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By

Stephen Wilson Ely

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ABSTRACT

FACTORS INVOLVED IN THE LOCAL AND REMOTE CONTROL
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Characterization of the factors which contribute to the regulation of blood flow through the right coronary vascular bed has not been adequately accomplished. This vascular system is of great importance in that the right coronary artery is the dominant coronary vessel in 50% of the human population. Therefore, a better understanding of the control of this vascular bed during both physiological and pathophysiological conditions is needed.

The purpose of this study is to evaluate several aspects of the local and remote control of the right coronary circulation. These studies were carried out in the anesthetized, open chest dog during constant flow and constant pressure perfusion of the right coronary vascular bed. In some experiments, an isolated donor lung was interposed in the perfusion line in order to selectively alter the coronary arterial blood gas tensions. Finally, experiments were performed on the conscious animal, chronically instrumented for the determination of right coronary hemodynamics in order to evaluate experimental interventions without the presence of anesthesia.

Stephen Wilson Ely

These studies were designed to evaluate the role of autoregulation and prostaglandins in the control of blood flow through this circulation. In addition, the effects of local changes in oxygen and carbon dioxide (pH) tensions, infused catecholamines and sympathetic (baroreflex) nerve stimulation were also determined. Selective adrenergic receptor blocking agent were also employed to define the mechanism of some of the responses seen.

The results indicate that the response of this vascular bed to adrenergic stimulation is similar to the left coronary vascular system in that the net effect is dictated by the competition between alpha receptor vasoconstriction and beta receptor (metabolic) vasodilation. However, since the right ventricle performs one sixth the work of the left ventricle, the metabolic influences attributable to myocardial oxygen consumption are less. Therefore, the response to sympathetic nerve stimulation is dominated by alpha mediated coronary vasoconstriction. The degree of coronary vasoconstriction is apparently enhanced when flow to this bed is decreased. Intracoronary infusion of NE produces a substantial coronary vasodilation which can be converted to a vasoconstriction in the presence of the beta receptor blocking agents propranolol or practolol. This suggests that infused norepinephrine produces a substantially greater stimulation of the myocardium, hence the metabolic effects dominate and a fall in coronary resistance is observed. The same basic effect was seen with intracoronary bolus injections of NE in the conscious dog. However, during right coronary ischemia, NE produced a substantial vasoconstriction. It was also

shown that local hypoxia or hypercapnia produces coronary vasodilation, while local or systemic hypocapnia produces substantial coronary vasoconstriction. The response of this vascular bed to sympathetic stimulation or norepinephrine infusion was attenuated when the bed was perfused with hypoxic or hypercapnic blood. This suggests that certain changes in local blood gas tensions may alter the response of this vascular bed to adrenergic stimulation.

The prostaglandins seem to play a minor role in the regulation of blood flow in this vascular bed. While the reactive dilation seen with 20 sec. interruptions of flow was slightly but significantly attenuated by the inhibition of prostaglandin synthesis with indomethacin, only the reactive hyperemia response to brief (3 second) occlusions was affected by indomethacin in the conscious dog. The coronary responses to sympathetic stimulation of norepinephrine infusion or systemic hypocapnia was unaffected by indomethacin, suggesting that prostaglandins do not play a role in the response of the right coronary circulation to these stimuli.

It was also determined in these studies that this circulation autoregulates to a slight extent during constant flow perfusion. However, with constant pressure perfusion or under natural flow conditions (in the conscious animal) the bed exhibits a fair degree of autoregulation, although not to the same extent as that seen in the left coronary vascular bed.

In conclusion, these studies suggest that the right coronary circulation differs in some important respects from that of the left coronary bed. Metabolic influences do not appear to play as large a

role in determining right coronary blood flow. In some instances neural (remote) influences may provide the dominant mechanism of regulating right coronary vascular resistance.

Dedication

To my good friend, Booty.

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Introduction

The coronary circulation supplies the myocardium with nutrients and removes metabolites in order to maintain cardiac function. This system must rapidly adjust to meet the ever changing demands of the heart. The heart extracts a very large fraction of the oxygen supplied by the coronary circulation. As a result, the coronary venous blood contains little reserve oxygen. The flow of metabolism ratio is the lowest of any organ bed in the body. The control of blood flow to the heart is under extrinsic neural influences, is affected by circulating vasoactive substances, and exhibits a great degree of local regulation. Three types of local control phenomena have been observed for the coronary circulation: autoregulation (the ability to maintain a near constant blood flow in the face of large variations in perfusion pressure), active hyperemia (the increase in blood flow that occurs in response to an increase in metabolic activity), and reactive hyperemia (the transient increase in blood flow above the control level following an interval of arterial occlusion).

Several theories have evolved which attempt to explain the mechanism of these local regulatory phenomena. Currently, the theory which has the greatest support is the metabolic theory, as described by Berne (1964) as well as Haddy and Scott (1968,1974,1975). This theory

proposes that changes in blood flow or tissue metabolism alter the interstitial concentration of vasoactive chemicals which cause subsequent changes in vascular smooth muscle tone and hence vascular resistance. As an example, an increase in the metabolic rate of a tissue would increase the interstitial concentration of vasodilator metabolites eliciting a metabolically induced vasodilation (active hyperemia). Similarly, if blood flow is suddenly increased to a vascular bed by an increase in perfusion pressure, a washout of these vasodilator substances would occur, thereby lowering the interstitial concentration. This would result in an increase in vascular smooth muscle tone and hence resistance (autoregulation). On the other hand, occlusion of the arterial inflow would result in a build-up of the interstitial concentration of vasodilator metabolites such that upon release of the occlusion, vascular resistance would fall below control and a transient hyperemia would occur. Resistance would gradually return to control as the interstitial metabolites are removed by the elevated flow (reactive hyperemia).

A second explanation which has been proposed to explain these local control phenomena is the myogenic hypothesis. This theory is based on the fact that vascular smooth muscle responds to stretch or increased tension with contraction, and responds to a reduction of stretch or decreased tension with relaxation. Thus, factors which alter transmural pressure across a vessel wall could elicit active changes in blood vessel caliber (Bayliss, 1902; Folkow, 1964; Johnson, 1977). It is therefore postulated that the myogenic response plays a role in autoregulation, active and reactive hyperemia since such

phenomena involve changes in transmural pressure (Folkow, 1949; Baez, 1968; Burton and Johnson, 1972).

A third hypothesis is the tissue pressure hypothesis which suggests that changes in tissue pressure cause compression of capillaries and venules thereby altering vascular resistance (Beer and Rodbard, 1970; Rodbard, 1966; Rodbard et al., 1971). A decrease in tissue pressure would therefore cause capillary and venule diameters to increase, thus decreasing vascular resistance. In support of this theory, it was thought that contraction of a muscle caused a translocation of fluid volume from the extravascular compartment to the intravascular compartment, thereby decreasing tissue pressure and decreasing vascular resistance. However, it has been demonstrated that tissue volume increases during skeletal muscle contraction thereby contradicting the application of this hypothesis (Haddy, Scott, and Grega, 1976). An elevation of perfusion pressure is thought to cause a net transfer of fluid to the extravascular space, causing an increased tissue pressure and compression of capillaries and veins. This would increase vascular resistance and limit the increase in blood flow, thereby producing an autoregulatory response (Beer and Rodbard, 1970; Rodbard, 1966). However, other investigators have shown that resistance changes in response to an increased perfusion pressure or blood flow occurs at the pre-capillary resistance vessels in skeletal muscle (Haddy and Scott, 1964; Hanson and Johnson, 1962; Mellander and Johansson, 1968; Nagle et al., 1968). Furthermore, Driscoll et al. (1964) showed that abrupt and sustained increases in left coronary perfusion pressure which elicited autoregulatory flow responses were associated with elevations

in intramyocardial (tissue) pressure. Following maximal pharmacologically induced coronary vasodilation, the autoregulatory response to increased perfusion pressure was abolished, yet the increment in intramyocardial pressure due to increased perfusion pressure was unchanged. Therefore, the tissue pressure hypothesis is not currently considered a plausible mechanism for local regulatory phenomena.

As a result of the balance between extrinsic neural control, circulating vasoactive agents, and local regulatory phenomena, blood flow to the heart is exquisitely regulated under normal conditions in order to match myocardial oxygen delivery (coronary blood flow) to myocardial oxygen demand (oxygen consumption).

The literature regarding the regulation of coronary blood flow (CBF) is extensive; however, most of the published observations were derived from experiments performed on the left coronary vascular bed. There is little experimental data available concerning the regulation of blood flow in the right coronary vascular bed. This survey will center on the important factors contributing to the regulation of CBF under both normal and pathophysiological conditions. The literature discussed will pertain to studies performed in the left coronary bed unless otherwise indicated. The limited data for the right coronary bed will also be presented.

Coronary Arterial Anatomy

There are two coronary arteries, the right and left, which take their origin from the right anterior and left anterior aortic sinuses of

Valsalva, respectively. The left coronary artery (c.a.) begins as the left main c.a., coursing anteriorly and to the left in the atrioventricular groove between the pulmonary artery and left atrial appendage. This portion of the left c.a. is 1 to 1.5 cm long in man and 2 to 4 mm long in the dog. The left main c.a. then bifurcates to form the left anterior descending (LAD) and the left circumflex (CRFX) coronary arteries. The LAD follows the anterior interventricular sulcus toward the apex. The CRFX follows the A-V groove to the left, passing under the left atrial appendage and terminating on the posterior aspect of the heart. The LAD supplies the interventricular septum via small septal perforating arteries, the anterior portion of the left ventricular wall, apex, and a portion of the right ventricular free wall adjacent to the interventricular septum. The CRFX supplies the left atrium, posterior and lateral walls of the left ventricle, and in dogs sends a branch to supply the A-V node and bundle of His. The right coronary artery passes anteriorly behind the pulmonary artery and follows the A-V groove to the right margin of the heart and passes beneath the right atrial appendage. In dogs this vessel terminates as the marginal branch, supplying most of the right ventricular free wall and right atrial tissue, including the S-A node. In pig and man, the right c.a. reaches the posterior aspect of the heart to become the posterior descending c.a., supplying the posterior wall of the left ventricle and giving off a branch which supplies the A-V node.

In the dog, the left coronary artery is dominant, supplying 85% of the myocardium. Left dominance in man is present only 20% of the time. Pigs are generally right coronary dominant, where as man has this

pattern 50% of the time. In man, 30% have equal distribution between right and left coronary arteries (Gregg, 1963). Anastomotic communication between coronary arteries (intercoronary collaterals) are usually well developed in the dog between the CRFX and LAD. While the LAD may supply a portion of the right ventricle in the dog, there are few collaterals between the LAD and right coronary artery (Gregg, 1960; Murray et al., 1978). In the pig, few if any collaterals can be demonstrated between any of the coronary arteries (Schaper, 1971). In man, the existence of intercoronary collaterals is variable; however, in normal human hearts relatively few collaterals can be demonstrated (Fulton, 1965).

Coronary Vascular Resistance

According to Poiseuille's law, the ratio of the pressure drop or pressure gradient across a vascular bed to the rate of flow is a function of the factors serving to resist flow; namely, viscosity (v), vessel length (l) and radius (r). Resistance to flow as derived from Poiseuille's law is directly proportional to viscosity and vessel length and inversely proportional to the radius of the vessel to the fourth power,

$$R = \frac{8\ v\ l}{\pi\ r^4}$$

The law applies to a system in which there is laminar flow of a viscous homogenous fluid through rigid tubes. Therefore, Poiseuille's law cannot be quantitatively applied to the cardiovascular system since 1) blood vessels are not rigid but will stretch in response to an

increased pressure which is seen during systole, 2) whole blood is not a homogenous fluid, and 3) blood is not truly viscous. While Poiseuille's law is not entirely applicable to the cardiovascular system, it certainly can be applied in a qualitative sense. In a strict hemodynamic sense, v, l and r are the factors which determine resistance to flow. However, in the normal animal, coronary vessel length is considered to be constant, as is blood viscosity. Therefore, these factors are not considered important determinants of coronary vascular resistance. Since resistance increases inversely to the fourth power of the radius, this aspect of vessel geometry is of paramount importance in the determination of vascular resistance. This is illustrated by the fact that a one-fold increase in vessel radius results in a sixteen-fold decrease in vascular resistance. As will be discussed in the following pages, many factors both active and passive may be involved simultaneously in the net determination of vessel radius and consequently coronary vascular resistance.

Regulation of Coronary Blood Flow

I. Physical Factors

Pressure-flow Relationships

The pressure gradient (aortic-right atrial pressure) across the coronary bed provides the driving force for blood flow. This force, although essential for blood flow, may not be of primary importance in determining CBF due to the reported ability of the coronary bed to autoregulate. Cross *et al.* (1961) reported the relationship between left

coronary perfusion pressure and blood flow in the dog heart to be linear and concluded from their analysis of correlation coefficients that coronary perfusion is the only factor which determines CBF. This group determined the coronary pressure gradient on the basis of the difference between aortic and intraventricular pressure rather than right atrial pressure. This has been shown to be an unreliable method of determining the coronary pressure gradient since intramyocardial pressure varies during the course of the cardiac cycle (Gregg and Eckstein, 1941). Eckel et al. (1949) first showed that in a beating heart of an open-chest dog with the left coronary artery perfused at constant pressure, sudden increments in perfusion pressure resulted in immediate increases in CBF which returned toward normal even though perfusion pressure remained elevated. Fishback and collegues (1959) reported that coronary resistance increased over the range of 60 to 130 mmHg during constant pressure perfusion of the dog heart. Scott et al. (1960) demonstrated that resistance decreased as flow was raised from 25 to 75 ml/min, and then increased, decreased or remained constant over the range of 75 to 220 ml/min in fibrillating and beating (non-working) dog hearts in which both right and left coronary arteries were perfused through the aortic root. Subsequent studies by Brandfonbrener (1969) and Driscol (1964) demonstrated that the pressure-flow relationships in the left coronary bed is curvilinear with a convexity toward the flow axis indicating that perfusion pressure increases out of proportion to flow. Therefore, the majority of studies support the concept that the left coronary vascular bed at least is capable of autoregulation.

Extravascular Compression

The heart contracts and relaxes from one cardiac cycle to the next, and in doing so causes a cyclic compression of the coronary vessels, thus contributing to the resistance of this vascular bed (Gregg, 1963). The greatest degree of compression on the coronary vessels occurs during ventricular systole. Intramyocardial pressure is responsible for vessel compression, and is primarily determined by interventricular pressure (Kirk and Honig, 1964). As a result, the vessels supplying the left ventricle are affected more by extravascular compression than the vessels supplying the right ventricle (Rubio and Berne, 1975). Phasic flow tracings from the left coronary artery demonstrate that at the onset of isovolumetric contraction, left CBF decreases abruptly to the point where zero flow or even back flow may occur (Gregg and Fisher, 1963; Folkow, 1971). As left ventricular ejection develops, aortic pressure increases and CBF increases to a systolic maximum shortly before aortic pressure peaks, then slightly declines to the end of systole. At the onset of isovolumetric relaxation, CBF suddenly increases to its peak value and then gradually declines as aortic pressure declines throughout diastole. Therefore, the largest fraction of total left CBF occurs during ventricular diastole. It is during this period of the cardiac cycle (diastole) that the passive changes in vessel caliber offered by extravascular compression is at its nadir. The resistance values calculated from the ratio of diastolic pressure to diastolic flow most accurately reflect the vasomotor state of the coronary vasculature (Rubio and Berne, 1975). The throttling effect of extravascular compression on CBF can be

demonstrated by suddenly producing ventricular asystole by vagal stimulation. This results in a 50% increase in CBF above the control flow, and the extent of this increment in CBF is believed to be representative of the magnitude of the mechanical compressive factors which impede CBF (Sabiston and Gregg, 1957; Berne, 1974). Such an impediment of flow increases with elevated heart rate due to a greater time spent in systole. Lewis et al. (1961) have shown that the contribution of systolic contraction to overall coronary vascular resistance is little altered following the administration of isoproterenol, norepinephrine or epinephrine when the chronotropic effect of these agents are prevented. This is unusual since it is generally accepted that positive inotropic agents increase tension development and intramyocardial pressure.

In the right coronary bed, an analysis of phasic flow shows that flow follows the aortic pressure tracing, owing to the fact that coronary artery pressure far exceeds the intramyocardial tension produced by right ventricular contraction (Folkow, 1971). As a result, systolic flow in the right coronary artery exceeds diastolic flow, and the flow pattern follows the contour of the coronary or aortic pressure curve (Gregg, 1937). Therefore, extravascular compression contributes little to passive changes in right coronary vessel caliber in the normal heart. However, Brooks et al. (1971) have shown that when right ventricular systolic pressure rises above normal levels, right CBF is impeded by systolic compression.

Vascular Waterfall Phenomenon

As previously pointed out, during ventricular systole, blood flow in the left coronary artery decreases, stops or in some cases reverses direction. The mechanism by which this occurs has not been completely delineated. One possible explanation is that during systole, dimensional changes in the ventricle occur which could produce pinching or kinking of the myocardial resistance vessels, thereby limiting coronary flow. Such dimensional changes have been shown to have only a minimal effect on the increases in resistance seen during systole (Downey, Downey, Kirk, 1974). A second hypothesis that has been put forth to explain this is the vascular waterfall phenomenon. An understanding of this phenomenon is gained by using the concept of the Starling resistor. The Starling resistor employs a thin walled collapsible tube traversing a chamber in which pressure surrounding the tube can be set at any desired level as a means of controlling resistance (Knowlton and Starling, 1912). In a study which focused on flow through collapsible tubes, Holt (1941) found that lowering the outflow pressure of the tube did not significantly change flow if the outflow pressure was less than the external pressure surrounding the collapsible segment of the tube. This concept was later applied by Permutt et al. (1962) to the regulation of blood flow through the pulmonary vascular bed. Under conditions where the downstream pressure is less than the external pressure surrounding the collapsible tube, the pressure gradient for flow is the difference between the upstream pressure or inflow pressure and the external pressure according to the waterfall theory. Therefore, downstream or outflow pressure may be raised or lowered and have no effect

on flow as long as the outflow pressure remains below external pressure.

Such a mechanism could play a role in the production of the unique phasic flow pattern seen in the left coronary artery throughout a cardiac cycle. In a recent study by Downey and Kirk (1975), the pressure-flow relationships of the maximally dilated (adenosine infusion) left coronary vascular bed were determined for the beating and arrested heart. A linear pressure-flow relationship was observed over the range of 20 to 200 mm Hg when tissue pressure was minimal (arrested state). In the beating heart, the pressure-flow curve was parallel to that of the arrested state but was shifted to the right indicating a higher perfusion pressure was needed to deliver the same amount of flow. A mathematical model, also developed in this report, predicted that if the pressure-flow relationships for the arrested and beating hearts were linear and parallel, the vascular waterfall was the only mechanism contributing to the systolic inhibition of coronary blood flow. If factors other than the vascular waterfall were acting to inhibit coronary flow, the two lines would be linear but not parallel.

The vascular waterfall undoubtedly has very little effect in the determination of right coronary blood flow in normal hearts. As previously mentioned, the phasic flow pattern follows that of the aortic pressure curve with the greatest flow occurring during systole. It is also likely that intraluminal coronary pressure at any point along the vascular circuit is equal to if not greater than the intramyocardial pressure generated during right ventricular contraction, although the

measurement of this pressure has not been reported. In a recent report, Bellamy and Lowensohn (1979) demonstrated that there was little measurable difference between the pressure-flow relationships obtained during systole (systolic pressure vs. systolic flow) and diastole (diastolic pressure vs. diastolic flow). The only condition in which a significant waterfall effect was seen was when right ventricular pressures (and muscle mass) were increased in dogs with congenital pulmonic stenosis. In such animals, the diastolic and systolic pressure-flow curves diverged considerably, indicating a significant inhibition of right coronary blood flow during systole.

It therefore appears that the vascular waterfall phenomenon may play a role in the limitation of left coronary blood flow during systole, but plays no role in the normal situation in the determination of blood flow in the right coronary artery.

Transmural Distribution of Blood Flow

Kirk and Honig (1964) measured intramyocardial pressure by using a 26 gauge curved needle with a 2 mm gap in the midsection (where the wall of the needle was filed away) and inserted it into the myocardium such that the open tip on the end of the needle emerged from the epicardial surface. The opening in the tissue created by inserting the needle forms a collapsible segment connecting the intact portions of the needle. Fluid is forced through the needle from a pressurized reservoir. Therefore, fluid flow should cease when the external pressure on the collapsible segment exceeds the distending pressure. By varying the pressure driving the fluid through the needle, a measure of

intramyocardial pressure could be obtained. This measurement was also accomplished with the use of catheters with pressure sensitive tips. They reported that subepicardial pressure is zero and increases linearly across the myocardial wall, with the greatest pressures developed in the subendocardium. Subendocardial pressure was found to be equal to or greater than interventricular pressure during both systole and diastole. Buckberg et al. (1972,1973) have demonstrated that blood flow is evenly distributed across the myocardial wall even though intramyocardial pressure may be different in each of the muscle layers. This is possible if diastolic resistance is relatively less in the subendocardium compared to subepicardium. Therefore, subendocardial layers will receive a greater amount of blood flow during diastole than subepicardial layers, with the next result over the period of a minute being equal distribution of blood flow between subendocardium and subepicardium (Moir, 1972).

Since the subendocardial vessels have relatively less vascular tone and are therefore more vasodilated than subepicardium, the degree of additional vasodilation obtainable in response to increased myocardial oxygen consumption, or decreased CBF as a result of decreased coronary perfusion pressure or stenosis, is limited (Rubio and Berne, 1974; Neill et al., 1975). In recent studies by Neill et al. (1975) and Griggs et al. (1972) in which CBF was decreased by coronary artery stenosis, the subendocardial layers became relatively more ischemic compared to subepicardial layers, and anerobic metabolism was found to increase in the subendocardial layers. These data would suggest that

the subendocardium is more susceptible to damage induced by hypoxic or ischemic conditions than is the subepicardium.

II. Neuro-humoral Factors

Coronary Adrenergic Receptors

It has been difficult to elucidate the direct effects of sympathetic nerve stimulation and subsequent norepinephrine release on the coronary vascular bed, since nerve stimulation results in a variety of other responses which produce secondary effects on the coronary bed, such as increased heart rate, contractility, extravascular compression and myocardial oxygen consumption (Berne, 1974; Berne, 1964). However, the direct effects of norepinephrine on coronary arteries have been demonstrated in experiments utilizing isolated coronary arterial strips, which removes the vessels from the mechanical and metabolic influence of the myocardium. Zuberbuhler and Bohr (1965) utilized this technique in demonstrating that norepinephrine (which has primarily alpha receptor activity with some beta receptor activity) causes relaxation of small (400 μ) left coronary vessels from dogs. Following administration of a beta receptor blocking agent, the relaxation in response to norepinephrine (NE) is blocked and constriction of the strips occurs. In large coronary artery strips, both NE and epinephrine (EPI) cause constriction, a response which can be blocked by the alpha receptor blocking agent dibenzyline. Isoproterenol (a beta agonist) causes relaxation of large coronary artery strips. From this study it appears that left coronary artery strips contain both alpha-vasoconstrictor receptors and beta-vasodilator receptors with large coronary arteries containing more

alpha than beta receptors and vice versa for small coronary arteries. Other experimental studies have demonstrated the presence of alpha-vasoconstrictor and beta-vasodilator receptors in man and pig as well (Anderson et al., 1972; Bayer et al., 1974). Population densities of adrenergic receptors may differ from one specific portion of the vasculature to another, and therefore the response of a particular agonist may also differ in different vascular segments. This concept is supported by the work of Malindzak et al. (1978) in which left coronary end-diastolic resistances were determined for the large and small coronary arteries in intact, anesthetized open chest dogs in response to NE, EPI and stellate ganglion (sympathetic) stimulation. This study demonstrated that large coronary artery end-diastolic resistance was increased 190, 195, and 130% by NE, EPI and stellate stimulation, respectively. Small artery resistance was decreased by 53, 49, and 60%, respectively. The increase in large artery resistance was blocked by phenoxybenzamine (an alpha blocker). Following propranolol administration (beta blockade) small artery resistance increased by 170, 180 and 125% in response to NE, EPI and nerve stimulation, respectively. This demonstrates that large and small coronary arteries may respond differently to adrenergic agonists. Other investigators have shown that the response of the total left or right and left coronary vascular bed to sympathetic nerve stimulation or intracoronary norepinephrine infusion is of a biphasic nature. Studies by Berne et al. (1958,1965) and Hardin et al. (1961) in which anesthetized dogs with beating working and nonworking hearts respectively, were subjected to stellate ganglion stimulation or NE administration. This resulted in a brief period of vasoconstriction which preceded the

increase in heart rate, followed by a prolonged vasodilation associated with a reduction in coronary sinus P_{O_2}. Feigl (1967) reported that following beta blockade (which prevents the beta mediated increases in heart rate and myocardial contractility) stellate ganglion stimulation produced only coronary vasoconstriction which could be blocked by alpha receptor blockade. These studies suggest that the coronary vasodilation seen with sympathetic nerve stimulation is probably due to the fact that myocardial metabolism is greatly enhanced due to beta stimulation in the myocardium. While alpha receptor activation is most likely occurring simultaneously, metabolic vasodilation is the dominant response. Only when the increase in myocardial metabolism is prevented does alpha mediated coronary vasoconstriction become manifest. Pitt et al. (1967) demonstrated that systemic administration of various catecholamines to conscious dogs resulted in coronary constriction when the animals were pretreated with a beta blocking agent. This constriction could be prevented by alpha blockade. A transient coronary vasodilation was sometimes seen in dogs which were not beta blocked in response to catecholamine administration which preceded changes in myocardial or systemic hemodynamics. This vasodilation could be blocked with propranolol, suggesting that the coronary vascular bed may exhibit direct beta receptor mediated vasodilation.

Klocke et al. (1965) demonstrated the presence of beta receptors in the coronary vasculature in a non-beating, non-working, K^+ arrested heart supported by an extracorporeal circulation. Injection of isoproterenol into the coronary arteries resulted in an increase in CBF which was accompanied by an increase in coronary sinus P_{O_2}. The effect could

be blocked by pretreatment with propranolol. These studies suggest that there are two types of beta receptors, one located in the myocardium and the other located in the coronary vasculature. The myocardial beta receptors are called Beta 1, and when stimulated by beta agonists such as isoproterenol, NE or EPI mediate the augmentation of heart rate and myocardial contractility. The vascular beta receptors Beta 2, when stimulated by the same agonists, mediate vascular smooth muscle relaxation and hence vasodilation (Braunwald et al., 1976). McRaven et al. (1971) demonstrated that coronary vasodilation induced by intracoronary isoproterenol was reduced by 30% after pretreatment with practolol, a specific beta 1 blocking agent. This study demonstrated that a significant amount of the coronary vasodilation seen with administration of beta agonists is due to direct stimulation of the vascular beta 2 receptors. Hamilton and Feigl (1976) also demonstrated the presence of coronary beta 2 receptors in the dog; however, they reported that the coronary vasodilation seen with intracoronary isoproterenol following beta 1 and alpha receptor blockade was slight and concluded that there is little functional significance of these vascular receptors. Baron and Bohr (1972) reported that practolol blocked the vasodilator action of isoproterenol in isolated strips of coronary arteries, which suggests that these coronary beta receptors could be of the beta 1 variety as well. These studies provide evidence for the presence of beta receptors mediating vasodilation in coronary arteries; however, the functional significance is controversial.

Vatner et al. (1974) demonstrated that intravenous norepinephrine infusion in conscious dogs produced a brief fall in left coronary

vascular resistance which was followed by a sustained rise in coronary resistance and a reduction in coronary sinus P_{O_2}. They also showed that the early vasodilation could be prevented by beta blockade and the prolonged vasoconstriction could be prevented by alpha blockade. This study was repeated on the same chronically instrumented animals during sodium pentobarbital anesthesia. Norepinephrine, in this case produced only coronary dilation. This study suggests that the alpha vasoconstrictor mechanism may be predominant over the vasodilator mechanism in the conscious dog. Pitt et al. (1967) reported similar findings for the conscious dog.

