a thoracotomy unnecessary since vessels originating off the subclavian artery do not contribute to cerebral blood flow. Even more attractive is the possibility that local brain hypoxia could be induced in the conscious animal. Another advantage of using sheep is that the efferent duct of the caudal mediastinal node can be easily cannulated (223a) thus allowing for collection of lung lymph during brain hypoxia. Finally, sheep pulmonary vessels are considered to be more responsive (compared to the dog) to nervous and humoral stimuli (111). Therefore, I believe utilizing sheep as a model to study the effects of brain hypoxia on pulmonary hemodynamics and lung water would be more appropriate in future investigations. If a viable and stable brain hypoxia model could

be developed, it would be extremely useful in further elucidating central control mechanisms on pulmonary hemodynamics as well as evaluation of various therapeutic interventions.

APPENDIX

Figure A1. Diagram showing relationship of the pulmonary artery wedge position to upstream (e.g., small artery) and downstream (e.g., left atrium) locations. When flow through a small pulmonary artery is stopped, as by a wedged catheter, pressure equilibration occurs between the catheter tip and the first collateral vessel which in this diagram is depicted after the capillary bed but before the large veins. Thus pulmonary artery wedge pressure is a downstream pressure at the site of the first postcapillary collateral venous vessel. ΔP, change in pressure; R, resistance; $\dot{Q}$, flow; $P_{\overline{PA}}$, mean pulmonary artery pressure; P_{PAW}, pulmonary artery wedge pressure; P_{LA}, left atrial pressure, PVR_T total pulmonary vascular resistance; PVR_p, pre-large vein pulmonary vascular resistance; PVR_V, large vein pulmonary vascular resistance.

resistance; PVR_p, pre-large vein pulmonary vascular resistance; PVR_v, large vein pulmonary vascular resistance.



$$PVR_T = \frac{P_{\overline{PA}} - P_{LA}}{\dot{Q}} \qquad PVR_P = \frac{P_{\overline{PA}} - P_{PAW}}{\dot{Q}} \qquad PVR_V = \frac{P_{PAW} - P_{LA}}{\dot{Q}}$$

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LIST OF REFERENCES

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