Other studies suggest that the overall response of the left coronary vascular bed to neurogenic, humoral and metabolic influences is in part dictated by the competition between alpha mediated vasoconstriction and metabolic or beta mediated vasodilation. Mohrman and Feigl (1978) demonstrated that adrenergic stimulation via intracoronary NE infusion or baroreflex mediated sympathetic stimulation produced a significantly higher oxygen delivery per unit increase in myocardial oxygen consumption after alpha receptor blockade than they did before. Prior to alpha block, adrenergic stimulation resulted in a significant increase in myocardial oxygen extraction and a decrease in coronary venous oxygen content, presumably as a result of an alpha mediated restriction of blood flow. Following alpha receptor blockade, myocardial oxygen extraction and coronary venous oxygen content changed only slightly. These authors concluded that the net effect of alpha receptor activiation was to restrict the metabolically related flow increase by approximately 30%, thus increasing oxygen extraction. This study demonstrates that alpha

mediated coronary constriction is present even in the presence of potent metabolic vasodilator influences. While vasodilator metabolites decrease coronary vascular resistance, they only act on small coronary resistance vessels. These vessels may be maximally dilated during enhanced metabolic activity, ischemia, etc., but concomitant alpha receptor activation may result in a superimposed increase in large artery resistance (Malindzak et al., 1978). This concept is also supported by a clinical investigation by Mudge et al. (1979) in which the coronary vascular response to adrenergic stimulation was obtained in 2 groups of patients, those with ischemic coronary artery disease (CAD) and those without (control group). Adrenergic stimulation was produced by the cold-pressor test, arterial blood pressure recorded, coronary blood flow determined by the continuous thermodilution method, and heart rate was held constant. In patients with CAD adrenergic stimulation resulted in a decrease in coronary blood flow in seven of thirteen patients, with a mean increase in coronary resistance of 24% for all thirteen patients. In the control group subjected to the cold-pressor test, coronary blood flow increased and resistance remained unchanged. This study suggests that patients with coronary stenosis may have limited coronary vasodilator reserve due to a significant degree of ischemia, with near maximal vasodilation of the (small) coronary resistance vessels. Consequently, adrenergic stimulation and alpha receptor activation results in vasoconstriction, possibly due to increases in large coronary artery resistances. This obviously would result in an even more pronounced ischemia.

Prinzmetal's Angina and Coronary Vasospasm

This concept of large coronary artery vasoconstriction has gained much attention in recent years as coronary artery vasospasm has been identified clinically, and found to be capable of producing transient myocardial ischemia seen in patients with Prinzmetal's angina (Oliva et al., 1973). It is also interesting to note that large coronary artery vasospasm can occur in normal vessels as well as vessels with significant stenotic lesions (Oliva et al., (1973). It can also occur in the denervated hearts of transplanted patients, and occurs with surprising frequency in the right coronary artery (Zacca et al., 1979). Coronary vasospasm has recently been shown to be intimately involved in the development and pathogenesis of myocardial infarction (Maseri et al., 1978). While the actual mechanisms involved in this severe form of large coronary artery vasoconstriction have yet to be defined, several physiological factors have been found to potentiate and/or initiate vasopastic activity; namely, systemic alkalosis and hypocapnia (Yasue et al., 1978), sympathetic nerve activity (Yasue et al., 1974), as well as the release of thromboxane A_2 from platelet aggregations (Ellis et al., 1976). The fact that alpha blocking agents have been successful in the treatment and prevention of large coronary artery vasospasm suggests that the mechanism may involve catecholamine activation of large coronary artery alpha receptors (Braunwald, 1978). Other drugs such as nifedipine (a coronary dilator which acts to block slow calcium channels in smooth muscle) and verapimil (another calcium antagonist) have also been successful in the treatment of this condition, suggesting that

vasospastic activity may be the result of deranged calcium transport or metabolism in coronary vascular smooth muscle.

Baroreceptor Reflex

Physiological neural reflexes such as the baroreceptor reflex have been shown to affect coronary vascular resistance. In 1963, Szentivanyi and Juhasz-Nagy demonstrated that carotid sinus hypotension produced by bilateral carotid occlusion in anesthetized, vagotomized dogs produced tachycardia, an increase in systemic arterial pressure and a decrease in left coronary vascular resistance. A repeat of this maneuver after beta-blockade with propranolol showed that the tachycardia and myocardial inotropy were prevented, and coronary resistance then increased. This increase in resistance in response to baroreflex sympathetic stimulation was prevented by cardiac sympathectomy. This study was later repeated by Feigl (1968) with similar results. Powell and Feigl (1979) subsequently published a report in which anesthetized, closed chest, vagotomized dogs were pretreated with propranolol and subjected to baroreflex stimulation. Myocardial oxygen consumption and heart rate did not change and the rise in arterial pressure was limited to 15 mmHg with the use of a pressure control reservoir. During baroreflex stimulation, left diastolic coronary resistance increased by 21%. Following alpha blockade, resistance increased only 5%. It appears that baroreceptor reflex stimulation produces left coronary vasoconstriction only in beta blocked animals, and this vasoconstriction is mediated by alpha receptor activation.

Sympathetic Tone

There is good experimental evidence to suggest that a degree of tonic coronary vasoconstriction exists which is mediated by outflow from sympathetic efferents. Brachfield et al. (1960) demonstrated that acute surgical denervation of the heart in the anesthetized dog produces a decrease in coronary vascular resistance and a fall in coronary arterio-venous oxygen extraction. Vatner et al. (1970) supplied further evidence to support the concept of tonic coronary vasoconstrictor tone mediated by sympathetic nerves. In this study on conscious dogs, electrical stimulation of the carotid sinus nerve resulted in a decrease in aortic blood pressure, heart rate and left coronary vascular resistance. After atropine (a parasympatholitic agent) and propranolol (a beta blocker) were administered, cartoid sinus nerve stimulation still produced a decrease in aortic pressure and coronary resistance. However, after alpha blockade alone with phentolamine or sympathetic blockade with guanethidine, carotid sinus nerve stimulation produced no change in coronary resistance. Furthermore, sinus nerve stimulation during treadmill exercise (which in itself decreases coronary resistance) produces a further decrease in coronary resistance. The authors conclude that a degree of resting sympathetic vasoconstrictor tone is present in the conscious dog which is withdrawn during carotid sinus nerve stimulation resulting in coronary vasodilation. They also suggest that resting sympathetic tone persists in the coronary bed of the dog even during exercise when there is concomitant metabolic vasodilation. Vatner et al. (1971) also demonstrated that alpha mediated constrictor tone in the coronary vascular bed may be rapidly withdrawn relexly.

This conclusion was drawn from their study in which baboons were chronically instrumented for monitoring left coronary blood flow by radiotelemetry. They reported that spontaneous increases in CBF and decreases in coronary resistance occurred periodically while the baboons were asleep, and that these changes were independent of changes in heart rate or arterial pressure.

Carotid Body Chemoreceptors

The effect of carotid body chemoreceptor stimulation on coronary vascular resistance was examined by Ehrhart et al. (1975). In this study, the carotid bodies of dogs were selectively stimulated with hypoxemia and hypercapnic blood. Left coronary resistance did not change under conditions of natural flow or constant flow perfusion, both with and without vagotomy. This study suggests that local stimulation of the carotid chemoreceptors has little effect on coronary resistance. This study is in apparent contrast to the work of Hackett et al. (1972) in which the circumflex coronary artery of dogs was perfused at constant flow, and the animals were treated with practolol (B1 blocker) and electrically paced in order to minimize the indirect effects of chemoreceptor induced myocardial responses on coronary resistance. The aortic or carotid chemoreceptors were stimulated by intra-arterial injections of nicotine or cyanide. Such activation of the chemoreceptors produced substantial coronary vasodilation which could be blocked by vagotomy or atropine. These authors suggest that chemoreceptor activation produces a substantial vagally mediated reflex which results in coronary vasodilation. Indeed, this study demonstrates the ability of

chemoreceptors to reflexly alter coronary resistance. However, this study was carried out using pharmacological stimulation of chemoreceptors. Therefore, this reflex may not be of functional significance when elicited by physiological stimuli in the basically intact animal as is suggested by Ehrhart et al. (1975), and by studies which are summarized below, dealing with the effects of acetylcholine and the vagus nerve.

Acetylcholine and Vagus Nerve

While most investigators agree that acetylcholine is a potent coronary vasodilator (Berne, 1958; Denison and Green, 1958; Gregg, 1950) there is less agreement concerning the effects of vagal stimulation on coronary resistance. Schreiner et al. (1957) demonstrated that vagus nerve stimulation in the open-chest dog produced no change in coronary inflow, outflow or coronary sinus oxygen saturation when heart rate was held constant. Other investigators using similar experimental techniques also failed to obtain any coronary vascular response to vagal nerve stimulation which could not be accounted for by reductions in blood pressure or heart rate (Denison and Green, 1958; Szentizanyi and Juhasz-Nagy, 1959; Wang et al., 1960). These studies were preceded by the work of Garcia-Ramos et al. (1950), in which vagal stimulation to paced or fibrillating dog hearts resulted in an increase in coronary blood flow using constant pressure coronary perfusion. This finding is supported by the work of Feigl (1969) who also demonstrated that electrical vagal stimulation of the heart in anesthetized, open-chest dogs that were beta blocked, paced and sympathectomized, resulted in a decrease in aortic blood pressure and an increase in left coronary blood flow.

Late diastolic coronary resistance fell 62% from control with 5 seconds of vagal stimulation. This effect could be blocked by atropine. This study provided evidence that vagal stimulation results in direct parasympathetic coronary vasodilation which is independent of vagally mediated negative inotropic and chronotropic effects. While this study demonstrates that the coronary bed receives parasympathetic innervation, the functional significance of this innervation may be limited in the intact animal.

III. Myogenic Factors

One of the possible mechanisms for regulating blood flow to a vascular bed is the direct response of smooth muscle to a change in transmural pressure or tension. This concept originated in 1902 with Bayliss who first suggested that an active myogenic relaxation of vascular smooth muscle could be the mechanism of the hyperemia seen following brief (8-15 sec) occlusions of the arterial supply to the dog hindlimb. This study came under criticism by Anrep in 1912, who concluded from his experiments that the periods of occlusion used by Bayliss were long enough to allow for tissue metabolite accumulation, and that the hyperemia was most likely due to a metabolic vasodilation. Folkow (1949) came to the defense of Bayliss with a study in which reactive hyperemia was produced by partially reducing intravascular pressure. He suggested that since flow was only minimally reduced the resulting hyperemia was most likely due to a myogenic phenomenon.

Berne (1964) has criticized the myogenic theory on the following basis: for flow to be maintained constant with an increase in perfusion

pressure (autoregulation), the vascular smooth muscle cells must contract to reduce the luminal diameter of the vessel. If stretch is the stimulus for smooth muscle contraction, then following an initial stretch, the vessel contracts to its original size and the stimulus for further contraction of the smooth muscle is gone, yet the newly achieved vessel diameter is maintained. Folkow (1960) addressed this problem by providing evidence to suggest that the resistance vessels respond to stretch by increasing their frequency of contraction and therefore these vessels spend a greater amount of time in the contracted state. The overall effect of this response would be an increase in vascular tone. This concept was supported by Johansson and Bohr (1966) who reported that helical strips from canine paw arteries responded to an increased passive stretch by increasing the frequency of spontaneous rhythmic contractions.

Another explanation for the myogenic theory is that vascular smooth muscle responds to changes in tension rather than changes in length. As perfusion pressure is increased, tension in the vessel wall is increased which elicits a contraction of the vascular smooth muscle. This reduces the luminal diameter until the total vessel wall tension returns to control levels. Burton and Stinson (1960) as well as Sparks and Bohr (1962) demonstrated that active tension due to vascular smooth muscle is increased in response to passive distension or stretch. Therefore, the increase in total wall tension in response to stretch can be restored only by a reduction in the internal radius of the vessel to a value less than the original control value, according to the law of Laplace ($T = PR/W$), where T = wall tension, P = transmural

pressure, R = vessel radius, W = vessel wall thickness. The mechanism by which this occurs is thought to be related to the cell membrane acting as a type of tension-receptor. Stretch causes changes in membrane activity of vascular smooth muscle cells (single unit) which precede the mechanical contractile response (Burnstock et al., 1963). Since the generator potential of the invertebrate stretch receptor is dependent on both the rate and amplitude of the applied stretch (Ezyguirre and Kufler, 1955), it was suggested that perhaps membrane depolarization of smooth muscle is also dependent on rate and amplitude of stretch. Sparks (1964) demonstrated that active tension development in the human umbilical artery in response to passive stretch is directly related to the resting tension, the rate and increment of stretch.

These data provide support for the theory that active responses by vascular smooth muscle could function in the local regulation of blood flow. As mentioned previously, autoregulation could be due to a constriction or relaxation of vascular smooth muscle in response to an increase or decrease in perfusion pressure, respectively. To what extent a direct response of vascular smooth to changes in transmural pressure is responsible for autoregulation in the coronary bed is difficult to ascertain. The little amount of evidence to support this is purely conjectural, and can be explained just as easily on the basis of changes in metabolic activity. The myogenic hypothesis has also been applied in theory to the genesis of exercise hyperemia, with the contraction of the exercising muscle passively decreasing the stretch of the vascular smooth muscle causing smooth muscle relaxation and hyperemia.

This theory is not substantiated by a recent study by Bacchus (1978) in which intramuscular pressure was passively increased to levels seen during contraction, and no evidence of myogenically mediated vasodilation was seen. The reduction in intravascular pressure as a result of coronary artery occlusion could theoretically cause relaxation of the vascular smooth muscle and vasodilation. Release of the occlusion would then result in a reactive hyperemia. One must bear in mind that coronary occlusion has profound effects on myocardial metabolism, and it is difficult to separate the myogenic and metabolic components of the post-occlusion hyperemia. However, Eikens and Wilcken (1974) have observed reactive hyperemia following coronary occlusions as short in duration as one to two beats, and they point out that occlusions this brief are unlikely to result in a significant degree of myocardial ischemia, therefore the hyperemic response following brief occlusions is probably myogenic in nature. Olsson (1975) supports the myogenic theory as the mechanism of the hyperemia following extremely brief coronary occlusions, but suggests that any contributions it might make to hyperemia following longer occlusions are obscured by dominant metabolic factors.

IV. Myocardial Oxygen Consumption

The heart relies almost exclusively on the (aerobic) oxidation of substrates for the generation of energy. Therefore it can only tolerate a small oxygen debt. In the steady state, myocardial oxygen consumption ($M\dot{V}O_2$) provides a relatively precise measurement of the hearts metabolic status. $M\dot{V}O_2$ is determined by the product of coronary blood flow and the coronary arterial-venous oxygen content. The normal left ventricle

in intact dog or man consumes 8-10 ml/min/100 gm (Folkow and Neil, 1971).

There are three major determinants of $\dot{M}VO_2$: myocardial wall tension, contractility and heart rate. Sarnoff et al. (1958) reported in a study which utilized the isolated perfused canine heart that total wall tension as estimated by the tension-time index is the primary determinant of $\dot{M}VO_2$. Tension time index is determined by area under the aortic systolic pressure curve or the mean systolic pressure x the duration of systole. This study also demonstrated the relative contribution of preload (flow work) and afterload (pressure work) to $\dot{M}VO_2$. To study pressure work, left ventricular work was increased by elevating aortic pressure (afterload) while cardiac output and heart rate were held constant. The increase in work (175%) was paralleled by an increase in $\dot{M}VO_2$ (178%), indicating that afterload is an important determinant of $\dot{M}VO_2$. To study flow work, left ventricular work was elevated by augmenting cardiac output (preload) while mean aortic pressure and heart rate were held constant. In this case, the increase in work (696%) was accompanied by only a 53% increase in $\dot{M}VO_2$, indicating that flow work is relatively unimportant in determining $\dot{M}VO_2$. The importance of heart rate as a determinant of $\dot{M}VO_2$ was also reported by Sarnoff et al. (1958). Using the same aforementioned preparation, flow work was increased by elevating cardiac output and holding aortic pressure constant at 120 mmHg and heart rate at 120 b/min. This type of flow run was again repeated at constant heart rates of 160 b/min, and 200 b/min. It was found that a higher heart rate at any given work level was accompanied by an increased $\dot{M}VO_2$, demonstrating the importance of

heart rate on $\dot{M}VO_2$. Klocke et al. (1966) demonstrated that the oxygen requirements of myocardial depolarization and repolarization constitute only 0.5% of the total oxygen consumed by the normal working heart. Therefore, the increase in $\dot{M}VO_2$ with increased heart rate is not due to the cost of electrical activity but due to the cost of contractile activity.

Braunwald et al. (1958) demonstrated that oxygen consumption and left coronary blood flow are well correlated, as had been previously shown by other investigations (Eckenhoff et al., 1947; Foltz et al., 1950; Alella et al., 1955). However, the study by Braunwald et al. (1958) demonstrated that coronary blood flow is significantly augmented by increased pressure work (afterload), and is slightly increased by flow work (preload). The same was also true for oxygen consumption, providing further evidence to support the concept that one of the primary determinants of coronary blood flow is myocardial oxygen consumption.

The importance of contractility as a determinant of $\dot{M}VO_2$ was demonstrated by Graham et al. (1968). In this study, which utilized the isovolumetrically contracting left ventricle, peak developed tension was increased at a constant calculated Vmax by increasing ventricular volume, and the effect on $\dot{M}VO_2$ was determined. Following this, calculated Vmax was increased at a constant peak developed tension by infusing norepinephrine and decreasing ventricular volume to match the tension existing before norepinephrine infusion, and $\dot{M}VO_2$ was redetermined. $\dot{M}VO_2$ consistently increased either with increased Vmax or increased developed tension, and were related by the following equation:

$\dot{M}VO_2$ ml/beat/100 gm LV = K + 0.25 peak developed tension (g/cm^2) + 1.43 Vmax (cm/sec). This study demonstrated that the rate of $\dot{M}VO_2$ is sensitive to both tension and contractility, and is 6 times more sensitive to changes in the maximum velocity of contraction (index of contractility).

The studies by Eckenhoff et al. (1947) demonstrated a correlation between the magnitude of coronary blood flow at any given level of myocardial oxygen consumption, suggesting a coupling mechanism between myocardial metabolic activity and blood flow. This study, which was later confirmed by other investigators, gave rise to the hypothesis that myocardial oxygen consumption is the primary determinant of coronary blood flow. This relationship shows a positive correlation even at very high heart rates where left CBF is impeded by a greater amount extravascular compression. The ratio of myocardial oxygen consumption to oxygen delivery determines myocardial tissue P_{O_2}. Tissue P_{O_2} is normally maintained at a very low level and is probably less than the P_{O_2} seen in coronary venous blood (25 mmHg). The coronary venous oxygen content is normally about 5 ml O_2/100 ml blood. Increasing myocardial metabolic activity (and hence $\dot{M}VO_2$) not only results in an increased CBF but an increased oxygen extraction such that venous oxygen content may fall to less than 1 ml O_2/100 ml blood (Berne et al., 1957; Scott, 1961). An elevation of tissue P_{O_2}, as judged by an elevated coronary venous oxygen content of > 6 ml O_2/100 ml blood, disrupts the correlation seen between oxygen consumption and CBF. During such conditions, CBF becomes primarily dependent on perfusion pressure

(Scott, 1961). This situation rarely occurs under physiological conditions however.

The precise mechanism responsible for maintaining CBF at a level appropriate for the existing metabolic needs of the myocardium is not known. One possible mechanism is a direct effect of tissue P_{O_2} or intraluminal P_{O_2} on vascular smooth muscle, thereby regulating coronary resistance and hence blood flow. A second possible mechanism is related to the release of vasoactive metabolites by cardiac cells in response to increased metabolic activity and subsequent lack of oxygen. There are several such vasoactive agents currently under investigation as potential mediators in the local metabolic regulation of blood flow. Among those that will be discussed in this review are oxygen, carbon dioxide, hydrogen ion, potassium ion, adenosine and adenine nucleotides, osmolality and the prostaglandins.

V. Metabolically Related Vasoactive Agents

For a chemical to be considered as an important factor in the local regulation of blood flow, it must satisfy all of the following criteria (Haddy and Scott, 1968; Haddy and Scott, 1975; Rubio and Berne, 1974):

a) It should be a naturally occurring substance that is present within the tissue, and its breakdown products should be detectable in the tissue or venous effluent.

b) Intra-arterial administration of the substance, in concentrations similar to those determined for a particular vascular bed should produce a response in the resting organ that is

similar to that seen during the conditions in which it is naturally produced.

c) It should not disrupt the normal function of the organ to which it is administered.

d) The time course of its appearance and disappearance should correspond to the time course of the local regulatory response.

Oxygen Tension

It is well-known that hypoxia is considered to be the most potent physiological stimulus in producing coronary vasodilation. But the mechanism by which low oxygen tension produces a reduction in coronary resistance is controversial. Such controversy began in 1913 when Maukwalder and Starling suggested that coronary vasodilation seen in the heart lung preparation in response to hypoxia or epinephrine administration was due to the production and release of vasodilator metabolites. This idea was challenged in 1925 by Hilton and Eichholtz who suggested that with hypoxemia, the reduced oxygen tension acts directly on the blood vessel wall to produce coronary vasodilation. Their assumption was based largely on the fact that $\dot{M}VO_2$ was constant during the hypoxemia and therefore no tissue oxygen deficit occurred.

It has been difficult to distinguish between the direct and indirect effects of low oxygen tensions during hypoxic vasodilation. Duling and Berne (1970) reported that in the rat cremaster muscle and the hamster cheek pouch, the arteriolar wall is freely permeable to oxygen, and that the P_{O_2} in the resistance vessel wall is largely

determined by the luminal P_{O_2}. Furthermore, there is a substantial loss of oxygen along the length of the arterial tree. However, it is reasonable to assume that the arteriolar P_{O_2} closely resembles arterial P_{O_2}. Low P_{O_2}, similar to that seen in coronary venous blood has had much attention as a possible mediator of vascular smooth muscle relaxation. Detar and Bohr (1968), using isolated helical strips of rabbit aorta, demonstrated that high oxygen tensions in the bathing solution produces contraction and low oxygen tension produces relaxation, indicating a direct effect of oxygen on the contractile activity of vascular smooth muscle. However, Gellai et al. (1973) demonstrated that resting tension of helical coronary artery strips was unaffected or only minimally decreased when the P_{O_2} of the bathing solution was decreased to 5-10 mmHg. Only at a P_{O_2} of 0 mmHg was contractile tension markedly depressed. Furthermore, Duling (1974) demonstrated that arteriolar diameters were not significantly different when a nitrogen containing bathing solution (P_{O_2} = 0 mmHg) or an oxygen rich bathing solution (P_{O_2} = 200 mmHg) were injected by micropipette around arterioles under direct observation in vivo. Therefore, there still is no definitive answer as to the direct role of oxygen in the regulation of resistance vessels.

Studies on the intact heart by Sobol et al. (1962) demonstrated that an increase in P_{O_2} induced by ventilation with 100% O_2 resulted in a decreased coronary blood flow as measured by coronary sinus effluent. Daugherty et al. (1967) demonstrated that a local decrease in left coronary artery P_{O_2} to < 40 mmHg resulted in a decrease in coronary resistance and left ventricular contractile force. Berne et al. (1957) studied the effect of local left coronary hypoxemia in the open chest

dog. At normal perfusion pressure, hypoxemia resulted in a large increase in CBF. After a return to normoxemia, CBF was increased by increasing perfusion pressure. Hypoxemia then produced a greater extraction of oxygen from coronary blood, a high coronary sinus P_{O_2} and no change in CBF. It was determined that if the hypoxemia produced a coronary sinus oxygen content above 5 vol%, CBF was unchanged, whereas it increased proportionately with a reduction of sinus O_2 content below this level. Therefore, they concluded that arterial P_{O_2} was not a critical factor in the production of hypoxic vasodilation, but that myocardial P_{O_2} (as estimated by venous P_{O_2}) may be the important factor through a mechanism by which low O_2 elicits the production of vasodilator metabolites. Finally the fact that the duration of coronary occlusion is approximately proportional to the duration of the hyperemia further supports the concept of vasodilation mediated by metabolite release. If P_{O_2} had a direct effect on the contractile state of vascular smooth muscle in resistance vessels, then the tone of this coronary smooth muscle should return upon the release of occlusion and immediate restoration of oxygen rich blood. This evidence is against the concept that oxygen plays a major role in the direct control of coronary resistance vessels.

Carbon Dioxide

There is evidence that CO_2 ($[H^+]$) is vasoactive in the left coronary circulation. Case and Greenberg (1976) reported that hypocapnia (P_{CO_2} = 23 mmHg), produced locally in the coronary arterial perfusate of open-chest dogs resulted in an increased coronary resistance of 84%

with myocardial metabolism held constant. Daugherty et al. (1967) also demonstrated that local coronary hypocapnia in open-chest dogs produced vasoconstriction, while hypercapnia produced vasodilation. Since CO_2 and H^+ ion are interrelated via the bicarbonate-buffer system, it is difficult to determine whether or not CO_2 is the locally vasoactive agent or whether the vasoactivity is mediated through the effect on pH. Hydrogen ions are known to exert a highly potent antagonistic action on calcium ions since these two ions compete for the same active sites, both on the transmembrane calcium transport system and at the myofibrillar ATPase. Thus, vasoconstriction occurs if the calcium concentration is increased or if the hydrogen ion concentration is decreased (Mrwa et al., 1974). The effect of CO_2 on coronary resistance may be a direct effect on the vascular wall, or an indirect effect through H^+ ion as mentioned previously, or by affecting the production or action of vasodilator metabolites. Alella et al. (1955) demonstrated that the coronary sinus P_{CO_2} may not always rise to vasoactive levels during enhanced cardiac activity. Furthermore, Case et al. (1978) demonstrated that CO_2 is a less potent coronary vasodilator than is hypoxia since coronary sinus P_{CO_2} had to be increased twice as much as coronary sinus P_{O_2} was decreased in order to achieve the same degree of vasodilation under constant flow conditions. Feinberg et al. (1960) also reported that CO_2 was a poor coronary vasodilator during natural flow, constant pressure perfusion. In 1973, Duling reported on experiments using the hamster cheek pouch preparation that elevation of the P_{CO_2} of the bathing solution from 0 to 32 mmHg increased arteriolar diameter by 18%. In any experiment in which blood P_{CO_2} is altered, there may be

concomitant changes in other parameters as well, such as serum ionized calcium, serum potassium, oxygen tension and sympatho-adrenal activity. Therefore, such experiments must be carefully interpreted.

There have been several studies which have examined the effects of hypo and hypercapnia on coronary vascular resistance. Such studies have also provided evidence that excess CO_2 produces coronary vasodilation and a lack of CO_2 produces coronary vasoconstriction (Kittle et al., 1965; Ledingham et al., 1970; Neill and Hattehauer, 1975; Vance et al., 1973). In a recent report by Rooke and Sparks (1978) the effects of systemic hyper and hypocapnia on coronary conductance during isoproterenol induced enhancement of cardiac activity were studied. They reported that large changes in arterial P_{CO_2} caused only minimal differences in CBF at any given level of myocardial oxygen consumption, which suggests that CO_2 plays a minor role, if any, in the regulation of CBF. This study as well as others in which systemic changes in CO_2 were elicited cannot be readily applied to the role of CO_2 in the local regulation of CBF since the results of such studies may easily be influenced by extrinsic neural (reflex) activity or changes in myocardial function other than that represented by oxygen consumption.

Another possible role of CO_2 in the local regulation of CBF may be that of functionally interacting with adenosine in modulating coronary vascular resistance. Degenring (1976) has shown that hypercapnia or acidosis is capable of increasing adenosine levels in the isolated perfused guinea pig heart. Furthermore, Raberger et al. (1975) have shown that elevated CO_2 can potentiate the coronary vasodilator activity of adenosine. This finding is also supported by the work of Merrill

et al. (1978) in the isolated perfused guinea pig heart. While there is no other information available on this point, it certainly represents an interesting topic worthy of further investigation.

Potassium

Katz and Linder (1938) first reported the effects of K^+ on the coronary circulation. It was demonstrated that in concentrations slightly above normal, K^+ was a vasodilator, and at high concentrations (above normal) or concentrations below normal it acted as a vasoconstrictor. These effects are opposite to those predicted by the Nernst or Goldman constant field equations. These equations predict that a reduction of $[K^+]_o$ should result in hyperpolarization of the vascular smooth muscle and hence decrease resistance and vice versa for an increase in $[K^+]_o$. This problem was addressed by Brace et al. (1974) who determined that when K^+ was removed by dialysis from blood perfusing the left common coronary artery of the dog at constant flow or constant pressure, a substantial increase in coronary resistance occurred, associated with an increase in left ventricular contractile force. They postulated that the increase in coronary resistance seen with local hypokalemia was the result of inhibition of the membrane NA^+-K^+-ATPase which cause depolarization of the smooth muscle cells and contraction, since ouabain infusion blocked most of the vasoconstrictor response to the hypokalemia. Driscol and Berne (1957) also demonstrated the vasoactivity of K^+ in the left coronary bed of the open-chest dog. However, they reported that the magnitude of increased flow with K^+ concentrations ranging from 4 to 12 meq/L was far less than

those observed in response to physiological stimuli. They also reported that increasing cardiac activity produced large increases in CBF but no significant changes in K^+ release into coronary sinus blood. Jelliffe et al. (1957) also demonstrated that coronary-sinus blood samples collected from a heart experiencing increased work or decreased O_2 supply, when reoxygenated and infused into a bioassay coronary vessel, failed to elicit any vasoactive response. Such data provided evidence against K^+ as an important factor in the metabolic adjustment of CBF.

There is some evidence to suggest that K^+ acts as an initiating factor in the vascular response to enhanced myocardial activity. Gellai and Detar (1974) reported that isolated coronary artery strips of rabbits responded to elevated potassium concentrations by a relaxation of resting tension, but that this response was only transient, lasting only 5-6 minutes. Furthermore, the release of K^+ into coronary venous blood is only seen transiently when heart rate or contractility are elevated (Gilmore et al., 1971; Sybers et al., 1971). Murray et al. (1979) utilized a compartmental mathematical model of the heart and its circulation which took into account vascular transit time effects to determine the magnitude of interstitial $[K^+]$ which accompanied stepwise increases in heart rate. In six of nine dogs coronary sinus $[K^+]$ was transiently elevated, and in three dogs it was sustained. The change in $[K^+]$ preceded the coronary vasodilation seen with increased heart rate, and the calculated rise in interstitial $[K^+]$ was suggested to be sufficient in magnitude to account for approximately half of the 75% decrease in coronary resistance seen. Therefore, this study suggests that under constant flow conditions, K^+ seems to be involved in the

initial coronary vasodilation seen with increased cardiac activity. However, under natural flow conditions, stellate ganglion stimulation produced no change in coronary sinus [K^+] (Scott and Radawski, 1971). Sybers et al. (1971) has provided evidence to suggest that the release of K^+ from the myocardium is prolonged and not transient when enhanced cardiac activity is produced during hypoxia. The role of K^+ in the control of coronary resistance may therefore be enhanced under such pathophysiological conditions.

Osmolality

Gellai and Detar (1971) using isolated rabbit coronary artery strips reported that a 30 milliosmole/liter increase in the osmolality of a solution bathing the strips produced a 30% relaxation which was only of a transient nature. While this study suggests that the coronary arteries are slightly sensitive to changes in osmolality, Scott and Radawski (1971) reported that increased cardiac activity produced by left stellate ganglion stimulation in anesthetized dogs was associated with substantial coronary vasodilation yet no change in coronary sinus plasma osmolality occurred. Furthermore, Brace et al. (1975) showed that by inducing hyposmolality in the blood perfusing the left coronary artery of anesthetized dogs inconsistently produced slight coronary vasoconstriction. Gazitua et al. (1971) demonstrated that infusions of hypertonic (350 mosm) sodium chloride into the left coronary artery produced a substantial fall in coronary resistance which was accompanied by an initial fall and subsequent rise in contractile force. Infusions of hypertonic dextrose or urea also produced a decrease in coronary

resistance which was accompanied by an increased contractile force. This study suggests that the coronary vascular bed may be slightly sensitive to changes in osmolality; however, it is not always clear whether the resistance changes seen when osmolality is altered are mediated directly through the effects of osmolality or indirectly through the effects on contractile performance. While it is apparent that osmolality does not measurably change in coronary venous blood during cardiac stimulation, it still is not certain whether changes in osmolality are involved in the local regulation of blood flow through the heart. In vitro evidence would suggest that changes in osmolality has a direct effect on the coronary vasculature. Krishnamurty et al. (1978) reported that small and medium coronary arteries perfused in a bath with a physiological salt solution showed relaxation when exposed to a 50 mosm increase in osmolality above normal with mannitol. Withdrawal of the mannitol from the perfusate produced contraction of the vessels which was not prevented by alpha or beta blockade, nitroglycerin or norepinephrine. Furthermore, the responses to nitroglycerin, norepinephrine and papaverine were attenuated in the presence of hypertonic mannitol. This suggests that local changes in osmolality may attenuate the vasodilator responses to various pharmacological agents, at least in the in vitro situation. The role of local changes in osmolality, if it even occurs, is yet to be determined.

Prostaglandins

The products of arachidonic acid metabolism (the prostaglandins) have been implicated as endogenous mediators of local blood flow

regulation in the heart. However, the evidence for this role is not generally agreed upon by most investigators.

In regard to the role of prostaglandins in the genesis of reactive hyperemia, Alexander et al. (1975) reported that indomethacin (prostaglandin synthesis inhibition) significantly attenuated the reactive hyperemia seen in response to 10, 15, and 20 second occlusions of the left coronary artery in the open-chest dog. Furthermore, a radioimmunassay for PGE detected a basal level of release from the heart which was increased by coronary occlusions. This effect was also blocked by indomethacin. Owen et al. (1975) provided evidence to suggest the opposite role of prostaglandin in reactive hyperemia. They reported that indomethacin had no effect on the reactive hyperemia seen following 5 and 15 second occlusions of the left coronary artery in closed-chest dogs. This result was also confirmed by Needleman (1975) and Hintze and Kaley (1977). All but a few investigators feel that the prostaglandins play a minor role if any in the hyperemic response seen following coronary occlusions; however, there still exists a great deal of controversy concerning the role of prostaglandins in the overall control of coronary flow.

There is experimental evidence, also controversial, to suggest that prostaglandins play a role in the coronary vascular response to hypoxia. Afonso et al. (1974) found that hypoxic coronary vasodilation was significantly attenuated following the administration of indomethacin in closed-chest dogs. Needleman et al. (1975) reported that hypoxia caused a transient release of prostaglandins from the isolated rabbit heart preparation. Wenmalm et al. (1974) demonstrated that the release

of prostaglandins occurred only upon a return to normal oxygen delivery following a hypoxic episode. Yet, Needleman et al. (1975) using the isolated perfused rabbit heart, and Hintze and Kaley (1977) using the open-chest dog demonstrated that the coronary vasodilation in response to hypoxia was not attenuated by prostaglandin synthesis inhibition. In vitro studies by Kalsner (1975,1976) demonstrated that isolated bovine coronary artery strips released baseline levels of prostaglandins, and upon decreasing the P_{O_2} of the bath from 515 to 38 mmHg, the rate of prostaglandin release increased and relaxation of the strips also occurred. Both of these responses to hypoxia were significantly reduced by the administration of prostaglandin synthesis inhibitors (aspirin and indomethacin). Other in vitro studies by Alexander and Gimbrone (1976) and Gimbrone and Alexander (1975) demonstrated the release of vasodilator (E type) prostaglandins from cultured human umbilical vein smooth muscle cells and from human vascular endothelial cells, respectively. While such in vitro evidence favors the involvement of prostaglandins in local blood flow regulation, its applicability to the role of prostaglandins in the intact animal is undetermined.

The role of prostaglandins in the regulation of coronary blood flow during enhanced cardiac activity was investigated by Sunahara and Talesnik (1973). They reported that norepinephrine, when given to isolated, perfused rat hearts, resulted in an increased contractile force and coronary blood flow. Following the blockage of prostaglandin synthesis with aspirin or indomethacin, the same dose of norepinephrine enhanced the coronary flow response but did not change the effect on contractile force. Furthermore, Talesnik and Sunahara (1974)

demonstrated that the administration of prostaglandins E_1 also attenuated the coronary flow response (compared to control) as a result of the administration of norepinephrine or isoproterenol. On the basis of these data, these investigators suggested that endogenously released prostaglandins may act as a brake on coronary metabolic vasodilation. In order to test the validity of this hypothesis in a more intact preparation, Harlan et al. (1978) studied the effects of isoproterenol on coronary blood flow and myocardial oxygen consumption before and after the blockade of prostaglandin synthesis with indomethacin. The results of this study demonstrated that indomethacin had no effect on the relationship between left coronary blood flow and myocardial oxygen consumption, or the degree of coronary vasodilation or myocardial oxygen consumption at any given dose of isoproterenol. This study suggests that prostaglandins do not play a role in the regulation of coronary blood flow during enhanced metabolic activity.

Adenine Nucleotides and Adenosine

The adenosine hypothesis for the regulation of coronary blood flow proposes that since there is rapid metabolism of the adenine nucleotides (ATP, ADP, AMP) in cardiac tissue, when any factor such as hypoxia, ischemia, or increased oxygen consumption contributes to an imbalance between oxygen delivery and oxygen utilization, net nucleotide degradation occurs resulting in increased levels of AMP in the myocardial cells. At the outer cell margin, the enzyme 5^1-nucleotidase catalyzes the hydrolysis of AMP to the nucleoside adenosine (Rubio et al., 1973). Adenosine, which can readily pass through cell membranes (Whittam, 1960),

enters the interstitial fluid and dilates the resistance vessels so that coronary flow increases and a new steady state is reached. Since adenosine is known as a potent vasodilator (Winbury et al., 1953), the role for adenosine in the metabolic regulation of coronary blood flow is attractive since the adenine nucleotides are so important in energy metabolism, and since such a high degree of correlation exists between coronary flow and oxygen consumption.

Adenosine, released from myocardial cells can either re-enter the myocardial cell where it can be rephosphorylated by adenosine kinase to AMP (Mustata et al., 1975) (Jacob and Berne, 1960), or enters the interstitium where it can act on the resistance vessels to cause vasodilation. Adenosine that is lost to the vascular system is acted upon by the degradative enzymes adenosine deaminase and nucleoside phosphorylase which rapidly break down adenosine to inosine and hypoxanthine respectively, as adenosine crosses the capillary endothelium (Rubio et al., 1972). Inosine and hypoxanthine are not vasoactive.

Just as there is good biochemical evidence to support the adenosine hypothesis, good experimental evidence exists as well. Rubio and Berne (1967) reported that adenosine is continuously produced by the normal heart in amounts sufficient to qualify it as a candidate for a role in local blood flow regulation. Furthermore, Berne and Rubio (1974) reported that brief (5 sec) coronary artery occlusions increase the adenosine concentration in the ischemic tissue, and also in 1974 demonstrated that adenosine is increased in the coronary venous blood during hypoxic perfusion or epinephrine stimulation of isolated perfused hearts. Fox et al. (1974) also reported that adenosine was

released from human hearts during angina pectoris induced by rapid atrial pacing in patients with ischemic coronary heart disease. Scott et al. (1965) reported that perfusion of the dog forelimb or kidney with venous blood from the active or hypoxic heart produces dilation and constriction, respectively, which also supports the adenosine hypothesis since the only known endogenous substances which elicit such responses in these vascular beds are adenosine and AMP. This study was followed by a similar report (Scott et al., 1979) in which coronary venous blood from the open-chest dog heart was perfused into an autologous (bioassay) kidney. During reactive dilation, the kidney responded with a large increase in resistance which was blocked by theophylline (a competitive inhibitor of adenosine and AMP) adenosine autoblockade and adenosine deaminase. Hypoxic dilation of the coronary also produced an increase in renal resistance. This response was also blocked by theophylline and adenosine autoblockade; yet, following the administration of adenosine deaminase the renal response was only reduced by 40%. This study suggests that adenosine is the vasoactive substance which appears in coronary venous blood during brief coronary occlusions and both adenosine and AMP appear during local cardiac hypoxic dilation. Rubio et al. (1974) demonstrated in the isolated perfused guinea pig heart preparation that a gradual decrease in the coronary perfusate O_2 content resulted in a continuous increase in coronary blood flow which is paralleled by an increase in the rate of adenosine release and tissue adenosine levels.

While the aforementioned evidence implicates a role for adenosine in the coronary vascular response to brief occlusions and hypoxia,

there exists good evidence to the contrary. Bittar and Pauly (1971) demonstrated in the open-chest dog that aminophylline produced a significant diminution of the coronary response to injected adenosine, and lidoflazine produced a significant enhancement of the coronary response to injected adenosine. However, they showed that the coronary flow response to 30, 60 and 120 second left coronary occlusions were unaffected by pretreatment with aminophylline or lidoflazine, indicating that adenosine is not a mediator of myocardial reactive hyperemia. Giles and Wilcken (1977) also reported that in open-chest dogs, aminophylline reduced the coronary blood flow response to adenosine by 80% yet attenuated the flow response to an 8 second coronary artery occlusion by only 20%, also indicating that adenosine does not play a major role in myocardial reactive hyperemia. Afonso et al. (1972) studied the effects of systemic hypoxia on coronary blood flow before and after the administration of aminophylline in the closed-chest dog. Coronary blood flow as determined by coronary sinus thermodilution technique, was significantly increased by 83% before aminophylline, and 74% after aminophylline. While the same degree of hypoxia was produced in each case, the slightly decreased coronary flow response after aminophylline could be explained on the basis of a greater heart rate and left ventricular work which occurred during hypoxia before the administration of aminophylline. These results suggest that adenosine is not involved in the coronary dilation seen during hypoxia. In an effort to answer this apparent discrepancy, Curnish et al. (1972) reported that aminophylline decreased the volume and duration of the coronary hyperemia following adenosine administration by 41 and 11% respectively. Following 5 to 60

second coronary occlusions, aminophylline decreased the volume and duration of the hyperemic flow by 42 and 31%, respectively, suggesting a role for adenosine in this response. These authors attribute the discrepancy between their results and the results of the aforementioned investigation as being due to 1) the duration of ischemia or hypoxia, since long periods of either condition could result in endogenous adenosine produced in such great concentrations as to negate the pharmacological antagonistic action of aminophylline, and 2) the analysis of data; they suggest that the reactive hyperemic response should be analyzed in terms of the volume of flow rather than the peak hyperemic response. Therefore, while there is a great deal of indirect evidence to support the adenosine hypothesis, several aspects of this theory are yet to be resolved, and are the subject of current investigation.

The role of ATP in the local regulation of coronary blood flow is a relatively unexplored topic. Chen et al. (1972) found evidence for ATP participating in the active hyperemia seen with stellate ganglion stimulation of the dog heart. ATP was assayed from the coronary sinus effluent and was found to increase by approximately 150% during active hyperemia. This corresponded with a similar increase in coronary blood flow. No evidence of ATP could be found in the coronary effluent during the reactive hyperemia following a 20 second occlusion. In a follow-up study, Stowe et al. (1974) reported that isolated guinea pig hearts perfused with a Krebs-Ringer solution showed no release of ATP in response to coronary occlusion and subsequent reactive hyperemia or to anoxia. They concluded that the ATP release in the study by Chen

and co-workers was probably not from the myocardium but could have come from nerves and/or formed elements in the blood.

VI. Right Coronary Blood Flow

The studies concerning the regulation of blood flow in the right coronary circulation are few; therefore, we lack a basic understanding of this vascular bed. However, from the few studies published on this topic, some information can be gleaned to establish a starting point for further investigation. As mentioned previously, Gregg (1937) determined that due to the low intramyocardial tension produced in the right ventricular wall, phasic flow in the right coronary artery (RCA) has the greatest magnitude during systole and the flow pattern follows the contour of the aortic pressure curve. Therefore, extravascular compression is not a significant factor in determining the passive changes in vessel caliber for this vascular bed. Lowensohn et al. (1976) using the conscious dog preparation, corroborated the early findings of Gregg. They also noted that dogs with congenital pulmonic stenosis, right ventricular hypertrophy and elevated right ventricular pressures demonstrated a reduction of systolic flow or sometimes a reversal of flow similar to that which occurs in the left coronary system. This throttling of right coronary blood flow was directly related to right ventricular systolic pressure. Lowensohn et al. (1978) also demonstrated that 10 second occlusions of the RCA produced a peak hyperemic response 300% above resting control values which is less than that reported (300-700%) by Olsson and Gregg (1975) for the left circumflex coronary artery. Since the peak hyperemic response to occlusion was less for the

RCA than that reported for the left coronary system, it could be concluded that the energy (oxygen) demands of this tissue are also significantly less than those of the left ventricle. This point is further supported by the fact that the right ventricle does much less pressure work than the left, and therefore creates less wall tension. In a recent publication by Manohar et al. (1979) right coronary and right ventricular hemodynamics were measured during normal resting conditions, systemic hypoxia and increased right ventricular afterload in the awake calf. Resting right coronary blood flow determined by the microsphere technique, was 73 ml/min/100 gm tissue, a value similar to that reported for the left ventricle. During increased right ventricular afterload, right coronary blood flow increased slightly even though coronary driving pressure decreased indicating a degree of coronary vasodilation. Right coronary blood flow increased 100% during systemic hypoxia (P_{O_2} = 43 mmHg), and the combination of hypoxia and increased afterload increased blood flow 400% above control values. These data for the right ventricle indicate that even though the oxygen consumption is in all likelihood relatively lower at the same rate of oxygen delivery as compared to the left (a state of hyperperfusion), the right coronary vascular bed is still sensitive to factors which alter the metabolic state of the tissue. That is, this vascular bed is capable of significant metabolic vasodilation.

Brooke et al. (1971) demonstrated that acute occlusion of the right coronary artery in the anesthetized open-chest dog caused no change in cardiac output or right ventricular pressure, although right ventricular contractile force was significantly reduced. This study

suggests that a normally contracting right ventricular free wall is not necessary for maintenance of normal cardiac output or right ventricular pressure. This finding could be due to the fact that adequate ventricular hemodynamic function can be maintained by septal wall contraction when the right ventricular free wall is removed and replaced by a Gortex patch graft (Peterson et al., 1978), or could be due to the fact that the right coronary artery of the dog does not supply the total right ventricular tissue mass as some of the arterial blood is supplied by the LAD branch of the left coronary artery (Murray et al., 1979).

The effects of right and left cardiac sympathetic nerve stimulation on left and right coronary blood flow in the anesthetized open-chest dog was reported by Ross and Mulder (1969). Both right and left nerve stimulation (10 V, 5 msec, 10/sec) apparently produced an initial rise in right coronary blood flow followed by right coronary vasoconstriction as demonstrated by a reduction of mean flow at an unchanged or increased aortic pressure. This response was slightly enhanced following beta blockade except that the initial vasodilation was blocked. Flow through the left coronary artery increased during stimulation, and following beta blockade, the dilation was converted to constriction. This study suggests that the right coronary circulation is more sensitive to the direct effects of sympathetic stimulation than is the left coronary circulation.

STATEMENT OF OBJECTIVES

A review of the literature discloses that the characterization of the regulation of blood flow through the right coronary vascular bed has never been adequately accomplished. The metabolic environment of the myocardial tissue supplied by the right coronary artery is much different from that of the left, and the balance of factors contributing to regulation of blood flow through this bed may also be quite different. This vascular system is of great importance since 50% of the human population is right coronary dominant. Therefore, it was felt that this circulation warranted further basic physiological investigation.

The studies described in this dissertation were designed to evaluate several aspects of local and remote control of the right coronary circulation during constant pressure and constant flow perfusion. This report attempts to define the role of autoregulation, infused catecholamines, sympathetic nerve stimulation, adrenergic receptors, prostaglandins, oxygen and carbon dioxide in the control of blood flow through this bed, as well as the interaction of several of these various factors.

Since this vascular bed has never been systematically investigated, these studies were conducted in order to determine if the response of this circulation to the aforementioned experimental interventions was similar or different from that reported for the left

coronary vascular bed. The right ventricular myocardium possesses some unique features that make it different in many respects when compared to the left ventricle. The work performed by the right ventricle is approximately six times less than that performed by the left ventricle. The wall tension generated by the right ventricle is similarly less. Therefore, the balance of forces acting to control blood flow in the right coronary circulation may be somewhat different than those reported for the left coronary vascular bed. The studies reported here were designed to test this hypothesis. Furthermore, because of the recent interest in the mechanisms responsible for coronary artery vasospasm, and the high frequency with which it is reported to occur in the right coronary artery, this study attempts to examine the effects of various vasoconstrictor influences and their interactions in order to determine if a maximal constriction of the right coronary artery could be induced.

METHODS

All experiments were performed on mongrel dogs of both sexes, weighting 25-35 kg. Anesthesia was achieved by initial induction with thiamylal (5 mg/lb) and maintenance with 100 mg/kg alpha chloralose and 500 mg/kg urethane, administered intravenously. The animals were intubated with a cuffed endotracheal tube and ventilated by a positive pressure respirator (Harvard Apparatus Company, Model 613, Millis, Mass.). Volume and rate of ventilation were adjusted to maintain arterial P_{CO_2} within the physiological range. If needed pH was adjusted by intravenous infusions of an isotonic NaH_{CO_3} solution. Arterial P_{O_2}, P_{CO_2} and pH were measured by radiometer blood gas analyzer (Radiometer-Copenhagen, blood micro system, acid base analyzer, Copenhagen, Denmark). Following surgical preparation, anticoagulation was achieved by the intravenous administration of sodium heparin in an initial dose of 600 USP units/kg followed by hourly supplements of 250 USP units/kg. Blood volume was maintained with a 6% solution of dextran (average molecular weight = 75,000) in saline. All blood pressures were continuously monitored with pressure transducers (Statham Laboratory, low volume displacement model P23 Gb, Hato Rey, Puerto Rico) and recorded via inputs into a direct writing oscillograph (Hewlett-Packard, Model 77964, Boston, Mass.).

Experimental Design

These experiments were designed such that paired comparisons could be made for each experimental maneuver. Steady state control conditions were reached before and during each experimental intervention. Where possible, the order of experimental maneuvers was randomized.

I. Studies on the Anesthetized Dog

Constant Flow Preparation

In Series I, II, III, and IV, a constant flow perfusion preparation was utilized. Following anesthesia, the animals were placed in a dorsal recumbancy and standard limb leads were attached to provide input into a bioelectric amplifier. Lead II of the electrocardiogram was monitored for detection of arrythmias and determination of heart rate. This preparation is schematically represented in Figure 1. The left femoral artery and vein were cannulated with polyethylene tubing, P.E. 240 (Intramedic Tubing, Clay Adams, Parsippany, N.J.), for the monitoring of arterial blood pressure and administration of intravenous fluids, respectively. The neck was opened in the midline and the common carotids and vagi isolated bilaterally. The vagi were cut and ligatures placed around each of the common carotid arteries. By applying a tourniquet to these ligatures, carotid sinus hypotension could be produced in most animals, thus eliciting a systemic sympathetic discharge via the baroreceptor reflex. The chest was opened by median sternotomy and the pericardium incised and sutured to the chest wall to form a cradle. Adequate lung inflation and deflation was obtained in

Figure 1. Preparation for constant flow or constant pressure perfusion of the right coronary artery

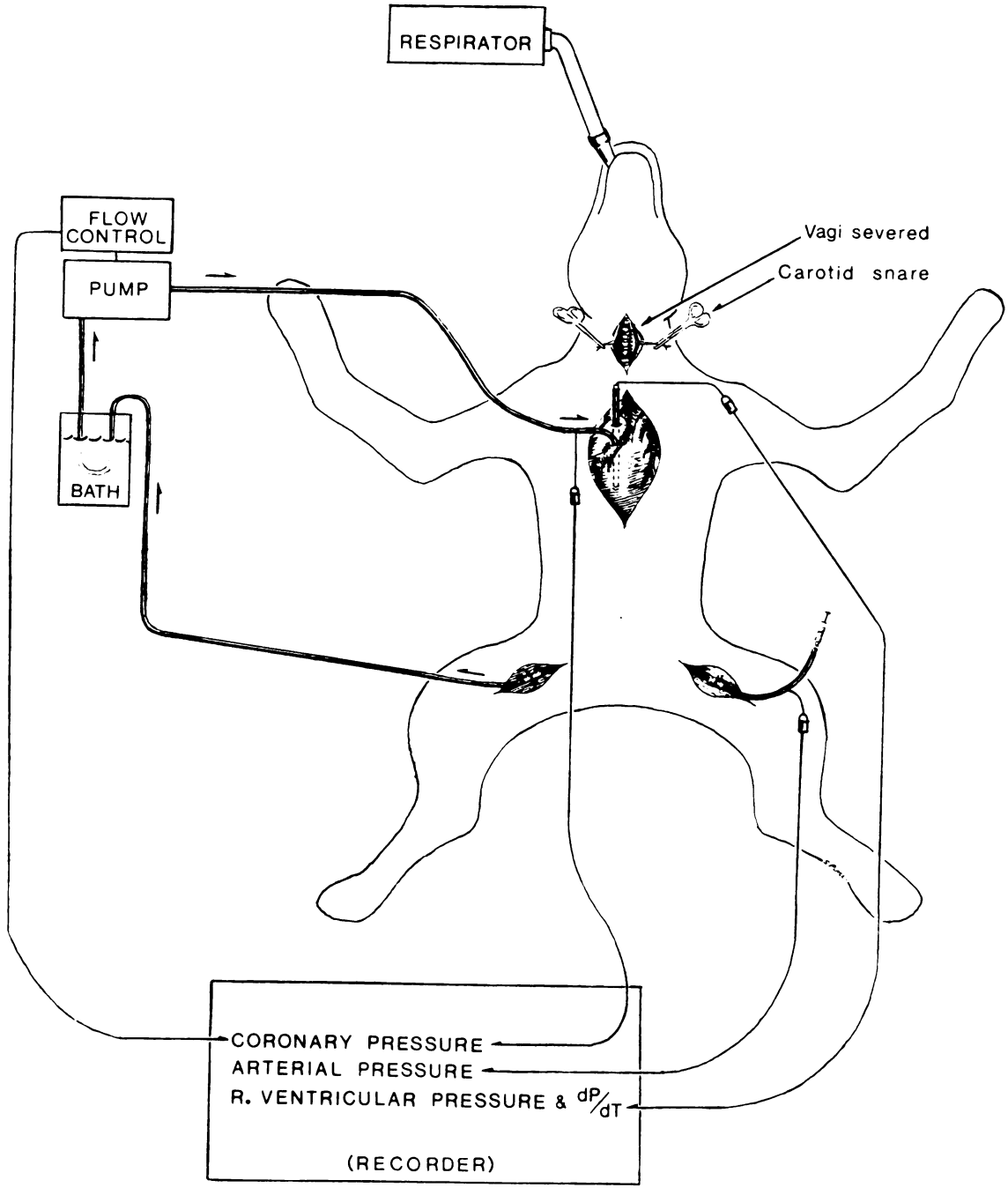

RESPIRATOR
FLOW CONTROL
PUMP
BATH
Vagi severed
Carotid snare
CORONARY PRESSURE
ARTERIAL PRESSURE
R. VENTRICULAR PRESSURE & dP/dT
(RECORDER)

Figure 1

the open chest by applying a 2 cm H_2O positive end expiratory pressure to the outflow tubing of the Harvard respirator. The right atrial appendage was retracted and the right coronary artery was isolated 1-3 cm from its origin, and two silk ligatures were placed loosely around it. Following heparinization, blood withdrawn from the cannulated right femoral artery was pumped (Sigmamotor Inc., Model T-6SH, Middleport, N.Y.) through a cannula which was placed in the isolated segment of the right coronary artery and secured by the silk ligatures. Perfusion pressure was monitored from the perfusion circuit just proximal to the cannula's entry into the vessel. Intracoronary drug infusions were achieved by a Harvard infusion pump (Harvard Apparatus, CO., Millis, Mass.) delivering the drug into the coronary perfusion circuit proximal to the Sigma-motor pump. To demonstrate that this vascular bed was free of collateral vessels from left coronary sources the perfusion pump was turned off briefly, and coronary perfusion pressure was found to fall to less than 20 mmHg. At the end of each experiment (with the exception of Series I) 5 ml of crystal violet dye, dissolved in ethanol and saline (Sigma Chemical Co., St. Louis, MO.) was injected into the perfusion circuit to stain the area of the myocardium perfused. This tissue was then excised and the wet weight determined. The Sigmamotor pump was calibrated for flow at the end of each experiment using timed collections of blood in a graduated cylinder. The flow measurements were multiplied by 100 and then divided by the weight of the tissue perfused in grams to give normalized blood flow in ml/min/100 gm tissue. Right coronary resistance was then calculated by the ratio of the perfusion pressure (mmHg) to flow (ml/min/100 gm) to yield resistance

in peripheral resistance units (mmHg/ml/min/100 gm or PRU 100).

Isolated Lung Preparation

Series IV (constant flow) and Series V (constant pressure) employed the use of an isolated perfused donor lung interposed in the coronary perfusion circuit in order to study the local effects of blood gas tension alterations on coronary resistance. To achieve this, a donor dog (10-12 Kg) was given intravenous heparin and dose of sodium pentobarbitol sufficient to produce euthanasia. A thoracotomy was performed in the fourth left intercostal space and the left lung and heart were removed by dividing the trachea, pulmonary artery, aorta and vena cavae. The lobes of the right lung were ligated at the hilus and cut off. The heart was cut in a transverse section just below the A-V groove. Blood withdrawn from the cannulated right femoral vein of the experimental animal was pumped (Masterflex pump, model 7564, Cole-Parmer, Chicago, Ill.) into the left pulmonary artery of the isolated lung. The trachea was connected to a Harvard positive pressure respirator and ventilated at the necessary rate and volume. Pulmonary venous blood flowed into a large bore cannula tied into the preserved left atrium, and was delivered at constant flow (via Sigmamotor pump) or constant pressure (Holter roller pump) to the right coronary artery. Pulmonary venous pressure was monitored from a catheter (PE60) advanced from the left atrial cannula into the left atrium and maintained constant at a pressure of 5 mmHg with the use of a feedback controller system (Leeds-Northrup Century CAT Controller, Oak Park, MI.) which varied the speed of the masterflex pump (and hence the pulmonary artery

inflow). In these experiments various gas mixtures were used to alter the blood gas tensions of the coronary perfusate. Hypoxia was produced by ventilating the isolated lung with 0% O_2, 5% CO_2, 95% N_2. Normoxia was produced with 20% O_2, 5% CO_2, and 75% N_2. Hypocapnia was produced by hyperventilation of the lung on room air. The combination of hypoxia and hypocapnia was produced by hyperventilating the lung on 100% N_2. Hypercapnia was produced by ventilating the lung with 20% O_2, 15% CO_2 and 65% N_2. This preparation is illustrated in Figure 2.

The use of the extracorporeal lung permitted rapid changes in local blood gas tensions without producing detectable changes in systemic blood gas tensions. Daugherty et al. (1967) have demonstrated that samplings of systemic arterial blood during ventilation of the isolated lung with hypoxic or hypercapnic gas mixtures showed no alteration of systemic blood P_{O_2}, P_{CO_2} or pH.

Constant Pressure Preparation

In this preparation, the surgical procedures and instrumentation were the same as the constant flow preparation except that an isolated lung was interposed in the perfusion circuit, and a Holter roller pump was used to deliver the coronary perfusate. Right coronary perfusion pressure was monitored and held constant by a second feedback control system similar to that described for the isolated lung preparation. Coronary flow was determined by delivering the coronary pump speed signal as an input into the Hewlett-Packard oscillograph. At the end of each experiment, the pump was calibrated by timed collection of blood in a graduated cylinder, and was found to be linear over the

Figure 2. Preparation for constant flow or constant pressure perfusion of the right coronary artery with isolated lung interposed in perfusion circuit.

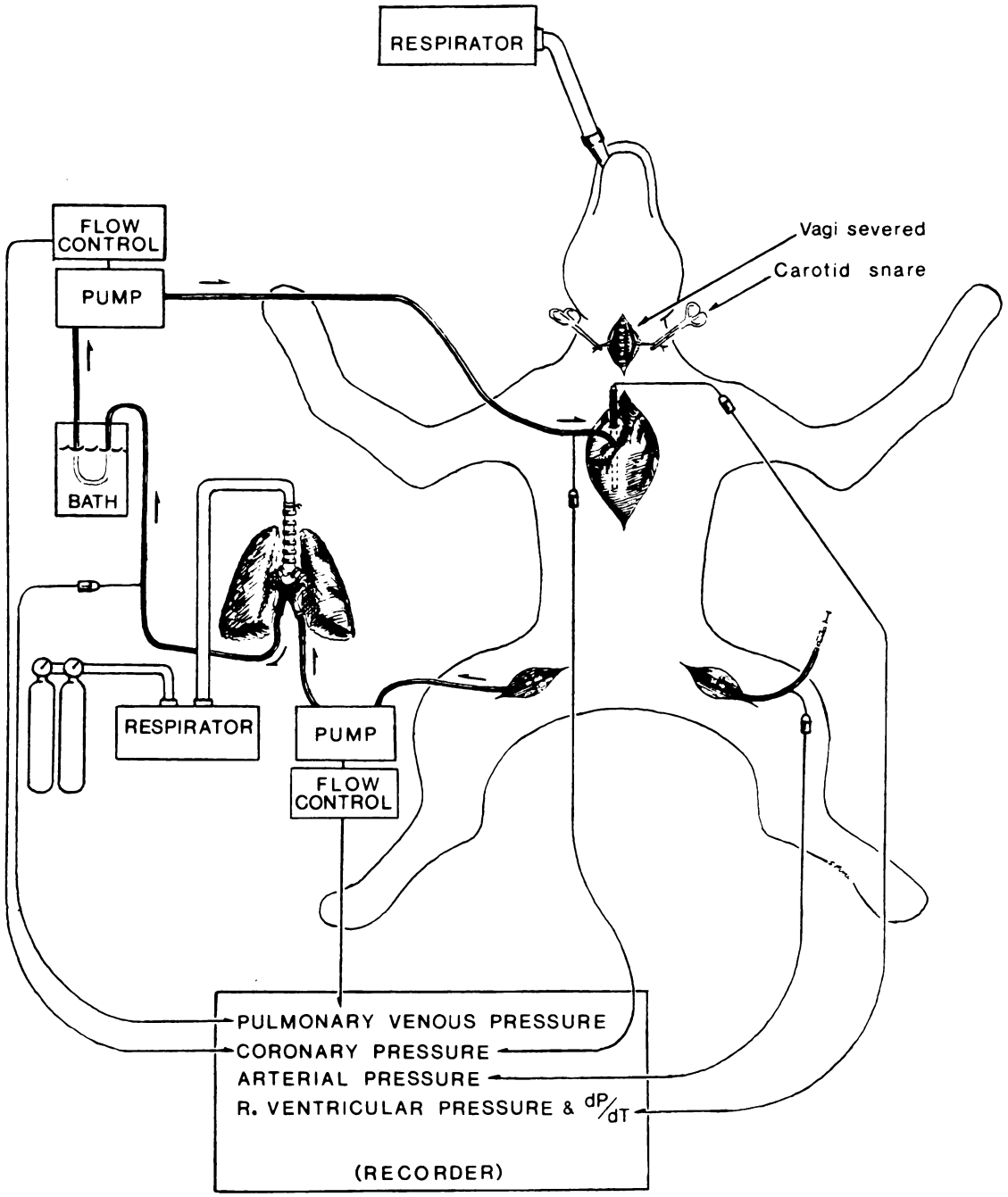

RESPIRATOR
FLOW CONTROL
PUMP
Vagi severed
Carotid snare
BATH
RESPIRATOR
PUMP
FLOW CONTROL
PULMONARY VENOUS PRESSURE
CORONARY PRESSURE
ARTERIAL PRESSURE
R. VENTRICULAR PRESSURE & dP/dT
(RECORDER)

Figure 2

entire range of flows used. This monitoring of the feedback system provided constant pressure perfusion and a permanent recording of instantaneous changes in coronary flow.

II. Studies on the Unanesthetized Dog

In order to determine if the data obtained in the anesthetized, open-chest dog are comparable to the responses found in the intact conscious animal, a second experimental method was employed.

Male mongrel dogs (25-35 Kg) were conditioned for one month prior to instrumentation. Conditioning included examination of the stool for parasites, examination of the blood for microfilaria, and vaccination against rabies, distemper, leptospirosis and hepatitis. During the course of the study, the dogs were maintained on a diet of standard dog chow (Wayne Dog Food, Allied Mills, Inc., Chicago, Ill.) and water ad libitum.

Procaine pencillin (1 million units) and streptomycin (0.5 gm) were given as single intramuscular injection as a prophylactic measure against wound infection on the day of surgery. This treatment was continued once a day for three days postoperatively. Following a fasting period of 24 hours, the animals were anesthetized with thiamylal (5 mg/lb) and maintained on methoxyflurane and oxygen delivered through a cuffed endothracheal tube. The dogs were positioned in a dorsal recumbency and the ventral surface of the chest prepped and draped in the usual manner. Under sterile conditions, the chest was opened by median sternotomy, and the pericardium opened to form a cradle. The proximal 1-3 cm of the right coronary artery was isolated in preparation

for instrumentation. Using the technique of Herd and Barger (1964), a small heparin-filled Teflon catheter was placed in the distal portion of the isolated segment for the measurement of right coronary perfusion pressure, and sutured to the vessel wall with 4-0 polyethylene. Proximal to the catheter, a 4 mm balloon-type occluder (Rhodes Medical Instruments Inc., Woodland Hills, CA.) was placed around the vessel to provide occlusive zero flow determinations, produce reactive hyperemic responses and to produce ischemic flow conditions. Proximal to the occluder, a 2.5 mm electromagnetic flow probe (Zepeda Instruments, Seattle, Wash.) with cables axial to the vessel was placed around the artery. Care was taken to assure that no side branches of the vessel existed between the flow probe and occluder. Electrocardiographic leads were sutured to the epicardial surface of the right ventricle in a region perfused solely by the right coronary artery and placed in the subcutaneous tissue of the back for ECG recording. The cables and catheters were exteriorized through the chest wall and tunneled subcutaneously to exit the skin on the right side approximately 10 cm lateral to the spine. The sternum was then reapproximated with 2.0 stainless steel sutures. The muscle and subcutaneous tissue sutured with 1-0 surgical silk, and the skin incision closed with 1-0 vetafil suture. A chest tube was used to evacuate air from the chest. The animals were allowed to recover for a period of 1-2 weeks before beginning data acquisition. Blood flow was measured with the use of a square wave electromagnetic flowmeter (Zepeda Instruments, Seattle, Wash.) which was demonstrated to be linear over the range of flows measured. Occlusive zero flow determinations were made immediately

before and after each experimental intervention. Right coronary vascular resistance could be calculated from the ratio of right coronary perfusion pressure and right coronary flow.

All recording was made with a Grass Model 7B direct writing polygraph via inputs from Stratham low volume displacement pressure transducers and the Zepeda flowmeter. The dogs were trained to lie quietly on their left side on a table during the experimental protocols.

Because of technical problems, we were unable to calibrate the flow probe in situ as was previously planned. Therefore, since the flow range measured was linear, flow was measured as an artitrary unit using mm divisions on the recorder strip chart.

The rationale for each series of experiments and their respective protocols are described below.

Series I

Using the constant flow perfusion technique, we examined the relationships between pressure and flow, and resistance and flow over the range of 35-175 mmHg in order to determine the autoregulatory characteristics of this bed. This series also examined the effects of adrenergic stimulation (intracoronary norepinephrine infusion and baroreflex sympathetic stimulation) on right coronary resistance at different flow rates both before and after beta blockade with propranolol (3 mg/Kg, Sigma Chemical Co., St. Louis, MO.) in order to evaluate the interaction between flow, neuro-humoral factors and beta receptor activity in the regulation of the right coronary circulation.

Protocol:

1. The pressure-flow relationships were determined over the range of 25-180 mmHg with flow being altered to produce changes in pressure in 25 mmHg steps.
2. Sympathetic stimulation (baroreflex) was studied during perfusion of the coronary at 30 mmHg (low flow conditions).
3. Norepinephrine was infused at a rate of 1 µg/min into the coronary perfusion circuit behind the perfusion pump during the low flow conditions.
4. Sympathetic stimulation (baroreflex) was studied during perfusion of the coronary at 100 mmHg (normal flow conditions).
5. Norepinephrine was infused at a rate of 1 µg/min into the coronary perfusion circuit during normal flow conditions.
6. Sympathetic stimulation (baroreflex) was studied during perfusion of the coronary at 170 mmHg (high flow conditions).
7. Norepinephrine was infused at a rate of 1 µg/min into the coronary perfusion circuit during high flow conditions.
8. Propranolol (3 mg/Kg) was given intravenously and a period of one hour was allowed for the drug to take effect.
9. Repeat steps 2-7.

Series II

The purpose of this series was to evaluate the effect of adrenergic stimulation at various flow rates before and after alpha-blockade with phentolamine (Ciba, Summit, N.J.) in order to determine the role of alpha receptor activation in these responses. The constant flow

preparation was again utilized with the addition of the measurement of right ventricular pressure and its first derivative (dP/dT) from a 6F USCI cardiac catheter advanced from the external jugular vein in the right ventricular chamber, and connected to a Statham pressure transducer, and derivative computer for dP/dT.

Protocol:

1. Sympathetic stimulation (baroreflex) was studied during perfusion of the coronary at 30 mmHg (low flow conditions).
2. Norepinephrine was infused at a rate of 1 µg/min into the coronary perfusion circuit behind the perfusion pump during low flow conditions.
3. Sympathetic stimulation (baroreflex) was studied during perfusion of the coronary at 100 mmHg (normal flow conditions).
4. Norepinephrine was infused at a rate of 1 µg/min into the coronary perfusion circuit during normal flow conditions.
5. Sympathetic stimulation (baroreflex) was studied during perfusion of the coronary at 170 mmHg (high flow conditions).
6. Norepinephrine was infused at a rate of 1 µg/min into the coronary perfusion circuit during high flow conditions.
7. Phentolamine was infused at a rate of 600 µg/min into the coronary perfusion citcuit.
8. Steps 1-6 were repeated during phentolamine infusion.

Series III

The purpose of this series of experiments was 1) to determine what role if any the prostaglandins play in the reactive dilation seen

in response to 20 second interruptions of right coronary flow, and 2) to determine the response of the vascular bed supplied by the right coronary to adrenergic stimulation and systemic hypocapnia (produced by hyperventilation of the animal to yield P_{CO_2} = 18 mmHg) following prostaglandin synthesis blockade by indomethacin. The indomethacin (Sigma Chemical Co.) was prepared by stirring the chemical in a solution of saline (90 ml) and 100 mg.HCO_3 until dissolved. The indomethacin was then infused into the coronary perfusion line at a rate of 2 ml/min. Experimental maneuvers were performed one hour after the administration of the indomethacin to assure its effectiveness. The constant flow perfusion preparation was again used in this series.

Protocol:

All meneuvers in this and subsequent series were performed during normal flow perfusion conditions with initial perfusion pressures set at approximately 100 mmHg.

1. Coronary flow was interrupted for a period of 20 seconds and the degree of reactive dilation was determined following the re-institution of flow.
2. The response to sympathetic stimulation (baroreflex) was determined.
3. The response to 0.25 μg/min intracoronary norepinephrine was obtained.
4. The animal was hyperventilated on room air to reduce the systemic arterial P_{CO_2} and the coronary response was determined.
5. The response to sympathetic stimulation was again studied while

the animal was systemically hypocapnic.

6. The response to 0.25 μg/min norepinephrine was obtained during systemic hypocapnia.
7. Prostaglandin synthesis was blocked by a intravenous 5 mg/Kg dose of indomethacin. One hour was allowed for the drug to take effect and the coronary response to indomethacin was recorded.
8. Steps 1-6 were repeated to observe the responses with prostaglandin synthesis blocked.

Series IV

This series employed the constant flow preparation with an isolated perfused donor lung interposed in the coronary perfusion circuit. The purpose of this series was to determine the local vascular effects of hypoxia (coronary arterial P_{O_2} = 12 mmHg), hypocapnia (P_{CO_2} = 6 mmHg) and the combination of hypoxia and hypocapnia (P_{O_2} = 13, P_{CO_2} = 7 mmHg). Moreover, we determined if these conditions alter the response of the right coronary to adrenergic stimulation.

Protocol:

1. The responses to sympathetic (baroreflex) stimulation were obtained, followed by 0.25 μg/min and 0.50 μg/min intracoronary norepinephrine infusions during perfusion with normoxic, normocapnic blood.
2. The response to local hypocapnia was obtained by hyperventilating the isolated lung on room air.

3. During hypocapnic perfusion, the responses to sympathetic stimulation, 0.25 μg/min and 0.50 μg/min norepinephrine were again obtained.
4. After reaching a control condition by switching back to normoxic normocapnic perfusion, the response to local hypoxia was obtained by ventilating the isolated lung with 5% CO_2. 95% N_2.
5. During hypoxic perfusion, the responses to sympathetic stimulation, 0.25 μg/min and 0.50 μg/min norepinephrine were again obtained.
6. After reaching a control condition by switching back to normoxic, normocapnic perfusion, the response to local hypoxia and hypocapnia was obtained by ventilating the isolated lung with 100% N_2.
7. With hypoxic and hypocapnic perfusion combined, the responses to sympathetic stimulation, 0.25 μg/min and 0.50 μg/min norepinephrine were again obtained.

Series V

In order to simulate a more physiologically normal situation, a constant pressure perfusion preparation was employed for this series experiments which included an isolated perfused donor lung interposed in the coronary perfusion circuit to locally alter coronary blood gas tensions. Indomethacin 5 mg/Kg was infused into the donor lung and experimental animal prior to performing the experimental maneuvers in order to preclude the involvement of the prostaglandins in any of the

responses observed. The purpose of this series was 1) to determine the pressure-flow relationships under these conditions for comparison to the constant flow preparation, 2) to determine the vasoactivity of local hypoxia, hypocapnia and hypercapnia during constant pressure perfusion, and 3) to determine if the effects of adrenergic stimulation are altered when local coronary blood gas tensions are altered.

Protocol:

1. The pressure-flow relationship during constant pressure perfusion were obtained over the range of 50-175 mmHg. Perfusion pressure was increased or decreased in steps of 25 mmHg and the steady state flow responses recorded.
2. The responses to sympathetic (baroreflex) stimulation and 0.25 µg/min intracoronary norepinephrine infusion were obtained. Perfusion pressure was held constant at 100 mmHg for all interventions in this series.
3. The response to local hypocapnia was obtained by hyperventilating the isolated lung on room air.
4. During hypocapnic perfusion, the responses to sympathetic stimulation and 0.25 µg/min norepinephrine infusion were obtained.
5. After reaching a control condition by switching back to normoxic, normocapnic perfusion, the response to local hypercapnia was obtained by ventilating the isolated lung with 15% CO_2. 20% O_2, 65% N_2.

6. During hypercapnic perfusion, the responses to sympathetic stimulation and 0.25 μg/min norepinephrine were again obtained.
7. After reaching a control condition by switching back to normoxic, normocapnic perfusion, the response to local hypoxia was obtained by ventilating the lung with 5% CO_2, 95% N_2.
8. During hypoxic perfusion, the responses to sympathetic stimulation and 0.25 μg/min norepinephrine infusion were again obtained.

Series VI

The purpose of this series was to determine the response of the right coronary circulation of the chronically instrumented unanesthetized dog to various physiological and pharmacological stimuli in order to compare these results with those obtained in the anesthetized preparations. This series presents the vascular responses of the right coronary to brief occlusions of flow of 3 seconds (reactive hyperemia) before and after inhibition of prostaglandin synthesis with 5 mg/Kg indomethacin. It also demonstrates the response to intracoronary bolus injections of NE during control and ischemic conditions, and the response to NE before and after alpha blockade with 1 mg/Kg phentolamine. The relationships between pressure and flow are presented for stepwise changes in perfusion pressure below 100 mmHg in order to determine the autoregulatory response of this vascular bed.

STATISTICAL ANALYSIS

The data presented in the figures and tables of this dissertation were analyzed using the student's t test modified for paired replicates. The experimental design of these experiments was such that a paired analysis was possible for each experimental intervention with initial non-experimental values serving as statistical controls. In the data presented, only the mean and standard error of the mean are depicted. A "p" value of less than 0.05 was taken as the level of statistical significance.

In some cases, it was important to know if the response to a particular stimulus was altered when the baseline conditions were altered. In most cases, altering the baseline conditions altered the initial resistance of the vascular bed. In order to determine if initial resistance was an important factor in the determination of the response to a stimulus, a linear regression analysis was performed for sympathetic stimulation and norepinephrine infusion for 23 and 13 animals respectively. This data is graphically represented in Figure 3. The regression analysis showed a correlation coefficient of 41% and 32% for sympathetic stimulation and norepinephrine infusion, respectively. An analysis of variance for the regression showed no significant correlation between the initial resistance and the change in resistance in response to stimulation or norepinephrine. The poor correlation between these factors is also borne out by the low coefficient of correlation.

Figure 3. Linear regression analysis for initial coronary resistance (R_i) vs. change in resistance (ΔR) for sympathetic (baroreflex) stimulation and norepinephrine infusion.

r = correlation coefficient
resistance = mmHg/ml/min/100 gm

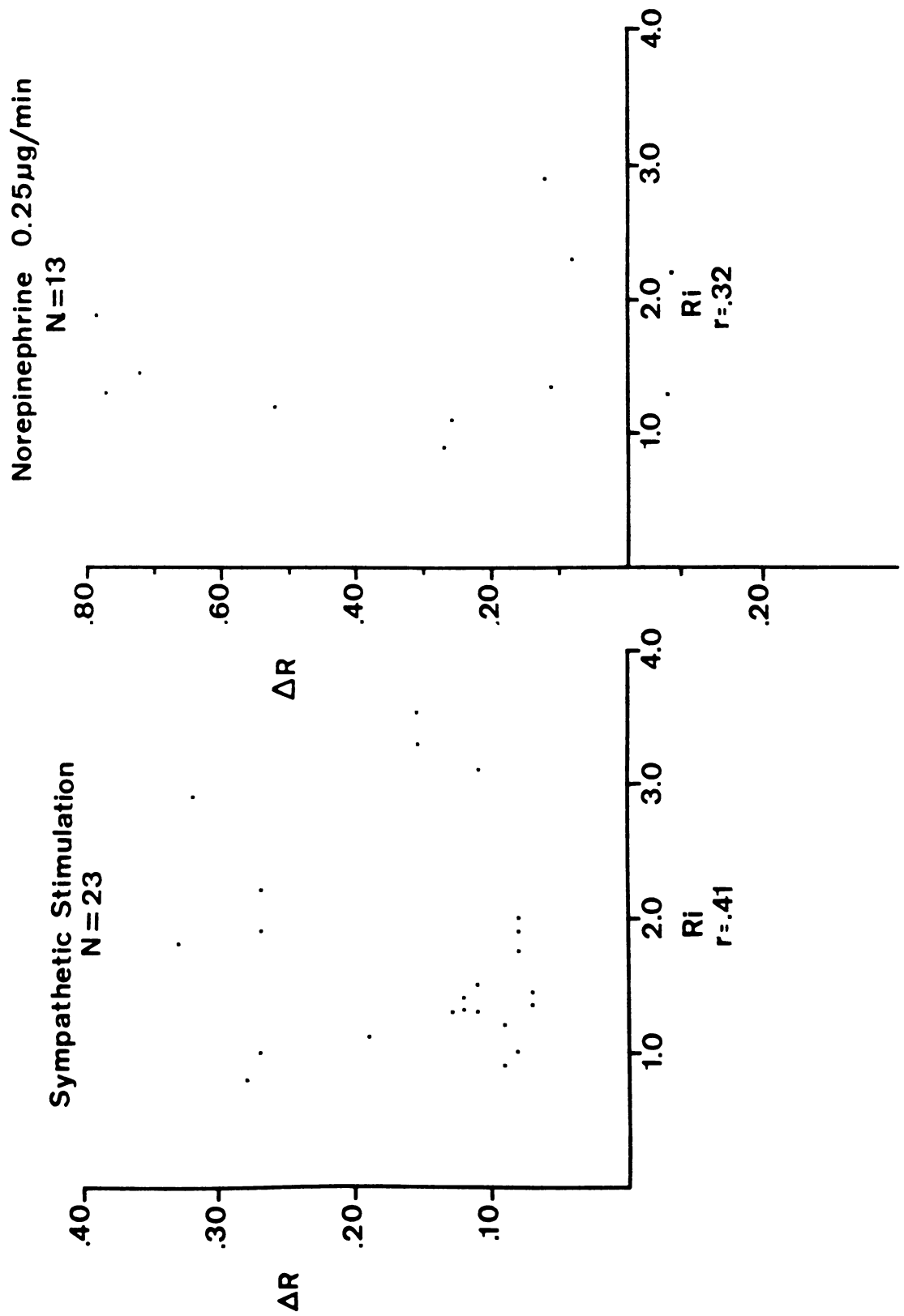

Norepinephrine 0.25µg/min
N=13
ΔR
.80
.60
.40
.20
1.0
2.0
3.0
4.0
Ri
r=.32
Sympathetic Stimulation
N=23
ΔR
.40
.30
.20
.10
1.0
2.0
3.0
4.0
Ri
r=.41

Figure 3

This analysis suggests that over the range of initial resistances studied, the response to a stimulus was not dependent on the initial resistance of the vascular bed. With this in mind, in order to determine if a response was altered when baseline or background conditions were changed, the absolute change in resistance (ΔR) for the control response was compared (using Student's t test, or paired t test) to the absolute change in resistance ($\Delta R'$) for the experimental response (that obtained during altered background conditions). It was felt that this type of analysis was preferential to a comparison of the percent changes from one group to that of another since percent change normalizes the data for initial resistance, a factor shown not to be important by the regression analysis. However, for each case in which it was desirable to determine whether or not a response was altered, both an analysis of ΔR as well as percent change was performed. Both of these analyses provided the same results in all cases.

RESULTS

Series I

Figure 4 presents average data from nine experiments in which the steady state effects of sympathetic (baroreflex) stimulation on heart rate, arterial blood pressure and right coronary vascular resistance were examined at normal flow rates (16 ml/min), low flow rates (4.5 ml/min) and high flow rates (27 ml/min) before and after beta blockade in vagotomized dogs. These flows produced coronary perfusion pressures of 106, 42 and 168 mmHg before beta blockade and 129, 55, and 188 mmHg after beta blockade, respectively. At each flow rate before beta block, sympathetic stimulation produced a significant increase in heart rate, arterial pressure and coronary resistance. By analyzing the change in resistance (ΔR) it was found that the vasoconstriction seen at normal flow was greater than that seen at high flow. The vasoconstriction seen at low flow was also greater than that seen at high flow, suggesting that the degree of sympathetic vasoconstriction is increased as flow is decreased. Following beta blockade with 3 mg/Kg d-l propranolol, resting coronary vascular resistance increased significantly by 38%. Sympathetic stimulation during these conditions resulted in a slight yet significant increase in heart rate, and increase in arterial pressure and coronary resistance at each of the three flow rates. The coronary response to sympathetic stimulation after beta blockade was

Figure 4. Effects of sympathetic stimulation (SS) via corotid occlusion during constant flow perfusion of the right coronary artery on heart rate, mean arterial blood pressure (MABP) and coronary vascular resistance (CVR) at normal flow (NF), low flow (LF) and high flow (HF) rates, before and after beta blockade with propranolol (3 mg/Kg).

N = 9
* = $P < 0.05$ compared to control
bars represent mean and standard error of the mean
C = control

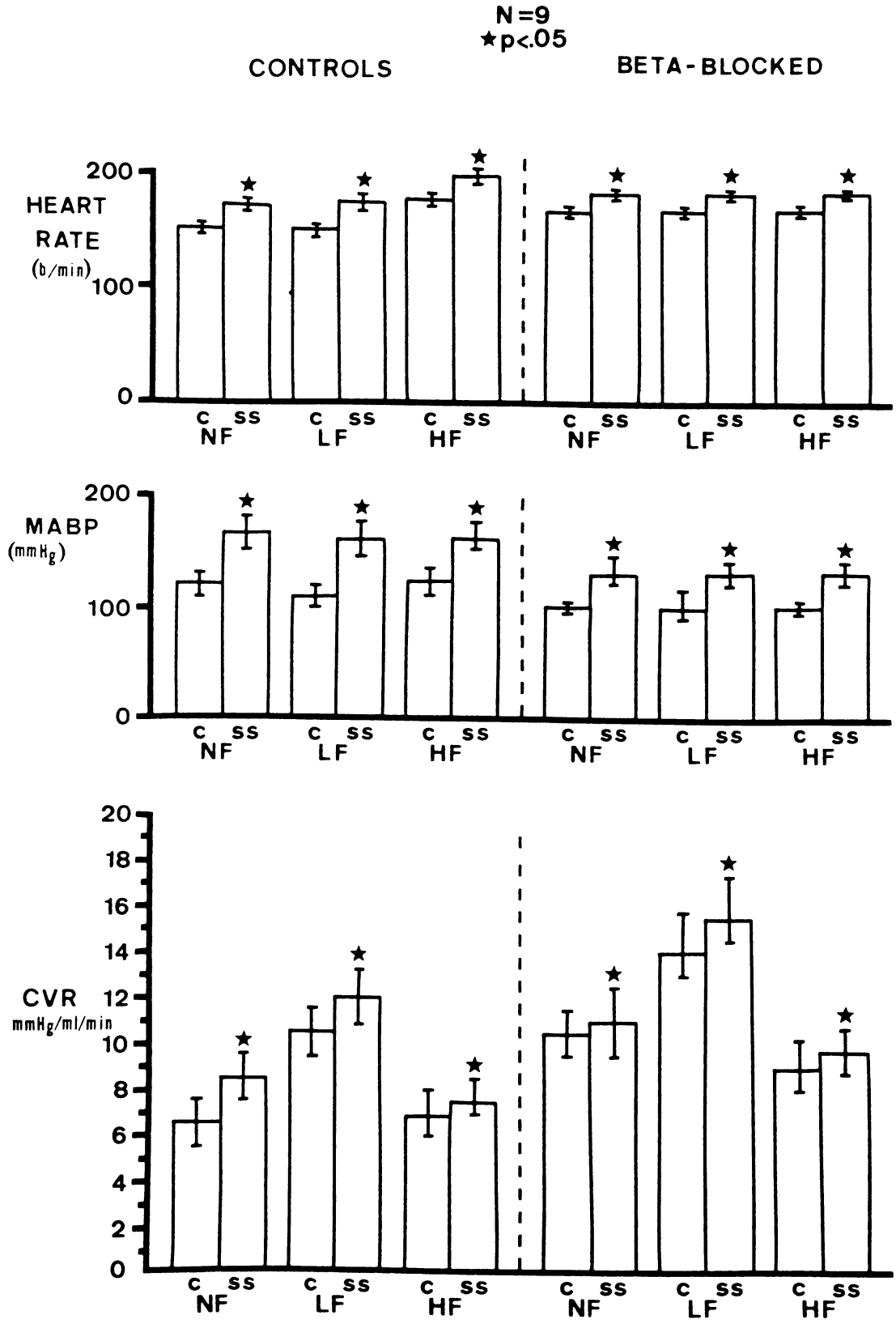

N=9
★p<.05
CONTROLS
BETA-BLOCKED
HEART RATE (b/min)
200
100
0
MABP (mmHg)
200
100
0
CVR mmHg/ml/min
20
18
16
14
12
10
8
6
4
2
0
C SS
NF
LF
HF

Figure 4

not different from that before beta blockade for any of the three flow rates studied.

Figure 5 presents data obtained in Series I in which the steady state effects of intracoronary norepinephrine infusion (1 μg/min) on heart rate, arterial blood pressure and right coronary vascular resistance were examined at the same three flow rates described previously, both before and after beta blockade. During control conditions norepinephrine produced a significant increase in heart rate, but had no effect on arterial pressure or coronary resistance at any of the three flow rates studied. Following beta blockade, norepinephrine had no effect on heart rate or blood pressure, yet produced a significant increase in coronary resistance at each of the three flow rates studied. The degree of coronary constriction produced by norepinephrine was not different between each of the three flow rates studied.

Figure 6 depicts the relationships between pressure and flow as well as resistance and flow through the right coronary artery of eight animals during constant flow perfusion. Flow was varied in a stepwise manner over a range of 3 to 60 ml/min., and the steady state perfusion pressures recorded at each step. The pressures ranged from 25-180 mmHg. Resistances were also calculated and related to coronary blood flow. The upper panel of Figure 3 demonstrates that as flow is decreased, resistance remains relatively constant until pressure is decreased below 30 mmHg at which point resistance increases substantially. The bottom panel depicts the pressure-flow relationships, and demonstrates that this relationship is virtually linear over the range studied.

Figure 5. Effect of 1 μg/min intracoronary infusion of norepinephrine (NE) during constant flow perfusion of the right coronary artery on heart rate, mean arterial blood pressure (MABP) and coronary vascular resistance (CVR) at three different flows, normal flow (NF), low flow (LF) and high flow (HF), before and after beta blockade with propranolol (3 mg/Kg).

N = 9
* = $P < 0.05$ compared to control
Bars represent mean and standard error of the mean
C = control

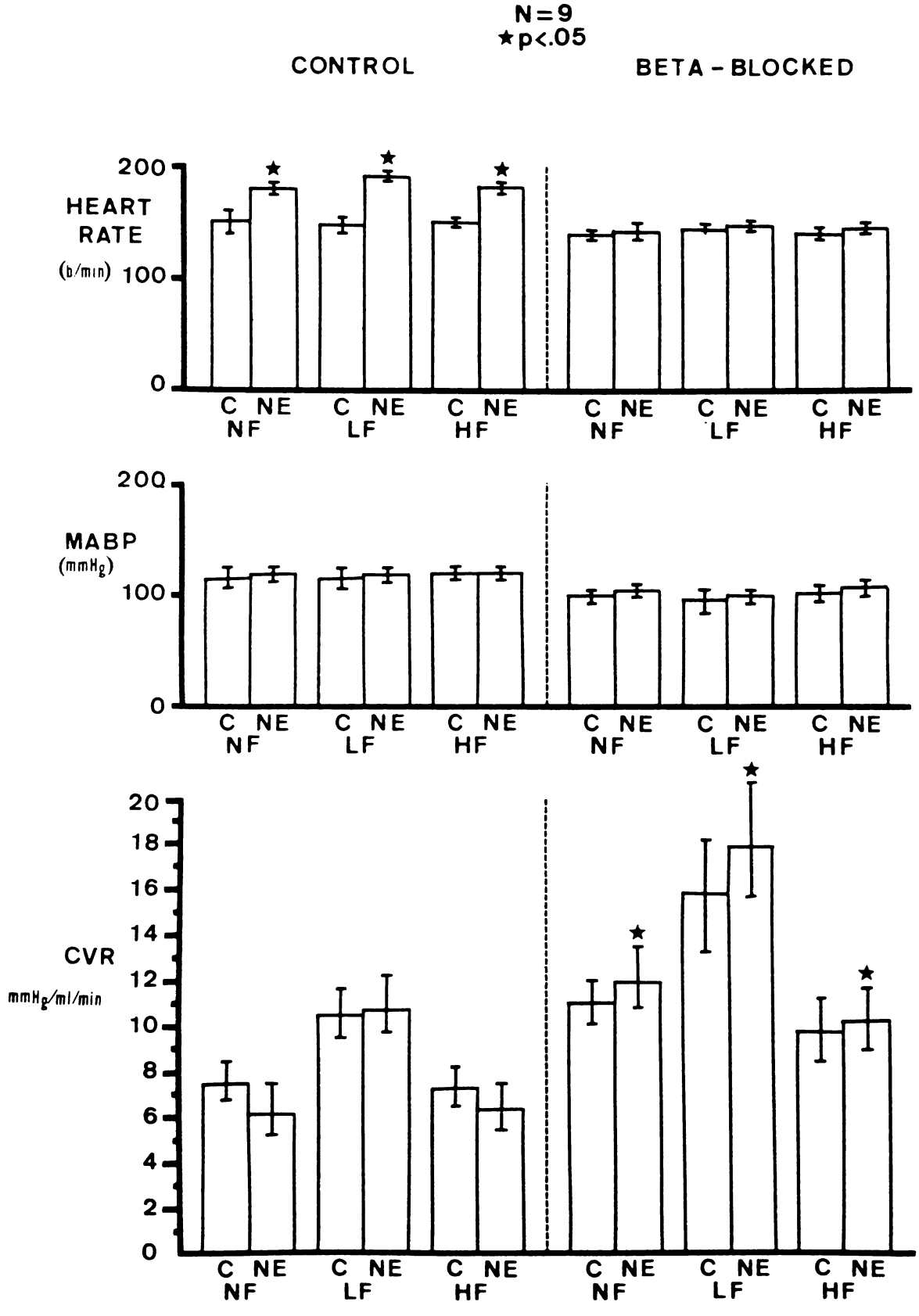

N=9
★p<.05
CONTROL
BETA-BLOCKED
HEART RATE
(b/min)
200
100
0
MABP
(mmHg)
CVR
mmHg/ml/min
20
18
16
14
12
10
8
6
4
2
C NE
NF
LF
HF

Figure 5

Figure 6. Relationship between pressure and flow, as well as resistance and flow during constant flow perfusion of the right coronary artery.

N = 8

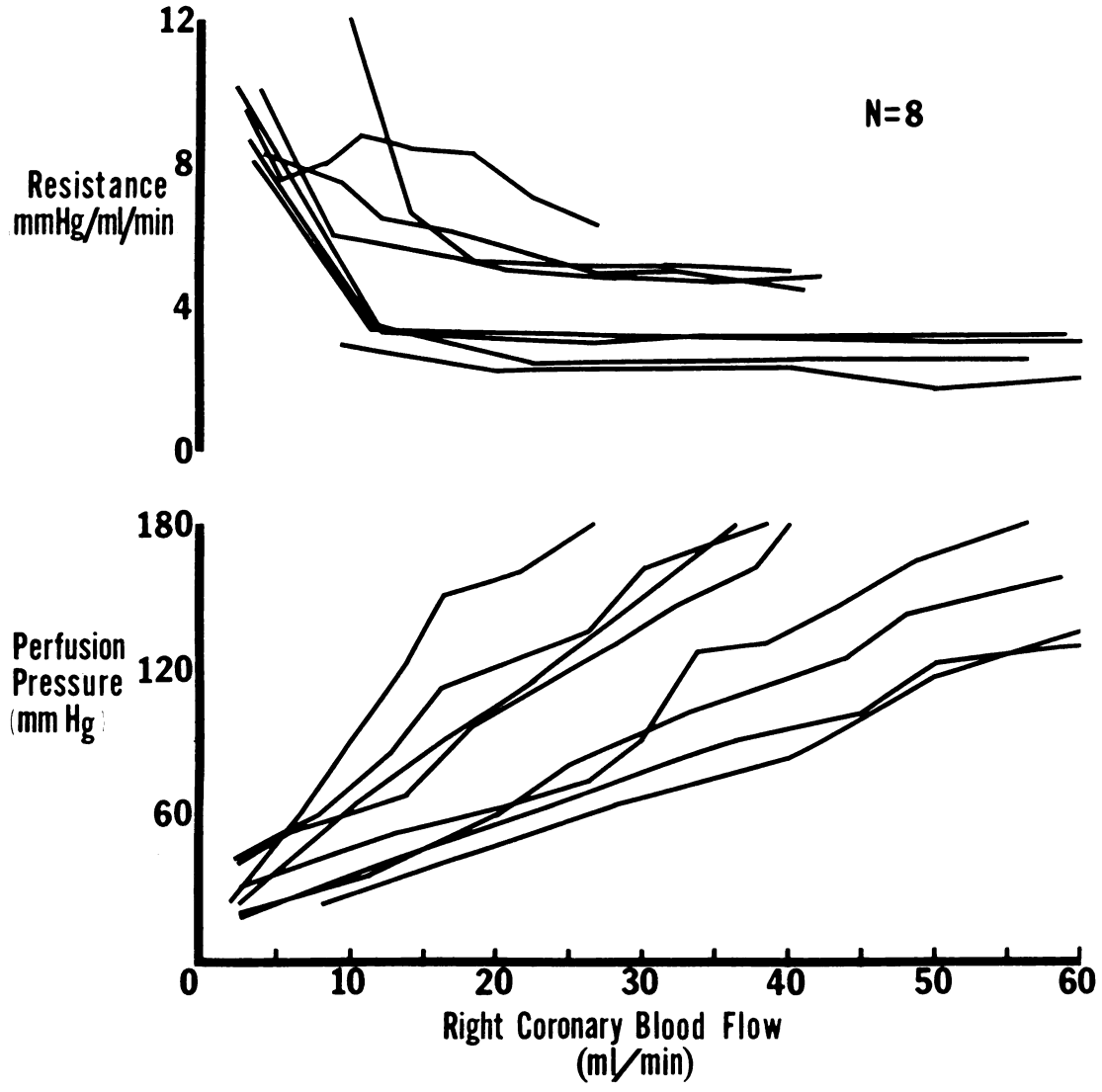

12
8
4
0
Resistance
mmHg/ml/min
N=8
180
120
60
Perfusion
Pressure
(mm Hg)
0
10
20
30
40
50
60
Right Coronary Blood Flow
(ml/min)

Figure 6

Mean arterial pressure, heart rate and right atrial pressure were not changed over the range of perfusion pressures studied.

Series II

Table 1 presents data demonstrating the effect of sympathetic stimulation, intracoronary phentolamine infusion and stimulation after alpha blockade with phentolamine infusion on heart rate, arterial blood pressure, right ventricular systolic pressure and its first derivative dP/dT, right coronary perfusion pressure and coronary resistance. Right ventricular diastolic pressure is not presented in this or any subsequent data analyses as it always fell within normal limits and was never significantly altered by experimental intervention. Coronary flow was held constant, and averaged 62 ml/min/100 g. In these experiments, sympathetic stimulation produced no change in heart rate or right ventricular systolic pressure, but increased arterial blood pressure, dP/dT, coronary pressure and resistance. Intracoronary phentolamine infusion produced no significant change in any of the measured variables. Sympathetic stimulation during alpha blockade produced increases in arterial blood pressure, right ventricular systolic pressure and dP/dT. However, no change was seen in heart rate, coronary perfusion pressure or coronary resistance.

Table 2 depicts the effects of intracoronary norepinephrine infusion before and after alpha blockade with an intracoronary infusion of phentolamine. Norepinephrine produced a slight increase in arterial blood pressure, a decrease in coronary perfusion pressure and coronary

Table 1. Effect of sympathetic stimulation via baroreflex during constant flow perfusion on heart rate, mean arterial blood presure (MABP), right ventricular systolic pressure (RVSP), right ventricular dp/dt, right coronary perfusion pressure (RCA_{pp}) and right coronary vascular resistance (CVR) before and after alpha receptor blockade with 600 µg/min intracoronary infusion of phentolamine. C = control; E = experimental
* = $p < 0.05$ compared to control.

	N=4 HEART RATE b/min		N=8 MABP mmHg		N=4 RVSP mmHg		N=4 RV dp/dt mmHg/sec		N=8 RCA_{pp} mmHg		N=8 CVR mmHG/ml/min/100g	
	C	E	C	E	C	E	C	E	C	E	C	E
Sympathetic stimulation	180 ±11	180 ±11	108 ±4	144* ±8	24 ±2	27 ±2	1537 ±201	2137* ±292	111 ±3	117* ±3	2.02 ±.32	2.13* ±.33
Phentolamine (600 µg/min)	170 ±10	210 ±10	104 ±2	99 ±2	21 ±3	25 ±5	2062 ±326	2362 ±384	126 ±6	107 ±6	2.28 ±.43	1.92 ±.31
Sympathetic stimulation during Phentolamine	210 ±10	210 ±19	99 ±2	121* ±4	25 ±4	28* ±4	2350 ±375	2475* ±834	108 ±6	108 ±6	1.93 ±.3	1.91 .2

Table 2. Effect of 1 μg/min. intracoronary infusion of norepinephrine during constant flow perfusion on heart rate, mean arterial blood pressure (MABP), right ventricular systolic pressure (RVSP), right ventricular dp/dt, right coronary perfusion pressure (RCA_{pp}) and right coronary vascular resistance (CVR) before and after alpha receptor blockade with 600 μg/min intracoronary infusion of phentolamine. C = control; E = experimental; * = $p < 0.05$ compared to control; values represent mean ± standard error of the mean.

	N=4 HEART RATE b/min		N=8 MABP mmHg		N=4 RVSP mmHg		N=4 RV dp/dt mmHg/sec		N=8 RCA_{pp} mmHg		N=8 CVR mmHg/ml/min/100g	
	C	E	C	E	C	E	C	E	C	E	C	E
Norepinephrine 1 μg/min i.c.	180 ±11	220 ±11	109 ±4	117* ±4	25 ±2	32 ±4	1662 ±167	2225 ±347	112 ±4	74* ±5	2.04 ±.32	1.26* ±.13
Norepinephrine During Phentolamine	210 ±19	210 ±10	91 ±3	92 ±4	23 ±4	30* ±5	2000 ±204	2612 ±311	111 ±8	77* ±7	1.99 ±.36	1.39* ±.29

resistance. No change was seen in heart rate, right ventricular systolic pressure or dP/dT. Following alpha blockade, norepinephrine infusion resulted in an increase in right ventricular systolic pressure, a decrease in coronary perfusion pressure and vascular resistance, and no change in heart rate, arterial pressure or dP/dT. The effect of norepinephrine infusion on coronary resistance was not different before alpha blockade when compared to that obtained after alpha blockade.

Figure 7 demonstrates the effects of sympathetic stimulation on arterial blood pressure, coronary perfusion pressure and coronary resistance at low and high flow rates of 28 and 166 ml/min/100 g before and after alpha blockade with phentolamine. At low flow, stimulation produced a significant increase in arterial pressure and coronary perfusion pressure which indicates coronary vasoconstriction. Coronary resistance was not significantly different from control. Following alpha blockade, the increase in coronary perfusion pressure was blocked during sympathetic stimulation, while arterial blood pressure increased significantly.

At the high flow rate, sympathetic stimulation produced a significant increase in arterial blood pressure, coronary perfusion pressure and coronary resistance. After alpha blockade, sympathetic stimulation produced an increase in arterial blood pressure but no change occurred in perfusion pressure or resistance. It is noted that phentolamine was given intracoronary as an infusion which effectively blocked the coronary alpha receptors and not the systemic alpha receptors located peripherally, hence the rise in arterial blood pressure during sympathetic stimulation.

Figure 7. Effect of sympathetic stimulation (SS) via carotid occlusion, during constant flow perfusion of the right coronary artery on mean arterial blood pressure (MABP), coronary perfusion pressure and coronary vascular resistance (CVR) at low flow and high flow rates, before and after alpha receptor blockade with 600 µg/min. intracoronary infusion of phentolamine.

N = 4
Bars represent mean and standard error of the mean
* = $P < 0.05$ compared to control

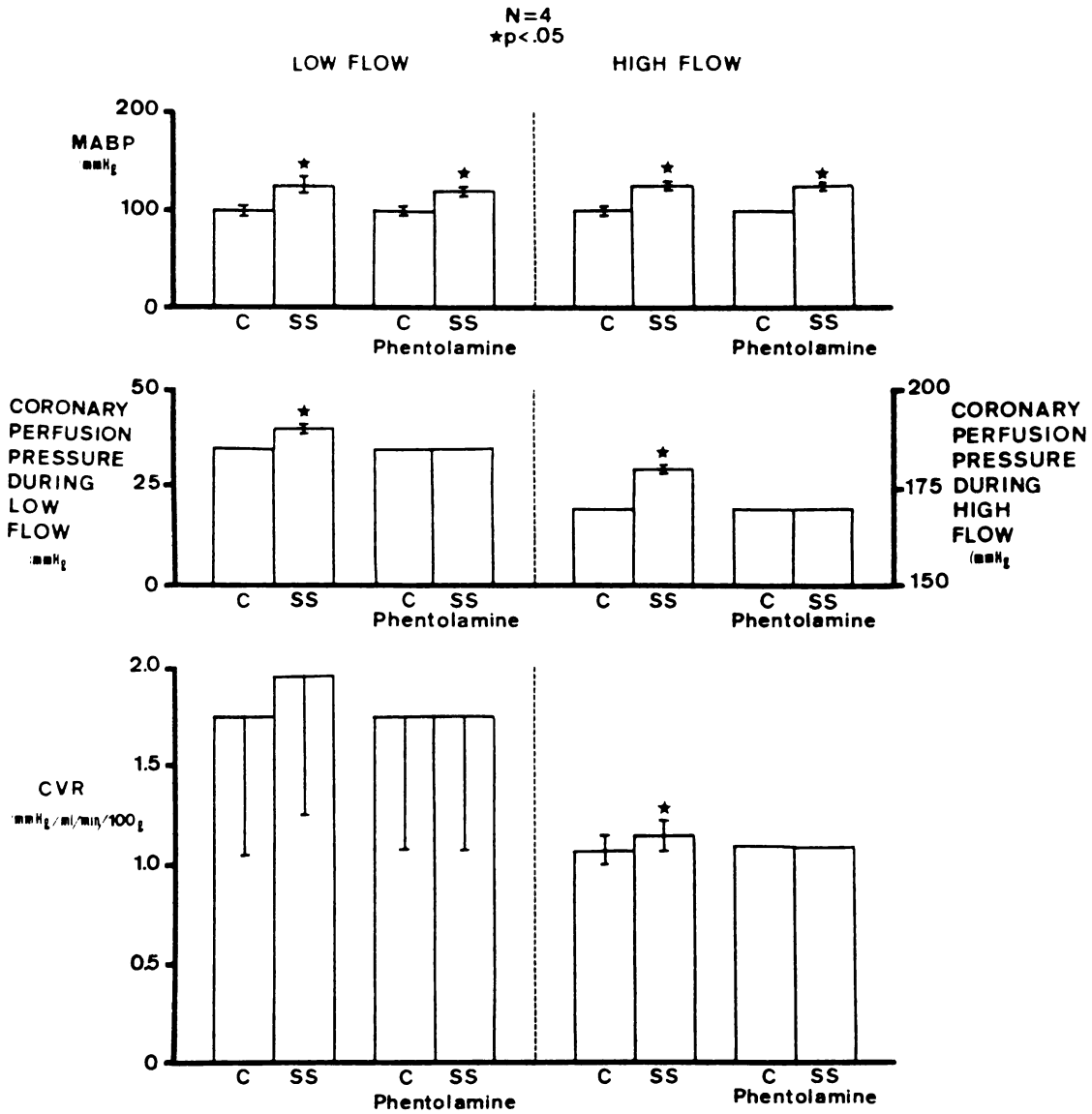

N=4
★p<.05
LOW FLOW
HIGH FLOW
MABP
200
100
0
C SS C SS
Phentolamine
C SS C SS
Phentolamine
CORONARY PERFUSION PRESSURE DURING LOW FLOW
50
25
0
CORONARY PERFUSION PRESSURE DURING HIGH FLOW
200
175
150
CVR
2.0
1.5
1.0
0.5
0

Figure 7

Figure 8 illustrates the effects of intracoronary norepinephrine infusion on arterial blood pressure, coronary perfusion pressure and coronary resistance before and after alpha blockade by intracoronary phentolamine infusion at low and high flow rates (same as those in Figure 4). At the low flow rate, norepinephrine caused a slight but significant increase in arterial blood pressure and no change in coronary perfusion pressure or resistance. Following alpha blockade norepinephrine produced no change in arterial blood pressure but produced a significant decrease in coronary pressure and resistance.

At the high flow rate, norepinephrine caused an increase in arterial blood pressure, and a decrease in coronary perfusion pressure and coronary resistance. Following alpha blockade, norepinephrine had no effect on arterial blood pressure, and significantly decreased coronary pressure and resistance. The fall in coronary resistance before alpha blockade was not different from that after alpha blockade in response to norepinephrine.

Series III

Figure 9 presents data from seven experiments in which the effects of sympathetic stimulation, intracoronary norepinephrine infusion and systemic hypocapnia on arterial blood pressure, coronary perfusion pressure and coronary resistance during constant flow perfusion were observed. In this series, flow averaged 84 ml/min/100 g. As had been shown previously, sympathetic stimulation produced an increase in arterial blood pressure and coronary perfusion pressure, and an increase

Figure 8. Effect of a 1 μg/min intracoronary infusion of norepinephrine (NE) during constant flow perfusion of the right coronary artery on mean arterial pressure (MABP), coronary perfusion pressure and coronary vascular resistance (CVR) at low flow and high flow rates, before and after alpha receptor blockade with 600 μg/min intracoronary infusion of phentolamine.

N = 4
Bars represent mean and standard error of the mean
* = $P < 0.05$ compared to control

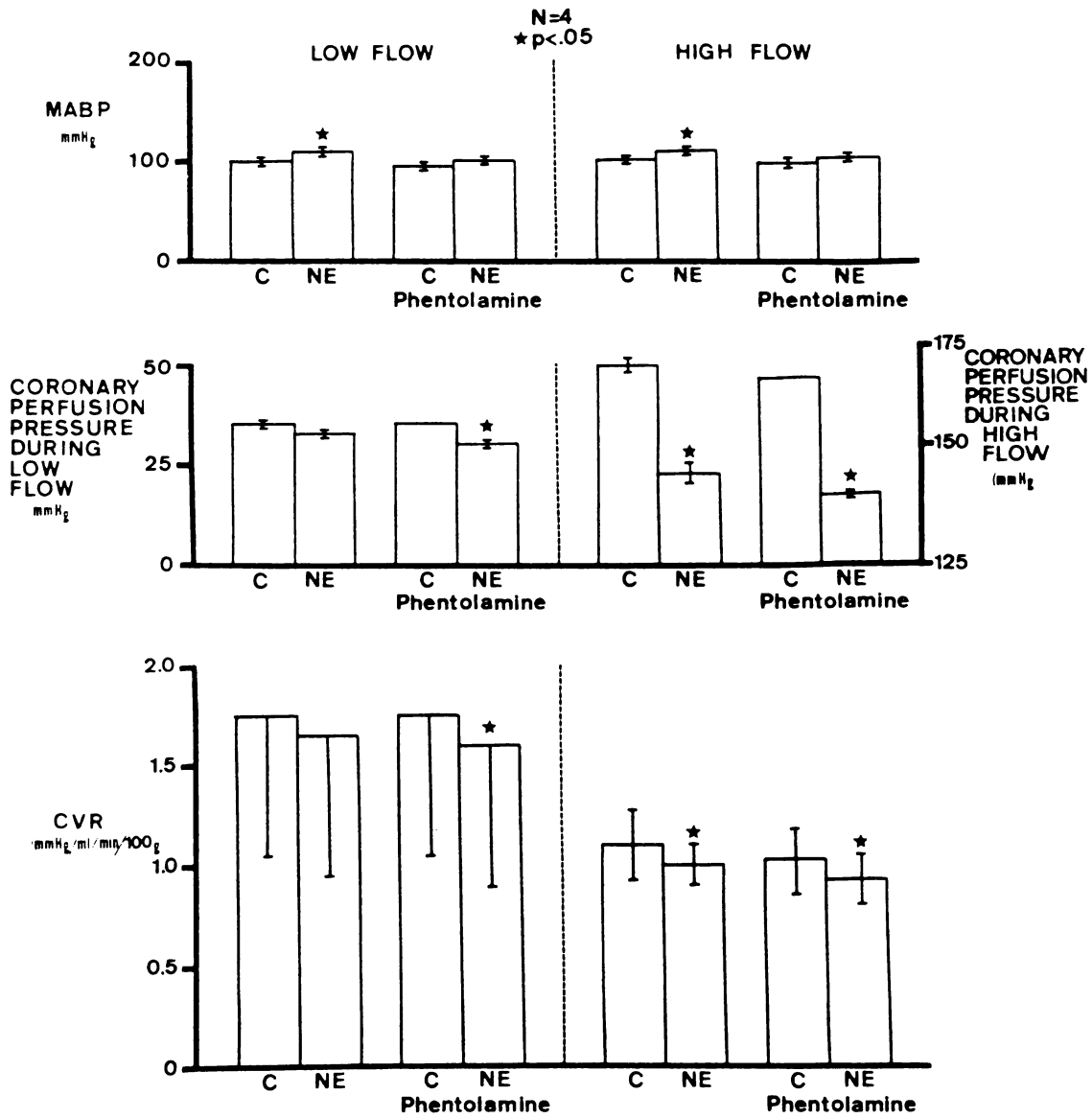

N=4
★p<.05
LOW FLOW
HIGH FLOW
MABP
mmHg
200
100
0
C NE C NE
Phentolamine
C NE C NE
Phentolamine
CORONARY PERFUSION PRESSURE DURING LOW FLOW
mmHg
50
25
0
CORONARY PERFUSION PRESSURE DURING HIGH FLOW
(mmHg
175
150
125
CVR
mmHg/ml/min/100g
2.0
1.5
1.0
0.5
0

Figure 8

Figure 9. Effect of sympathetic stimulation (SS) via carotid occlusion, 0.25 μg/min intracoronary norepinephrine infusion (NE), systemic hypocapnia (HC) and the interaction of these factors on mean arterial blood pressure (MABP), coronary perfusion pressure and coronary vascular resistance (CVR) during constant flow perfusion.

Bars represent mean and standard error of the mean
* = $P < 0.05$ compared to control

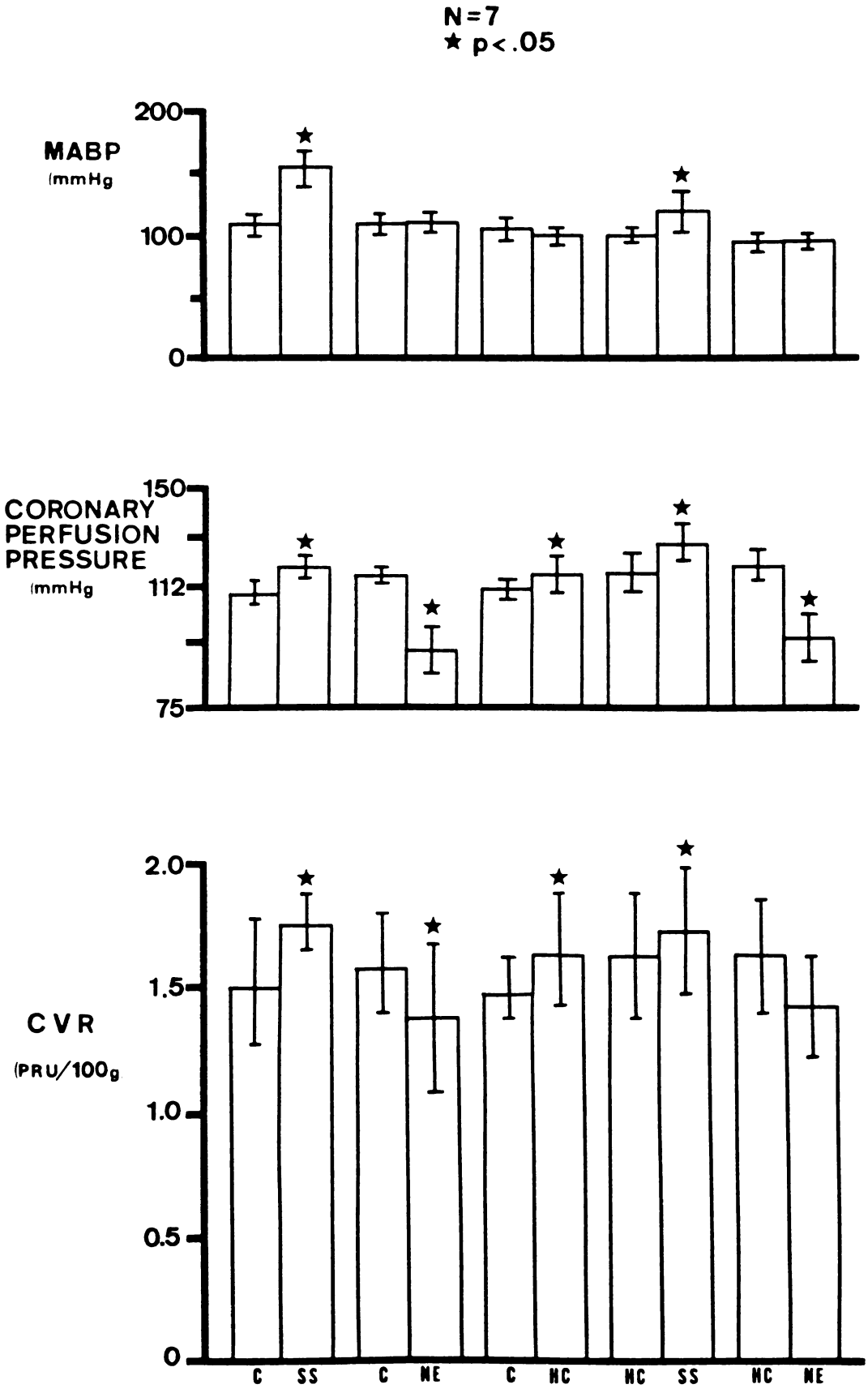

N=7
★ p<.05
MABP
(mmHg
200
100
0
CORONARY
PERFUSION
PRESSURE
(mmHg
150
112
75
CVR
(PRU/100g
2.0
1.5
1.0
0.5
0
C
SS
C
NE
C
HC
HC
SS
HC
NE

Figure 9

in coronary resistance. Norepinephrine on the other hand had no effect on arterial blood pressure and decreased coronary perfusion pressure and coronary resistance. Systemic hypocapnia alone resulted in no change in arterial pressure but produced an increase in coronary pressure and resistance which was not different in magnitude from that produced by sympathetic stimulation alone. While the animals were hypocapnic, the responses to sympathetic stimulation and norepinephrine infusion were again observed. Under these conditions (which produced an increase in pH to 7.58 and P_{O_2} to 103 mmHg, and a decrease in P_{CO_2} 18 mmHg from control values of 7.38, 86 and 36, respectively), sympathetic stimulation produced an increase in arterial blood pressure, and an additional increase in coronary pressure and coronary resistance. The increase in coronary resistance in response to stimulation during systemic hypocapnia was not statistically different from the rise which occurred during control (normocapnic) conditions.

Norepinephrine infusion during hypocapnia produced no change in arterial pressure, but produced coronary vasodilation as demonstrated by the decrease in coronary perfusion pressure. Coronary resistance was not significantly altered. This statistical result was due to the fact that one animal in the group exhibited an increase in coronary resistance while the rest showed a decrease thereby rendering the difference to be non-significant by paired analysis. However, the trend for coronary vasodilation is apparent. The decrease in perfusion pressure during hypocapnia in response to norepinephrine was not different from that seen during normocapnic control conditions, indicating that the response to norepinephrine is not altered by hypocapnia.

Figure 10 depicts the responses to sympathetic stimulation and norepinephrine infusion obtained before and after the blockade of prostaglandin synthesis with a 5 mg/Kg i.v. dose of indomethacin. The control response to adrenergic stimulation were similar to those mentioned in Figure 9. Indomethacin had no significant effect on arterial blood pressure, coronary pressure or coronary resistance. However, indomethacin did cause an increase of approximately 10% in coronary pressure and resistance in eight out of nine animals studied. Following administration of indomethacin, sympathetic stimulation produced an increase in arterial pressure, coronary pressure and coronary resistance which was not significantly different from that which occurred prior to indomethacin.

Norepinephrine infusion after indomethacin produded no change in arterial pressure, coronary pressure or coronary resistance. As in the previous analysis (Figure 9), one animal exhibited an increase in resistance and perfusion pressure while all others exhibited a decrease, therefore rendering the analysis nonsignificant. Therefore, it is not clear whether or not indomethacin altered the response to norepinephrine.

Figure 11 presents data examining further interactions between adrenergic stimulation, hypocapnia and indomethacin. The first pair of bars represent the effect of systemic hypocapnia following administration of indomethacin. Hypocapnia produced a significant decrease in arterial blood pressure, and a significant increase in coronary perfusion pressure and coronary resistance which was not different in magnitude from that which occurred prior to indomethacin. The second pair

Figure 10. Effect of sympathetic stimulation (SS) via carotid occlusion, 0.25 μg/min intracoronary norepinephrine infusion (NE), 5 mg/Kg intracoronary infusion of indomethacin (I) and the interaction of these factors on mean arterial blood pressure (MABP), coronary perfusion pressure and coronary vascular resistance (CVR) during constant flow perfusion of the right coronary artery.

Bars represent mean and standard error of the mean
* = $P < 0.05$ compared to control

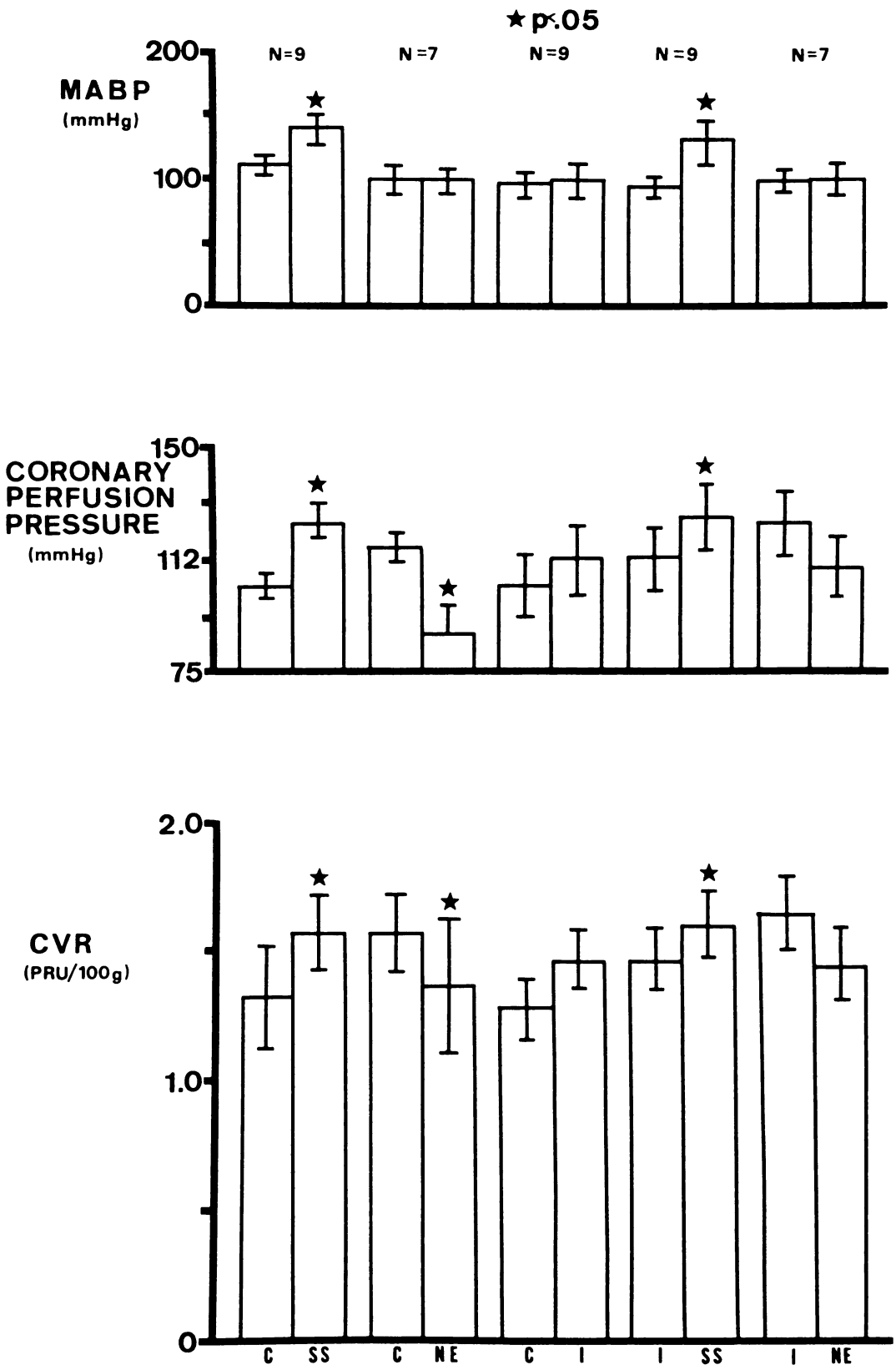

★p<.05
N=9
N=7
N=9
N=9
N=7
MABP
(mmHg)
200
100
0
CORONARY
PERFUSION
PRESSURE
(mmHg)
150
112
75
CVR
(PRU/100g)
2.0
1.0
0
C
SS
C
NE
C
I
I
SS
I
NE

Figure 10

Figure 11. Interaction of indomethacin (I), systemic hypocapnia (HC), sympathetic stimulation (SS) and 0.25 μg/min intracoronary norepinephrine infusion (NE) in relation to their effects on mean arterial blood pressure (MABP), coronary perfusion pressure and coronary vascular resistance (CVR) during constant flow perfusion of the right coronary artery.

Bars represent mean and standard error of the mean
* = $P < 0.05$ compared to control

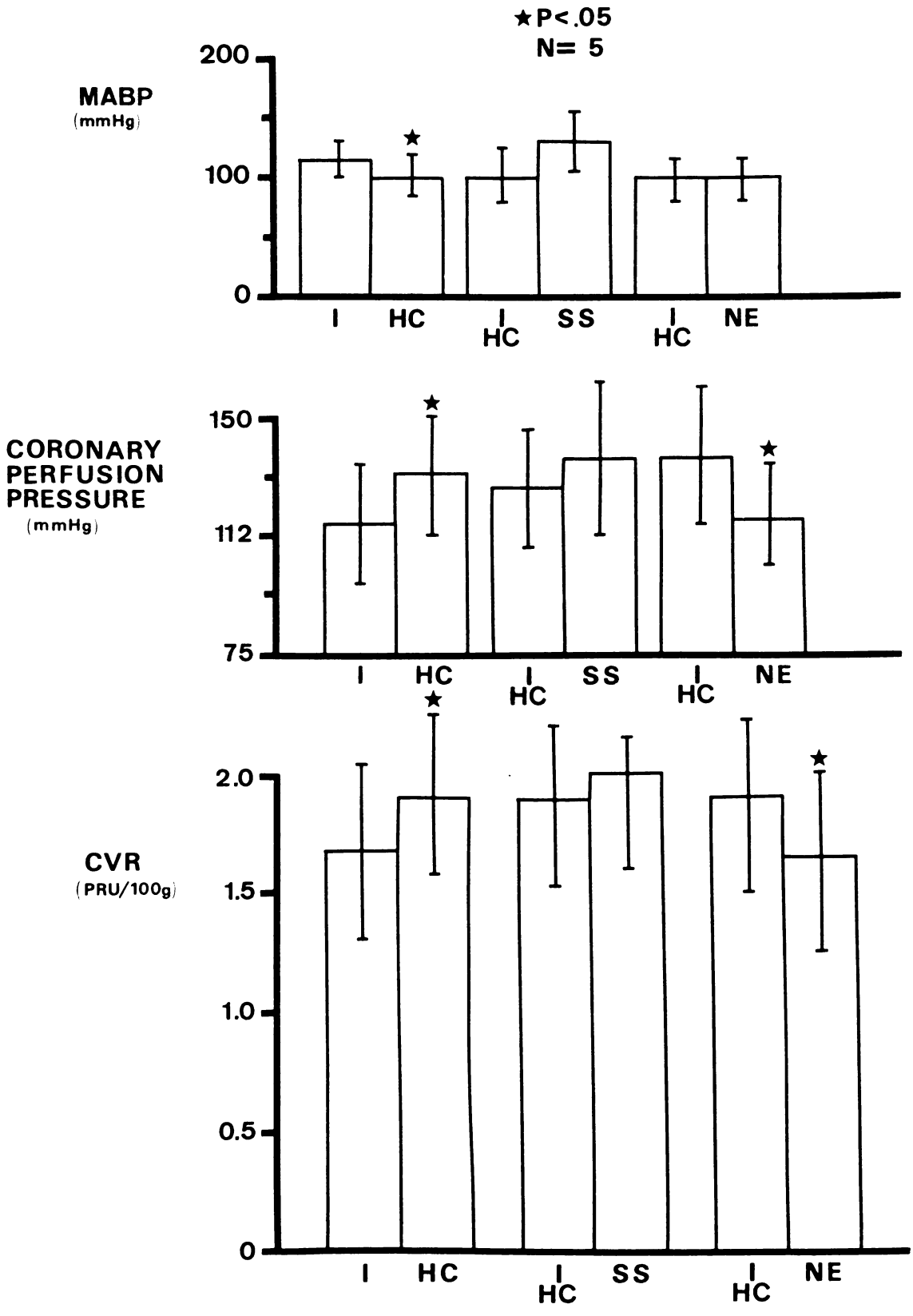

★P<.05
N= 5
MABP
(mmHg)
200
100
0
I
HC
I
HC
SS
I
HC
NE
CORONARY
PERFUSION
PRESSURE
(mmHg)
150
112
75
I
HC
I
HC
SS
I
HC
NE
CVR
(PRU/100g)
2.0
1.5
1.0
0.5
0
I
HC
I
HC
SS
I
HC
NE

Figure 11

of bars represent the effect of sympathetic stimulation during hypocapnia and indomethacin combined. No effect was seen on arterial pressure, coronary pressure or coronary resistance. Out of the five animals studied in this group, four animals had responses that were similar to the responses seen during control conditions, while one animal in this group was unresponsive to sympathetic stimulation. Therefore, whether or not the combination of hypocapnia and indomethacin alters the coronary response to sympathetic stimulation is unclear. However, it appears that the differences may be minimal to none. The third pair of bars represent the effect of norepinephrine infusion in the presence of hypocapnia and indomethacin combined. During these conditions norepinephrine had no effect on blood pressure but produced a significant decrease in coronary pressure and coronary resistance which was not different in magnitude from that which occurred during control conditions.

Figure 12 demonstrates the response of the right coronary circulation to a 20 second interruption of flow before and after the inhibition of prostaglandin synthesis with indomethacin. Following indomethacin, there was no change in the percent decrease in perfusion pressure measured immediately after the reinstitution of flow. However, the magnitude of the reactive dilation, as determined by the area above the curve, as well as the duration of the response were significantly less by 24% and 7%, respectively. Pressure flow curves were also obtained during constant flow perfusion before and after the administration of indomethacin. No changes were seen in the pressure-flow or

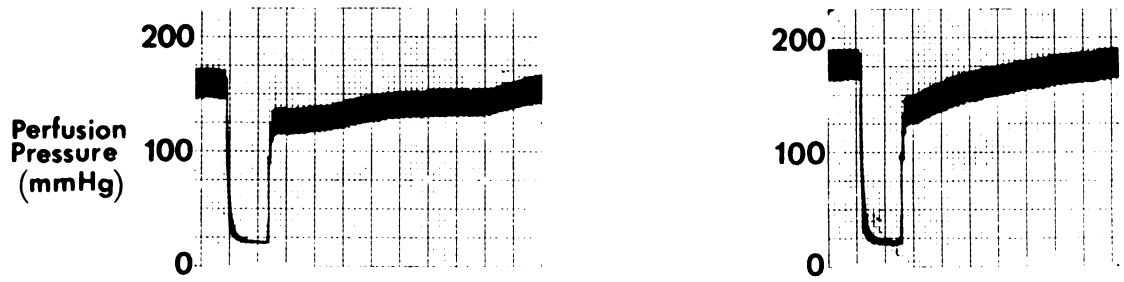
Figure 12. Response of the right coronary vascular bed perfused at constant flow to 20 second interruptions of flow before and after prostaglandin synthesis inhibition with 5 mg/Kg indomethacin.

N = 8
* = $P < 0.05$ compared to control
%ΔPP = percent change in perfusion following flow interruption compared to control
Area = area attributed to reactive dilation
Duration = time from the point of re-institution of flow to the point at which pressure returns to control
Chart speed = 0.25 mm/sec

RIGHT CORONARY RESPONSE TO 20 SEC INTERRUPTION OF FLOW

CONTROL

INDOMETHACIN 5 MG/KG



EXPT.#	AREA MM^2	%ΔPP	DURATION (SEC)	AREA MM^2	%ΔPP	DURATION (SEC)
1	195	26	180	138	32	188
2	188	20	180	110	21	140
3	83	36	144	42	23	100
4	383	52	320	272	50	300
5	101	58	150	65	36	108
6	54	19	60	30	29	28
7	120	27	175	94	29	155
8	102	45	160	110	42	165
X	153	94	159	116*	99	148*
SEM	±37	±23	±18	±15	±13	±27

*P<0.05

Figure 12

resistance flow relationships, and the results were similar to those seen in Figure 6.

Series IV

Table 3 presents data obtained in six experiments which examined the effects of local hypoxia, hypocapnia and the combination of hypoxia and hypocapnia on heart rate, mean arterial blood pressure right ventricular systolic pressure and dP/dT, coronary perfusion pressure, coronary resistance and coronary blood gas tensions. Coronary flow was held constant, and averaged 70 ml/min/100 g. With perfusion of the coronary bed with hypoxic blood (pH = 7.34, P_{O_2} = 12 mmHg, P_{CO_2} = 40 mmHg), heart rate, arterial pressure, ventricular pressure and dP/dT are unaffected, but coronary perfusion pressure and coronary resistance are decreased substantially. When the coronary perfusate is made hypocapnic (pH = 7.77; P_{O_2} = 138, P_{CO_2} = 6) no effect is seen on heart rate, arterial pressure, ventricular pressure or dP/dT. However, a significant coronary vasoconstriction is seen as indicated by the increase in coronary pressure and resistance. When the coronary is perfused with blood that is both hypoxic and hypocapnic (pH = 7.80, P_{O_2} = 13, P_{CO_2} = 7), again no effect is seen on heart rate, arterial pressure, ventricular pressure or dP/dT, but a significant coronary vasodilation is seen as indicated by a fall in coronary pressure and resistance. The magnitude of the decrease in resistance seen during these conditions was not significantly different from that which occurred during hypoxic perfusion alone.

Table 3. Effect of local hypoxia, hypocapnia, and the combination of hypoxia and hypocapnia during constant flow perfusion on heart rate, mean arterial blood pressure (MABP), right ventricular systolic pressure (RVSP), right ventricular dp/dt, right coronary perfusion pressure (RCA_{pp}), right coronary resistance (CVR), and coronary arterial pH, O_2 and CO_2. C = control; E = experimental; * = $p < 0.05$ compared to control; values represent mean ± standard error of the mean.

	N=5		N=6		N=5		N=6		N=6		N=6		N=6		N=6		N=6	
	HEART RATE b/min		MABP mmHg		RVSP mmHg		RV dp/dt mmHg/sec		RCA_{pp} mmHg		CVR mmHg/ml/min/100g		pH		pCO_2 mmHg		pO_2 mmHg	
	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
Hypoxia	183 ±20	184 ±23	117 ±6	115 ±5	37 ±4	34 ±2	1350 ±224	1270 ±197	117 ±3	50* ±5	1.79 1.20	0.88* ±.21	7.27 ±.01	7.34* ±.01	45 ±2	40 ±2	144 ±2	12* ±1
Hypocapnia	186 ±24	182 ±22	119 ±5	115 ±5	38 ±2	37 ±3	1890 ±384	1740 ±352	117 ±2	155* ±11	1.80 ±.31	2.46* ±.43	7.27 ±.01	7.77* ±.03	45 ±2	6* ±.8	144 ±2	138 ±7
Hypoxia and Hypocapnia	184 ±27	192 ±21	115 ±4	120 ±5	39 ±3	39 ±3	1550 ±274	1570 ±290	126 ±8	55* ±5	1.91 ±.11	0.87* ±.15	7.27 ±.01	7.80* ±.01	45 ±2	7* ±.5	144 ±2	13* ±1

Table 4 summarizes the effect of sympathetic stimulation on each of the variables listed above during perfusion with normoxic, hypoxic, hypocapnic and a combination of hypoxic and hypocapnic blood. During normoxic control conditions (pH = 7.27, P_{O_2} = 144, P_{CO_2} = 45), sympathetic stimulation produced a significant increase in heart rate, arterial pressure, ventricular pressure, dP/dT, coronary perfusion pressure and coronary resistance. During hypoxic conditions, sympathetic stimulation produced an increase only in arterial pressure demonstrating an intact reflex, but no effect was seen on ventricular pressure, dP/dT, coronary pressure or resistance. During hypocapnic perfusion, stimulation resulted in an increase in heart rate, arterial pressure, ventricular pressure, dP/dT, coronary pressure and coronary resistance. This increase in coronary resistance was not significantly different in magnitude from that which occurred during normoxic conditions. When the coronary blood is rendered hypoxic and hypocapnic, stimulation produces an increase in arterial pressure, ventricular pressure, dP/dT, coronary pressure and coronary resistance. The rise in resistance again is not different in magnitude from that seen during normoxic conditions. These data demonstrate that the responses to sympathetic stimulation are not different during hypocapnia or hypoxia + hypocapnia compared to normoxia, but are blocked during hypoxic conditions.

Table 5 summarizes the effect of intracoronary norepinephrine infusion at a dose of 0.25 µg/min on the same variables as listed above during normoxic, hypoxic, hypocapnic and the combination of hypoxic and hypocapnic conditions. During normoxia, norepinephrine at this dose

Table 4. Effect of sympathetic stimulation (SS) during local normoxia, hypoxia, hypocapnia and the combination of hypoxia and hypocapnia during constant flow perfusion on heart rate, mean arterial blood pressure (MABP), right ventricular systolic pressure (RVSP), right ventricular dp/dt, right coronary artery perfusion presure (RCA_{pp}), coronary vascular resistance (CVR) and coronary arterial pH, pO_2 and pCO_2. C = control; E = experimental; * = $p < 0.05$ compared to control; values represent mean ± standard error of the mean.

	N=5 HEART RATE b/min		N=6 MABP mmHg		N=6 RVSP mmHg		N=5 RV dp/dt mmHg/sec		N=6 RCA_{pp} mmHg		N=6 CVR mmHg/ml/min/100g		N=6 pH	N=6 pCO_2 mmHg	N=6 pO_2 mmHg
	C	E	C	E	C	E	C	E	C	E	C	E			
SS During Normoxia	183 ±23	221* ±22	129 ±5	184* ±9	41 ±3	51* ±3	1645 ±310	2233* ±392	125 ±5	136* ±3	1.93 ±.26	2.09* ±.26	7.27 ±.01	45 ±2	144 ±2
SS During Hypoxia	184 ±23	202 ±24	115 ±6	151* ±11	34 ±2	38 ±4	1270 ±197	1480 ±162	50 ±6	50 ±5	0.77 ±.13	0.78 ±.13	7.34* ±.01	40 ±2	12* ±1
SS During Hypocapnia	182 ±22	210 ±23	115 ±5	156* ±11	37 ±3	42* ±3	1740 ±352	2100* ±322	155 ±11	162* ±11	2.45 ±.43	2.57* ±.44	7.77* ±.03	6 ±.8	138 ±7
SS During Hypoxia and Hypocapnia	192 ±21	198 ±21	120 ±5	160* ±9	39 ±3	45* ±1	1570 ±290	1870* ±254	55 ±5	60* ±5	0.87 ±.15	0.93* ±.14	7.80* ±.01	7* ±.5	13* ±1

Table 5. Effect of 0.25 µg/min intracoronary infusion of norepinephrine (NE) during local normoxia, hypoxia, hypocapnia and the combination of hypoxia and hypocapnia during constant flow perfusion on heart rate, mean arterial blood pressure (MABP), right ventricular systolic pressure (RVSP), right ventricular dp/dt, right coronary artery perfusion pressure (RCA_{pp}), coronary vascular resistance (CVR) and coronary arterial pH, pO_2 and pCO_2. C = control; E = experimental; * = $p < 0.05$ compared to control; values represent mean ± standard error of the mean.

	N=5 HEART RATE b/min		N=6 MABP mmHg		N=6 RVSP mmHg		N=5 RV dp/dt mmHg/sec		N=6 RCA mmHg		N=6 CVR mmHg/ml/min/100g		N=6 pH	N=6 pCO_2	N=6 pO_2
	C	E	C	E	C	E	C	E	C	E	C	E			
.25µg/min NE During Normoxia	190 ±20	216 ±14	124 ±5	125 ±5	42 ±2	51 ±3	1733 ±305	2256 ±511	131 ±3	93* ±17	2.03 ±.27	1.55* ±.45	7.27 ±.01	45 ±2	144 ±2
.25µg/min NE During Hypoxia	184 ±23	194 ±19	109 ±6	110 ±5	32 ±3	34 ±3	1370 ±150	1520 ±285	49 ±6	45* ±6	0.76 ±.14	0.74 * ±.14	7.34 ±.01	40 ±2	12* ±1
.25µg/min NE During Hypocapnia	188 ±18	220 ±11	115 ±6	113 ±6	35 ±3	41 ±2	1583 ±280	2042* ±297	155 ±13	133 ±21	2.47 ±.46	2.18 ±.55	7.77* ±.03	6* ±.08	138 ±7
.25µg/min NE During Hypoxia and Hypocapnia	186 ±22	186 ±22	116 ±6	115 ±6	39 ±3	42* ±3	1640 ±357	1920 ±361	55 ±5	53 ±5	0.87 ±.15	0.85 ±.15	7.80* ±.01	7* ±.5	13* ±1

had no significant effect on heart rate, arterial pressure, ventricular pressure or dP/dT, but produced a significant decrease in coronary pressure and coronary resistance. A closer examination of the ventricular pressures and dP/dT for this group of animals indicates that one animal in the group did not respond to the norepinephrine while in all other animals ventricular pressure and dP/dT were significantly elevated when these animals were analyzed alone. This increase in ventricular function may therefore account for the coronary vasodilation seen. During hypoxia, norepinephrine had no effect on heart rate, arterial pressure, ventricular pressure or dP/dT, yet produced a slight but significant decrease in coronary pressure and coronary resistance. During hypocapnia, norepinephrine had no effect on heart rate, arterial pressure,ventricular pressure, coronary pressure or coronary resistance but did produce a significant increase in dP/dT. During the combination of hypoxia and hypocapnia, norepinephrine produced a significant increase in ventricular pressure but had no effect on heart rate, arterial pressure, dP/dT, coronary pressure or coronary resistance.

In Table 6, the dose of norepinephrine was increased to 0.5 μg/min, and these effects observed. During normoxia, norepinephrine had no effect on heart rate, arterial pressure, ventricular pressure or dP/dT, but produced a significant decrease in coronary perfusion pressure and resistance. Again, one animal in the group showed no ventricular response and resistance. Again, one animal in the group showed no ventricular response to the norepinephrine; however, all other animals did show an increase in ventricular pressure and dP/dT which was significant when these animals were analyzed together. During hypoxia

Table 6. Effect of 0.5 μg/min intracoronary infusion of norepinephrine (NE) during local normoxia, hypoxia, hypocapnia, and the combination of hypoxia and hypocapnia during constant flow perfusion on heart rate, mean arterial blood pressure (MABP), right ventricular systolic pressure (RVSP), right ventricular dp/dt, right coronary artery perfusion pressure (RCApp) coronary vascular resistance (CVR) and coronary arterial pH, pO_2 and pCO_2. C = control; E = experimental; percent Δ = percent change from control; * = $p < 0.05$ compared to control; values represent mean and ± standard error of the mean.

	N=5 HEART RATE b/min		N=6 MABP mmHg		N=6 RVSP mmHg		N=5 RV dp/dt mmHg/sec		N=6 RCA mmHg		N=6 CVR mmHg/ml/min/100g		N=6 pH	N=6 pCO_2	N=6 pO_2
	C	E	C	E	C	E	C	E	C	E	C	E			
.5μg/min NE During Normoxia	200 ±17	217 ±14	124 ±6	123 ±7	43 ±2	55 ±5	1660 ±376	2190 ±538	131 ±4	86* ±18	2.15 ±.30	1.49* ±.44	7.27 ±.01	45 ±2	144 ±2
.5μg/min NE During Hypoxia	190 ±29	210 ±17	107 ±7	110 ±5	32 ±3	35* ±4	1275 ±165	1350 1236	51 ±7	47* ±7	0.83 ±.15	0.77* ±.15	7.34* ±.01	40 ±2	12* ±1
.5μg/min NE During Hypocapnia	197 ±20	217 ±14	114 ±8	112 ±7	35 ±3	44* ±3	1687 ±403	2027* ±335	161 ±14	133* ±20	2.69 ±.50	2.28* ±.53	7.77* ±.03	6* ±.08	138 ±7
.5μg/min NE During Hypoxia and Hypocapnia	195 ±27	212 ±24	114 ±7	113 ±7	40 ±4	44 ±3	1675 ±458	1775 ±502	58 ±6	51* ±6	0.96 ±.18	0.85* ±.17	7.80* ±.01	7* ±.5	13* ±1

norepinephrine had no effect on heart rate, arterial pressure or dP/dT, but produced a slight but signigicant increase in ventricular pressure and a decrease in coronary pressure and resistance. With hypocapnia, norepinephrine had no effect on heart rate or arterial pressure but produced an increase in ventricular pressure and dP/dT, and a decrease in coronary pressure and resistance. With combined hypoxia and hypocapnia, norepinephrine had no effect on heart rate, arterial pressure, ventricular pressure or dP/dT, yet it decreased coronary pressure and resistance. Again one animal did not respond to norepinephrine while all others showed increased ventricular pressure and dP/dT, accounting for the fall in coronary resistance. Examining the magnitude of change in resistance in response to this dose of norepinephrine during various alterations in coronary blood gas tensions, it was concluded that the response to norepinephrine was attenuated when the bed was rendered hypoxic or hypoxic and hypocapnic, but the response was not different during hypocapnia as compared to normoxic control conditions.

Series V

Table 7 presents data obtained in eight experiments in which the effects of local hypoxia, hypercapnia and hypocapnia on heart rate, arterial pressure, ventricular pressure, dP/dT, coronary pressure and resistance were examined during constant pressure perfusion. Perfusion of the coronary bed with hypoxic blood (pH = 7.30, P_{O_2} = 17 mmHg, P_{CO_2} = 49 mmHg) had no effect on heart rate, arterial pressure, ventricular pressure or dP/dT, but produced a significant increase in coronary blood flow and decrease in coronary resistance. Perfusion pressure was

Table 7. Effect of local hypoxia, hypecapnia and hypocapnia during constant pressure perfusion on heart rate, mean arterial blood pressure (MABP), right ventrical systolic pressure (RVSP), right ventricular dp/dt, right coronary flow, right coronary resistance (CVR), and coronary arterial pH, pO_2 and pCO_2. C = control; E = experimental; * = $p < 0.05$ compared to control; values represent mean ± standard error of the mean; coronary perfusion pressure held constant at 100 mmHg.

	HEART RATE b/min		MABP mmHg		RVSP mmHg		RV dp/dt mmHg/sec		RCA FLOW ml/min/100g		CVR mmHg/ml/min/100g		pH		pCO_2 mmHg		pO_2 mmHg	
	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
Hypoxia N=8	157 ±9	156 ±9	83 ±9	77 ±8	23 ±1	24 ±2	1531 ±505	1523 ±625	57.6 ±6.1	211.3* ±11.6	1.89 ±.19	0.48* ±.02	7.36 ±.02	7.30 ±.03	46 ±1	49 ±2	144 ±2.7	17* ±1
Hypercapnia N=7	155 ±8	142 ±11	92 ±10	85 ±10	25 ±2	23 ±1	1707 ±420	1357* ±304	67.1 23.9	133* ±12.5	1.53 ±.09	0.81* ±.07	7.36 ±.02	7.05* ±.04	46 ±1	105* ±11	144 ±2	145 ±13
Hypocapnia N=7	157 ±9	175* ±9	94 ±10	85* ±10	26 ±2	24* ±2	1721 ±482	1800 ±561	63.2 ±4.0	55.3 ±9.1	1.62 ±.18	1.96 ±.34	7.36 ±.02	7.74* ±.05	46 ±1	8* ±1	144 ±2	146 ±10

held constant at 100 mmHg throughout this series. Local hypercapnia (pH = 7.05, P_{O_2} = 145 mmHg, P_{CO_2} = 105 mmHg) had no effect on heart rate, arterial pressure or ventricular pressure, but significantly depressed dP/dT while increasing coronary blood flow and decreasing coronary resistance. Hypocapnia increased heart rate, arterial pressure and ventricular pressure but had no effect on dP/dT, coronary blood flow or coronary resistance (pH = 7.74, P_{O_2} = 146, P_{CO_2} = 8). While no statistical difference was seen for resistance, it is of interest to note that resistance increased in six out of seven animals with the seventh animal showing a decrease in resistance. This explains the nonsignificant finding with a paired t analysis.

Table 8 represents the effects of sympathetic stimulation during normoxia, hypoxia, hypercapnia and hypocapnia. During normoxic conditions, sympathetic stimulation had no effect on heart rate or ventricular pressure, but significantly increased arterial blood pressure and dP/dT, while coronary blood flow decreased and coronary resistance rose. During hypoxia, sympathetic stimulation increased arterial pressure but no effect was seen on heart rate, ventricular pressure, dP/dT, coronary flow or resistance. During hypercapnia, stimulation resulted in an unchanged heart rate and ventricular pressure, but increased arterial pressure, dP/dT, decreased coronary blood flow, and increased coronary resistance. During hypocapnia, stimulation increased arterial pressure but had no effect on heart rate, ventricular pressure, dP/dT, coronary flow or coronary resistance. Coronary resistance was elevated in four out of seven animals. Analysis of the magnitude of the change in coronary resistance shows that the response is significantly attenuated

Table 8. Effect of sympathetic stimulaton (SS) during local noromoxia, hypoxia, hypercapnia and hypocapnia during constant pressure perfusion on heart rate, mean arterial blood pressure (MABP), right ventricular systolic pressure (RVSP), right ventricular dp/dt, right coronary artery flow, coronary vascular resistance (CVR) and coronary arterial pH, pO_2 and pCO_2. C = control; E = experimental; * = $p < 0.05$ compared to control; values represent mean ± standard error of the mean; perfusion pressure held constant at 100 mm Hg.

	HEART RATE b/min		MABP mmHg		RVSP mmHg		RV dp/dt mmHg/sec		RCA FLOW ml/min/100g		CVR mmHg/ml/min/100g		pH	pCO_2 mmHg	pO_2 mmHg
	C	E	C	E	C	E	C	E	C	E	C	E			
SS During Normoxia N=8	170 ±3	172 ±7	100 ±10	130* ±17	27 ±2	30 ±1	1412 ±376	1762* ±475	51.5 ±4.5	48.9* ±4.2	2.03 ±.21	2.21* ±.22	7.36 ±.02	46 ±1	144 ±2
SS During Hypoxia N=4	150 ±10	157 ±6	86 ±2	103* ±8	24 ±4	25 ±3	2400 ±1308	2587 ±1354	215.5 118.5	209.0 ±14.7	0.48 ±.04	0.49 ±.03	7.30 ±.03	49 ±2	17* ±1
SS During Hypercapnia N=5	152 ±14	170 ±17	95 ±11	124* ±18	22 ±1	24 ±1	890 ±114	1080* ±149	128.8 ±10.1	119.7* ±10.1	0.80 ±.06	0.86* ±.07	7.05* ±.04	105* ±11	145 ±13
SS During Hypocapnia N=7	175 ±9	170 ±10	85 ±10	105* ±15	24 ±2	24 ±2	1800 ±561	1735 ±539	55.6 ±9.1	53.7 ±8.9	2.09 ±.29	2.20 ±.35	7.74* ±.05	8* ±1	140 ±10

during hypoxia and hypercapnia, but is not significantly different during hypocapnia compared to normoxic, normocapnic conditions.

Table 9 represents the effects of 0.25 μg/min intracoronary norepinephrine infusion during normoxic, hypoxic, hypercapnic and hypocapnic conditions. During normoxia, norepinephrine significantly increased heart rate, ventricular pressure, dP/dT and coronary flow while decreasing coronary resistance. Arterial pressure was not changed. During hypoxic perfusion, norepinephrine had no effect on heart rate, arterial pressure, ventricular pressure, dP/dT, coronary flow or coronary resistance. During hypercapnia, norepinephrine again had no effect on heart rate, arterial pressure, coronary flow or coronary resistance, but significantly increased ventricular pressure and dP/dT. It is interesting to note that coronary blood flow decreased in four out of five animals in response to norepinephrine during hypercapnia. During hypocapnia norepinephrine failed to effect changes in heart rate or arterial pressure but increased ventricular pressure, dP/dT and coronary flow, and decreased coronary resistance. The magnitude of the decrease in resistance associated with norepinephrine during hypocapnia was not different from that seen during normoxic control conditions. The response seen during hypoxia and hypercapnia was significantly attenuated relative to that seen during normoxia.

Figure 13 depicts the relationships between pressure and flow, as well as pressure and resistance during constant pressure perfusion in five experimental animals. Pressure was increased or decreased in a stepwise fashion by 25 mmHg gradations over the range of 50-175 mmHg. The steady state flows were recorded at each level and the resistance

Table 9. Effect of 0.25 µg/min intracoronary infusion of norepinephrine (NE) during constant pressure perfusion on heart rate, mean arterial blood pressure (MABP), right ventricular systolic pressure (RVSP), right ventricular dp/dt, right coronary artery flow, coronary vascular resistance and coronary arterial pH, PO_2 and pCO_2. C = control; E = experimental; * = $p < 0.05$ compared to control; values represent mean ± standard error of the mean; perfusion pressure held constant at 100 mmHg.

		HEART RATE b/min		MABP mmHg		RVSP mmHg		RV dp/dt mmHg/sec		RCA FLOW ml/min/100g		CVR mmHg/ml/min/100g		pH	pCO_2	pO_2
		C	E	C	E	C	E	C	E	C	E	C	E			
.25µg/min NE During Normoxia	N=8	161 ±4	181* ±6	93 ±9	95 ±9	27 ±2	31* ±2	1593 ±493	2156* ±601	53.8 ±4.2	78.0* ±7.4	1.98 ±.18	1.41* ±.19	7.36 ±.02	46 ±1	144 ±2
.25µg/min NE During Hypoxia	N=4	140 ±11	145 ±9	80 ±9	80 ±7	21 ±3	23 ±3	2100 ±992	2175 ±954	199.2 ±26.6	201.0 ±26.6	0.60 ±.17	0.53 ±.08	7.30 ±.03	49 ±2	17* ±1
.25µg/min NE During Hypercapnia	N=5	148 ±12	160 ±14	92 ±10	100 ±10	22 ±2	25* ±2	880 ±96	1210* ±95	125.6 ±10.2	124.0 ±6.1	0.83 ±.07	0.84 ±.06	7.05* ±.04	105* ±11	145 ±13
.25µg/min NE During Hypocapnia	N=5	167 ±7	175 ±9	83 ±10	82 ±11	23 ±2	29* ±2	1714 ±568	2321* ±519	55.0 ±9.1	79.7* ±10.8	2.10 ±.29	1.39* ±.16	7.74* ±.05	8* ±1	140 ±10

Figure 13. Relationship between pressure and flow, as well as pressure and resistance during constant pressure perfusion of the right coronary artery.

N = 5
CVR = coronary resistance (mmHg/ml/min/100 g)
Dashed line represents mean values.

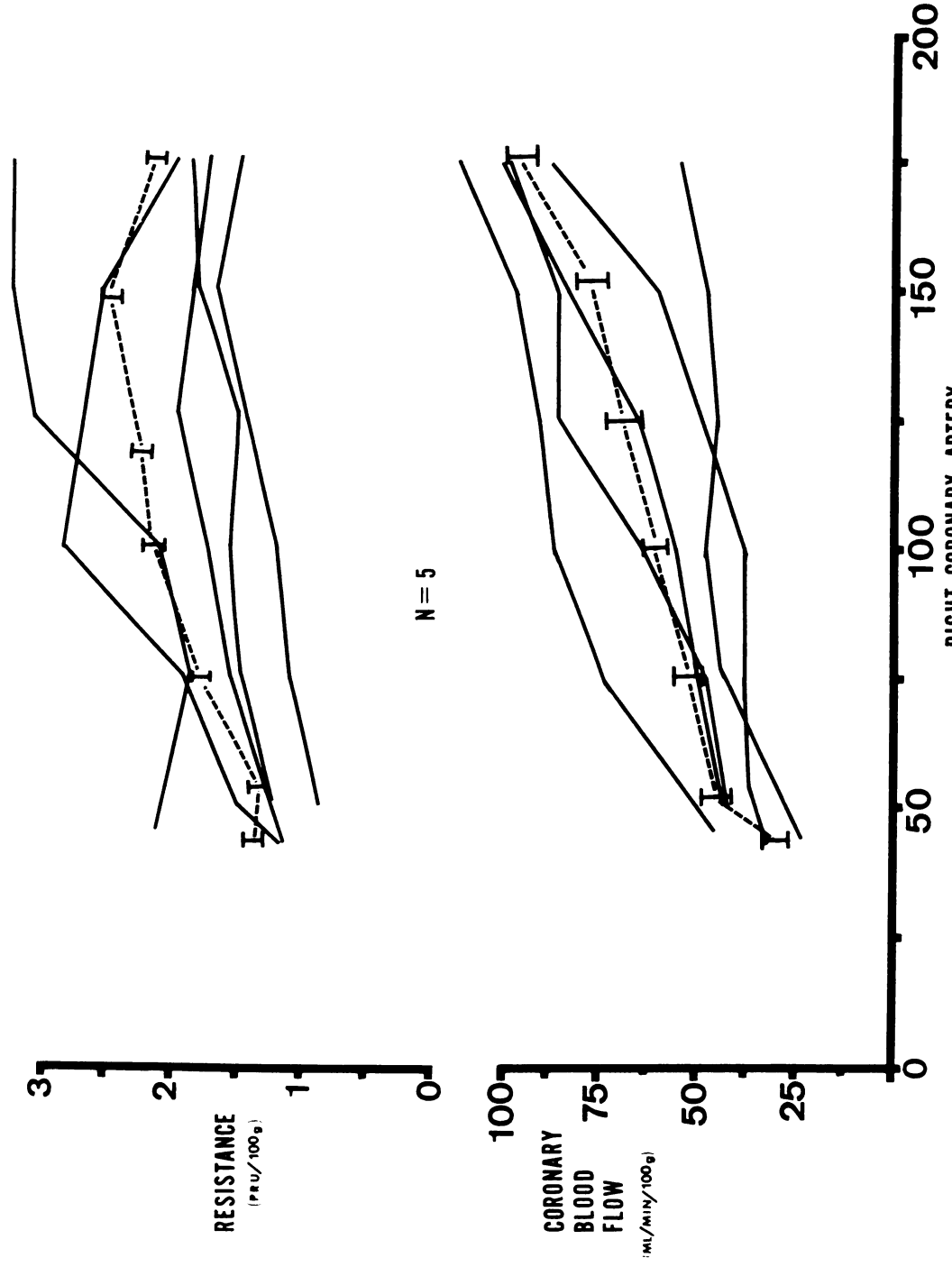

RESISTANCE
(PRU/100g)
3
2
1
0
N = 5
CORONARY
BLOOD
FLOW
(ML/MIN/100g)
100
75
50
25
0
50
100
150
200
RIGHT CORONARY ARTERY
PRESSURE
(mmHg)

Figure 13

calculated. In the pressure-flow diagram it is apparent that as pressure is increased from 50-75 mmHg flow increased in a relatively proportionate fashion. From 75-150 mmHg, flow remains relatively constant until pressure exceeds 150 mmHg, at which point flow increases again. The pressure-resistance diagram indicates that calculated resistance generally increases over the range in which flow is seen to remain relatively constant.

Series VI

Data presented for this series was obtained from two animals which were chronically instrumented for the determination of right coronary blood flow in the unanesthetized state in response to a variety of stimuli. While it is recognized that this small N number may not provide information that is applicable to the rest of the population, and the data is not analyzed by statistical methods, it is still of interest and provides some information that can be used to compare to the results obtained in the acute, anesthetized preparations.

Figure 14 depicts phasic coronary blood flow and coronary pressure tracings for one animal in which blood flow was stopped for three seconds by inflating a balloon cuff which was implanted around the proximal right coronary artery. Following release of the occlusion, a reactive hyperemic response is seen. This maneuver was repeated after a systemic blocking dose of the prostaglandin synthesis inhibitor indomethacin had been given. A comparison of the control and experimental responses to a three second occlusion reveals that the duration

Figure 14. Response of the right coronary circulation of the unanesthetized dog to three second occlusion of flow before and after blockade of prostaglandin synthesis with 5 mg/kg indomethacin.

N = 1

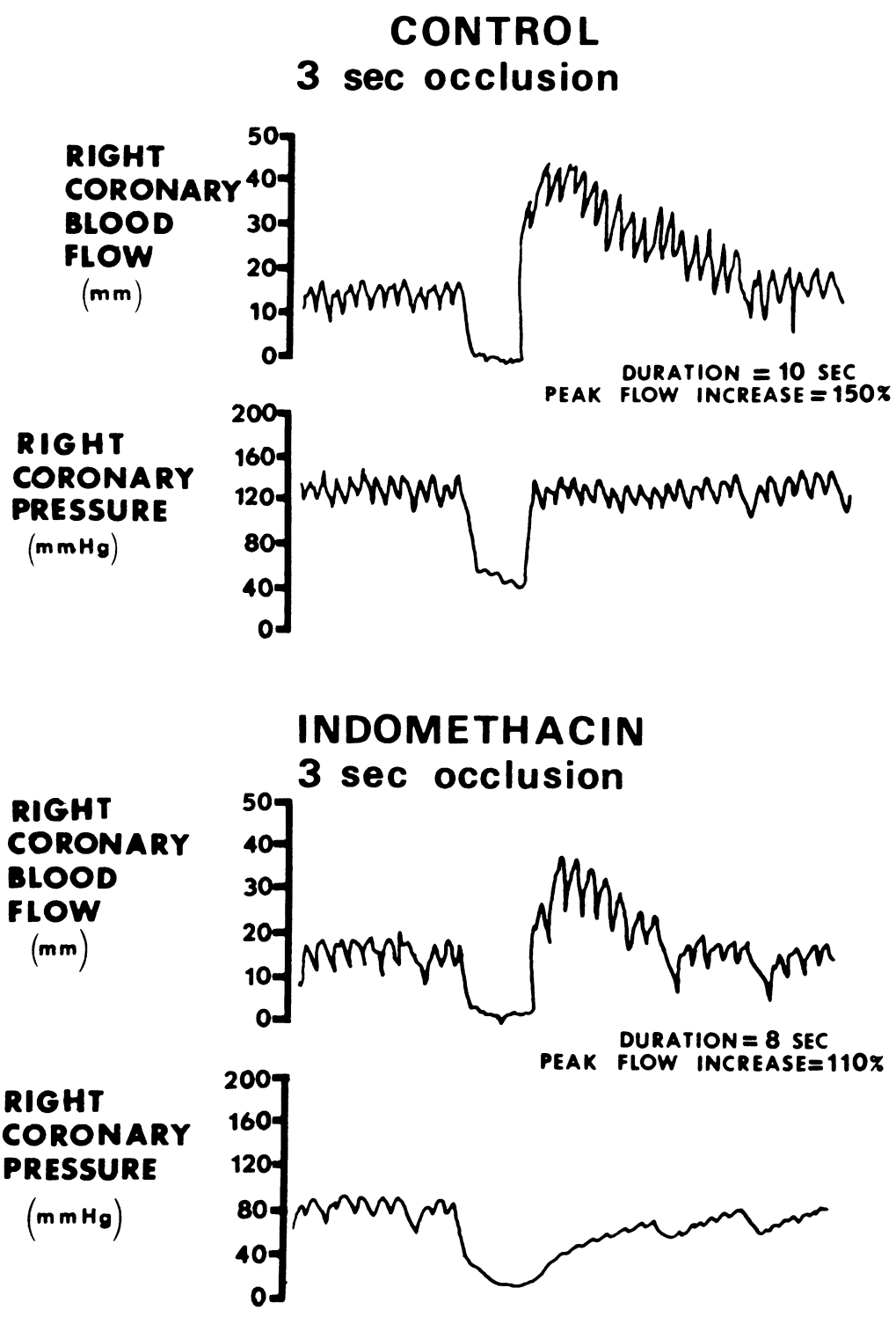

CONTROL
3 sec occlusion
RIGHT CORONARY BLOOD FLOW (mm)
50
40
30
20
10
0
DURATION = 10 SEC
PEAK FLOW INCREASE = 150%
RIGHT CORONARY PRESSURE (mmHg)
200
160
120
80
40
0
INDOMETHACIN
3 sec occlusion
RIGHT CORONARY BLOOD FLOW (mm)
50
40
30
20
10
0
DURATION = 8 SEC
PEAK FLOW INCREASE = 110%
RIGHT CORONARY PRESSURE (mmHg)
200
160
120
80
40
0

Figure 14

of the hyperemia was shorter (10 vs 8 seconds) after indomethacin, as was the peak flow (150% vs 110% above control flow). This indicates that indomethacin had a slight affect on the reactive hyperemic response. Responses were also obtained for 5 second, 10 second and 30 second occlusions before and after indomethacin. No differences were seen between these two conditions for these longer occlusion periods. The hyperemic response was noted to increase as the duration of occlusion increased.

Figure 15 depicts the pressure-flow relationships and the pressure resistance relationships (solid line and dashed line, respectively) for one animal in which coronary pressure was decreased in a stepwise fashion by inflation of the occluder cuff. At each new pressure level, the steady state blood flow was recorded and an arbitrary resistance unit calculated. From the diagram it can be demonstrated that as pressure is decreased, flow is maintained at a relatively constant level over the range of 90-30 mmHg. Over this range, calculated resistance is seen to fall until a pressure of 30 mmHg is reached. At this point a further decrease in pressure appears to be associated with a proportionate fall in blood flow with no change in resistance. This data supports the findings of Series V in which the pressure flow relationships were determined during constant pressure perfusion.

Figure 16 demonstrates the effects of intracoronary bolus injections of norepinephrine before and after alpha blockade in one unanesthetized dog. At a dose of 0.05 μg norepinephrine, a biphasic response is seen. There is an early decrease in blood flow associated with an increase in calculated resistance, followed by a prolonged

Figure 15. Relationships between pressure and flow, as well as pressure and resistance in the right coronary artery of the unanesthetized dog.

N = 1

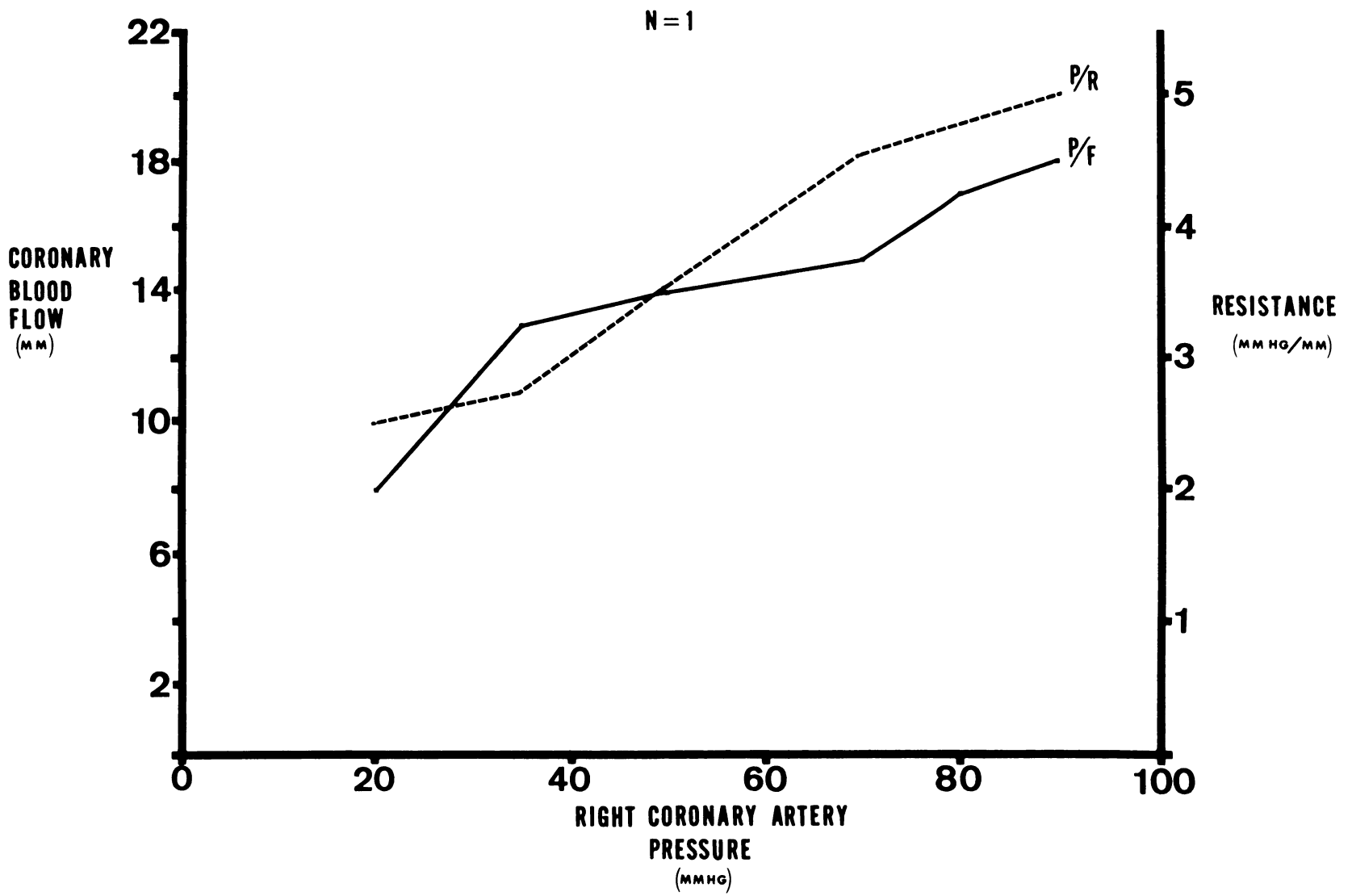

N = 1
P/R
P/F
CORONARY BLOOD FLOW (MM)
RESISTANCE (MM HG/MM)
22
18
14
10
6
2
5
4
3
2
1
0
20
40
60
80
100
RIGHT CORONARY ARTERY PRESSURE (MMHG)

Figure 15

Figure 16. Effect of intracoronary bolus injections of norepinephrine (NE) on right coronary perfusion pressure, coronary blood flow, and vascular resistance before and after alpha blockade in the unanesthetized dog.

N = 1
C = Control
E = Early Transient Response
L = Late Steady State Response

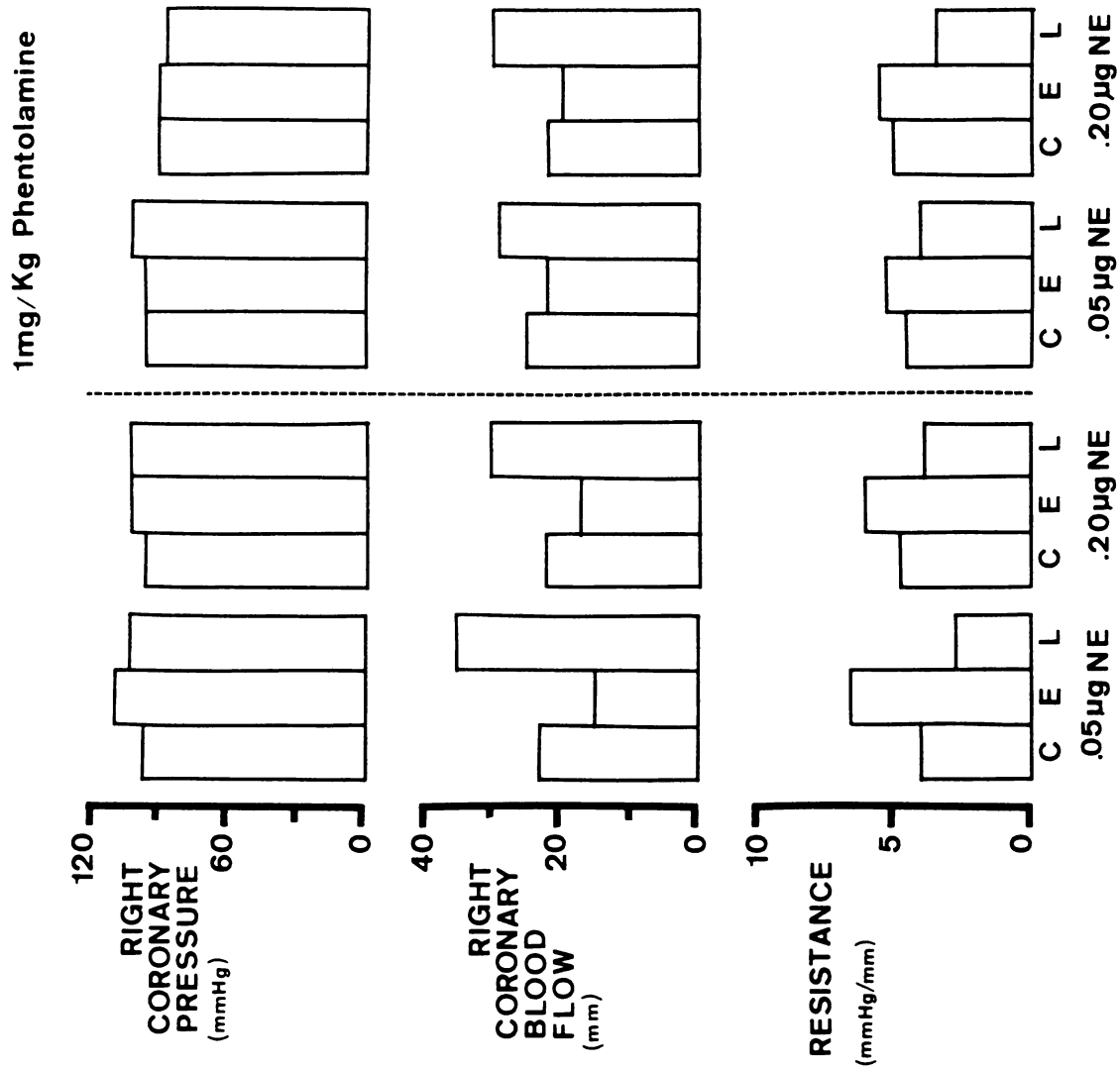

1mg/Kg Phentolamine
RIGHT CORONARY PRESSURE (mmHg)
120
60
0
RIGHT CORONARY BLOOD FLOW (ml)
40
20
0
RESISTANCE (mmHg/ml)
10
5
0
CELL
.05µg NE
.20µg NE
CELL
.05µg NE
.20µg NE

Figure 16

increase in blood flow and decrease in calculated resistance. The same response is seen when the dose of norepinephrine is increased to 0.2 μg. Phentolamine was then given at a dose of 1 mg/kg intravenously and the responses to norepinephrine again obtained. Norepinephrine (0.05 μg) again resulted in a biphasic response except that the initial increase in resistance was limited to 15% where it had been 78% in the control situation. This was followed by a mild decrease in resistance in the steady state. At 0.2 μg injection of norepinephrine, the initial rise in resistance was also limited to only 10% (vs 45% at control) and was followed by a 30% fall in resistance in the steady state.

Figure 17 depicts the effects of intracoronary bolus injections of adenosine and norepinephrine on coronary pressure, blood flow and resistance in a second unanesthetized animal. A 1 μg injection of adenosine produced a substantial increase in coronary blood flow, and a decrease in coronary resistance of approximately 66%. A 0.3 μg norepinephrine injection produced an increased coronary blood flow and a decreased coronary resistance of approximately 57% in the steady state. No transients were noted in these recordings. Coronary pressure was then decreased from 80 to 50 mmHg and norepinephrine was again injected. The response seen was a decrease in coronary blood flow and a substantial increase in coronary resistance (100%).

Figure 17. Effects of intracoronary bolus injections of adenosine and injections of norepinephrine before and during myocardial ischemia on right coronary perfusion pressure, coronary blood flow and vascular resistance in the unanesthetized dog.

N = 1
C = Control
E = Experimental

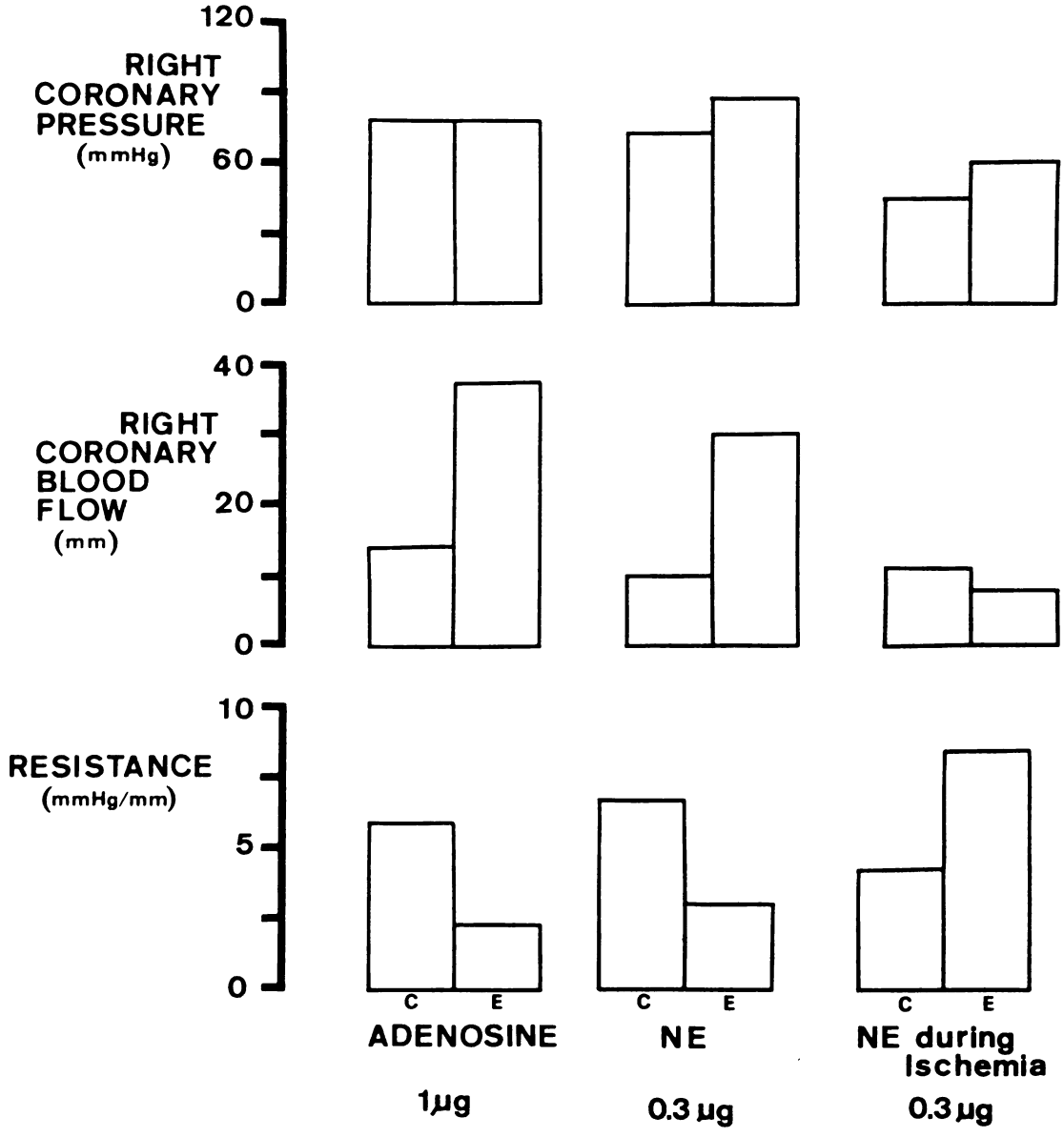

120
RIGHT
CORONARY
PRESSURE
(mmHg)
60
0
40
RIGHT
CORONARY
BLOOD
FLOW
(mm)
20
0
10
RESISTANCE
(mmHg/mm)
5
0
C
E
C
E
C
E
ADENOSINE
1µg
NE
0.3 µg
NE during
Ischemia
0.3 µg

Figure 17

DISCUSSION

Methodology

It was important to determine at the onset of this study whether or not significant collateral vessels exist between the right coronary artery and branches of the left coronary artery. To test this possibility, the pump perfusing the right coronary artery was stopped. This yielded a non-pulsatile baseline perfusion pressure of approximately 15 mmHg. A tourniquet was then applied to the descending thoracic aorta which increased pressure in the ascending aorta to approximately 170 mmHg. It was assumed that if any significant collaterals were present between the right and left coronary arteries, this maneuver would result in an increase in the baseline (pump off) perfusion pressure in the right coronary artery. However, no such effect was seen. Furthermore, infusion of crystal violet dye into the right coronary artery at perfusion pressures up to 180 mmHg in both the beating and fibrillating heart produced staining of a discrete portion of the right ventricular free wall, with no staining occurring in the interventricular septum or left ventricular free wall. This evidence indicated that the right coronary circulation was essentially free of any significant collateral communication with the left coronary system.

Microsphere studies in the dog have shown that a portion of the right ventricular free wall and the interventricular septum are

perfused by branches of the left coronary artery (Murray et al., 1979), although as previously mentioned, these vessels apparently do not anastomose with those from the right coronary artery. However, the fact that the right ventricle is supplied by both right and left coronary arteries in the dog is important when attempting to interpret the ventricular hemodynamic data obtained in the present study. Therefore, the effect of experimental interventions which only affect the portion of the ventricle perfused by the right coronary artery may not be clearly seen when overall right ventricular hemodynamic data is analyzed.

Is it also important to note that all anesthetized animals in this study were vagotomized. This was performed in order to eliminate the buffering effect of the baroreceptors located in the aortic arch from the baroreflex obtained by the production of carotid sinus hypotension. Vagotomy was associated with a high resting heart rate in nearly every animal. As a result, heart rates were not consistently seen to rise in response to stimuli which have known positive chronotropic effects.

Adequate characterization of the factors which contribute to the regulation of blood flow through the right coronary vascular bed has never been accomplished. Since this vascular system is of great importance in the majority of the human population, further physiological investigation was warranted. The studies described herein have attempted to better define the role of autoregulation, circulating catecholamines, adrenergic receptor activity, prostaglandins, oxygen and carbon dioxide and sympathetic nerve stimulation in both the local and remote control of blood flow through this vascular bed.

Briefly, the results of this study have shown that in anestetized dogs, the pressure/flow relationships are virtually linear over the physiological range of pressures during constant flow perfusion of the right coronary artery. During constant pressure perfusion, flow is maintained relatively constant over the range of 75-150 mmHg, indicating that this bed exhibits autoregulation to a greater extent during constant pressure perfusion than during constant flow perfusion.

Constant Flow Studies

In the constant flow studies it was demonstrated that sympathetic stimulation increased heart rate, mean arterial blood pressure, right ventricular systolic pressure, and right ventricular dP/dT, yet caused an increased coronary vascular resistance. This increased resistance is undoubtedly related to active coronary vasoconstriction since there was no change in hematocrit, hence, no change in viscosity. The coronary vasoconstriction was enhanced as flow to the bed was decreased. Infusion of norepinephrine on the other hand usually increased heart rate, right ventricular systolic pressure, dP/dT, and produced a significant reduction in coronary resistance. In the presence of propranolol (beta blockade), no greater vasoconstriction was seen in response to sympathetic stimulation, but the vasodilation seen with norepinephrine was converted to a vasoconstriction. The vasoconstriction seen with sympathetic stimulation could be blocked with phentolamine, indicating that it is an alpha adrenergically mediated phenomenon.

During constant flow perfusion, both systemic and local hypocapnia significantly increased coronary vascular resistance. Subsequent sympathetic stimulation produced an additive vasoconstriction, however, the response was not enhanced during these conditions. The vasodilatory response to norepinephrine was either attenuated (high dose) or blocked (low dose) in the presence of systemic or local hypocapnia.

Inhibition of prostaglandin synthesis by indomethacin had no significant effect on resting coronary resistance and had no apparent effect on the response to sympathetic stimulation, norepinephrine infusion or hypocapnia. The reactive dilation seen with 20 second interruptions of coronary flow was significantly decreased by indomethacin.

Local hypoxia or the combination of hypoxia and hypocapnia resulted in a profound coronary vasodilation. The response to sympathetic stimulation was not changed by the combination of hypoxia and hypocapnia, but the response was absent in the presence of hypoxia alone. Norepinephrine (low dose) produced the same degree of dilation during hypoxia but had no significant effect during the combination of hypoxia and hypocapnia. At the higher dose, norepinephrine produced a coronary vasodilation that was significantly less in magnitude during hypoxia and the combination of hypoxia and hypocapnia.

Constant Pressure Studies

In other studies, a constant pressure perfusion technique was used to determine if the responses seen previously were dependent on constant flow perfusion conditions. Under these conditions, hypoxia produced a profound decrease in coronary resistance with no measurable change in

ventricular function. Hypercapnia was found to produce a significant decrease in coronary resistance as well, even in the face of a decrease in dP/dT. Hypocapnia was found to increase arterial blood pressure, heart rate, and ventricular pressure, but had no consistent effect on coronary resistance. Sympathetic stimulation had no effect on coronary resistance or ventricular performance when the bed was rendered hypoxic, but increased resistance and dP/dT during local hypercapnia. During hypocapnic perfusion, sympathetic stimulation had no consistent effect on coronary resistance or ventricular performance; however, resistance was seen to increase in four out of seven animals. Infusion of norepinephrine during hypoxic or hypercapnia perfusion had no effect on coronary resistance; whereas, ventricular function was increased during hypercapnia with norepinephrine. During hypocapnia perfusion, norepinephrine increased ventricular function and decreased coronary resistance to a similar degree as during normoxic, normocapnic perfusion.

In order to relate some of the findings in the anesthetized, open-chest preparation to those that might occur in the conscious animal, two dogs were chronically instrumented for the determination of right coronary hemodynamics. Following recovery from the surgery required for instrumentation, data was obtained from these animals while awake and resting quietly. These results showed that as coronary pressure was decreased from 90-30 mmHg, a substantial degree of autoregulation was seen. Blood flow was fairly well-maintained over this range and calculated coronary resistance fell. The reactive hyperemic responses before and after prostaglandin synthesis inhibition with indomethacin to 3, 5, 10, and 30 second coronary occlusions were obtained.

Indomethacin had no effect on the responses to 5, 10, or 30 second occlusions. However, it appeared that the hyperemic response to 3 second occlusions was slightly attentuated following indomethacin. Intracoronary bolus injections of norepinephrine resulted in a biphasic response in one animal. Coronary resistance increased transiently, followed by a prolonged decrease in resistance. The initial increase in resistance could be prevented with alpha receptor blockade. In a second animal, norepinephrine produced only a prolonged decrease in resistance, except when the bed was rendered ischemic, in which case norepinephrine increased resistance substantially.

Early work by several investigators has shown that sympathetic stimulation via stellate ganglion stimulation or mediated through the baroreceptor mechanism produces an increase in heart rate and systemic arterial pressure and a fall in left coronary vascular resistance (Berne et al., 1958; Szentivany and Juhasz-Nagy, 1963; Feigl, 1968; DiSalvo et al., 1971). The decline in resistance was sometimes preceded by a transient rise in resistance. Furthermore, other studies have attempted to delineate the direct and indirect effects of the release of norepinephrine from sympathetic nerves on left coronary vascular resistance. Following beta receptor blockade, stellate stimulation produces only coronary vasoconstriction which, in turn, can be blocked by alpha receptor blockade (Feigl, 1967). It therefore appears that with sympathetic stimulation, alpha (coronary vasoconstrictor) and beta (myocardial and vascular) receptors are activated simultaneously, and coronary vasodilation is the dominant response in the left coronary circulation. This was confirmed by a study in which

the net effect of adrenergic stimulation through the sympathetic nerves was an increase in myocardial oxygen extraction, a decrease in coronary venous oxygen content coupled with a rise in coronary blood flow. After alpha receptor blockade, stimulation produced only slight changes in oxygen extraction and coronary venous oxygen content and a 30% greater increase in coronary blood flow (Mohrman and Feigl, 1978). These studies suggested that the overall response of the left coronary vascular bed to sympathetic nerve stimulation is in part dictated by the competition between alpha mediated vasoconstriction and beta 1 or 2 receptor mediated vasodilation. In a more recent report, Powell and Feigl (1979) demonstrated that baroreflex stimulation produced a 21% increase in left coronary disatolic resistance when the metabolic factors are eliminated by beta blockade and maintenance of a constant afterload. The rise in resistance was shown to be mediated by alpha receptor activation.

In the present study, the effects of baroreflex sympathetic stimulation on right coronary hemodynamics and right ventricular performance were determined. It was hypothesized that the metabolic influences in the right ventricular myocardium would be considerably less than in the left ventricular myocardium since myocardial wall tension and cardiac work are much less. This point cannot be documented since it is not technically feasible to directly measure myocardial oxygen consumption for the right ventricle because it is impossible to obtain right coronary venous blood in the dog. However, because the predicted metabolically related influences in the right ventricle would be less during sympathetic stimulation, then perhaps the response of this vascular

bed would be different from that observed for the left coronary vascular bed.

The results of the present study demonstrate that under constant flow or constant pressure perfusion, sympathetic stimulation via the baroreflex mechanism produces an increase in heart rate and mean arterial pressure which indicates an intact reflex. During stimulation, right ventricular performance was enhanced, and was accompanied by a paradoxical increase in right coronary vascular resistance. During such conditions, coronary resistance would be expected to decrease in order to accommodate an increase in coronary oxygen delivery at a time when oxygen demand is apparently increased.

Following beta blockade with 3 mg/Kg propranolol, sympathetic stimulation produced an increase in coronary resistance that was not different in magnitude from that seen prior to beta blockade. It should be noted that beta blockade did not completely prevent the increase in heart rate seen with sympathetic stimulation. This could be interpreted as an incomplete degree of beta blockade which could explain why the coronary vasoconstriction in response to nerve stimulation was not enhanced during these conditions. However, Donald et al. (1968) demonstrated that propranolol does not totally prevent the increase in heart rate in conscious dogs in response to exercise or reflex sympathetic activity, but it does prevent the increase in heart rate during exercise or reflex nerve activity when the hearts are totally denervated. Unblocked denervated hearts show an increase in heart rate during exercise due to elevated levels of circulating catecholamines. These authors suggested that propranolol does not completely block the heart rate

response to exercise or reflex sympathetic activity but does block the response to circulating catecholamines. This report aids in the explanation of the results obtained in the present study. It appears that propranolol is incapable of totally blocking the heart rate response to sympathetic nerve activity.

The administration of propranolol resulted in an increase in resting coronary resistance by approximately 38% in the current study. Whitsitt et al. (1967) demonstrated that the administration of propranolol produced a 37% increase in resting coronary resistance in the left coronary artery. These investigators attributed the increase in resistance to a decrease in heart rate and contractile force which would tend to decrease oxygen consumption and hence oxygen demand. While contractile force was not measured in the present study, heart rate was seen to decrease by approximately 7% in response to beta blockade. It is assumed that the rise in resistance seen with beta blockade is the result of a decrease in the oxygen demand of this vascular bed.

Because the increase in right coronary resistance seen with sympathetic stimulation is not any greater in magnitude following beta blockade, it is conceivable that the vasodilator influence from beta 1 myocardial and/or beta 2 vascular receptor activation are minimal, and only a dominant alpha mediated vasoconstriction is seen in both the normal and beta blocked condition. This point is supported by the work of Murray and Vatner (1979) who recently reported that baroreflex stimulation in the conscious dog produced that same degree of right coronary vasoconstriction after beta blockade as before.

The results presented in Table 1 reaffirm this hypothesis. Sympathetic stimulation produces a significant increase in right coronary resistance, and this increase in resistance can be completely abolished by the infusion of the competitive alpha receptor blocking agent phentolamine. This demonstrates that the mechanism of the neurally induced coronary vasoconstriction involves alpha receptor activation. These results also demonstrate that following alpha blockade, sympathetic stimulation produces no change in coronary resistance. This indicates that in the absence of alpha receptor activity, activation of myocardial and vascular beta receptors through sympathetic nerve activity has no vasodilator effect on the right coronary vascular bed. This is a situation that is quite different from that reported for the left coronary system (Feigl, 1967; Mohrman and Feigl, 1978; Powell and Feigl, 1979; Szentivanyi and Juhasz, 1963) in which sympathetic stimulation produced a substantial decrease in coronary resistance. It seems unlikely that such stimulation would not increase myocardial oxygen consumption of the bed supplied by the right coronary artery to some extent. Manohar et al. (1979) and Murray et al. (1979) have recently shown that blood flow to the right ventricular myocardium is on the order of 70-80 ml/min/100 gm tissue using the microsphere technique. This value is very close to that reported for the left ventricular myocardium. It seems that the right ventricular myocardium may be hyperperfused such that the oxygen delivery to this tissue may actually exceed oxygen demand. If this were the case, it is possible that with enhanced metabolic activity as should be seen with sympathetic stimulation, the increased oxygen demand could be met simply with an increased oxygen

extraction, without a need for an increased coronary flow. A resistance change would not necessarily occur in this situation.

It was also important to determine if the coronary vasoconstriction seen with sympathetic stimulation was altered during constant flow conditions when flow rate was set at levels above and below normal values. These results are depicted in Figure 4. These data show that as flow is decreased from a state of hyperperfusion (perfusion pressure = 170 mmHg) to a state of hypoperfusion (perfusion pressure = 30 mmHg), the degree of vasoconstriction associated with sympathetic stimulation is enhanced. It therefore appears that flow may influence the degree of sympathetic coronary vasoconstriction. This may be the result of low flow producing a higher local concentration of norepinephrine due to a decreased rate of washout, enzymatic degradation or neuronal reuptake.

A further objective of the present study was to determine if the response of the right coronary circulation to adrenergic stimuli is altered when local blood gas tensions are altered. However, as a prelude to this study, it was important to determine the right coronary response to alterations in local blood gas tensions.

It has been well-established that hypoxia is a potent coronary vasodilator. As early as 1913, Markwalder and Starling demonstrated that hypoxia produces coronary vasodilation in the heart-lung preparation. The controversy which has ensued since that time has been whether the vasoactivity associated with low oxygen tensions is a direct effect on the vascular smooth muscle or an indirect effect mediated through the release of vasodilator metabolites. While the work of Berne *et al.* (1958,1964,1974,1975) supports the metabolite theory, other

workers have shown that in isolated strips, the contraction and relaxation of vascular smooth muscle can be induced directly by raising and lowering the oxygen tension of the bathing solution (Detar and Bohr, 1968). The local vasoactivity of oxygen in the intact animal has been demonstrated for the left coronary bed by Daugherty et al. (1967). These investigators reported that oxygen tension had to be decreased below 40 mmHg before a fall in coronary resistance could be seen. Manohar et al. (1979) demonstrated that systemic hypoxia (P_{O_2} = 43 mmHg) produced a 100% increase in right coronary blood flow as determined in the calf using the microsphere technique. However, systemic hypoxia also produces chemoreceptor activation and catecholamine release. Therefore, it is impossible to relate the coronary response seen to the direct effect of hypoxia.

The results from the current study support the pre-existing evidence that hypoxia is a potent coronary vasodilator. The data presented here demonstrates that local hypoxia is associated with a 50-75% decrease in right coronary resistance during both constant flow and constant pressure perfusion. The mechanism by which hypoxia produces coronary vasodilation (direct or indirect) can not be elucidated from this study. It is noted that hypoxia had no effect on right ventricular pressure or dP/dT. However, as previously mentioned, the right ventricle gets a substantial amount of blood supply from the left coronary artery which probably serves to maintain right ventricular function.

The local effects of changes in carbon dioxide tensions (and/or hydrogen ion concentration) on coronary vascular resistance is somewhat controversial. First, it is unclear whether carbon dioxide acts

directly on vascular smooth muscle or whether it acts indirectly through the bicarbonate-buffer system to effect changes in hydrogen ion and consequently calcium ion activity (Mrwa et al., 1974). Reference to carbon dioxide in this discussion will also imply the involvement of the hydrogen ion as well. Second, it appears that the degree of vasoactivity associated with changes in carbon dioxide tension is also related to the experimental conditions under which the studies are made. Daugherty et al. (1967) demonstrated that a decrease in local carbon dioxide tension produced an increase in left coronary vascular resistance when the bed was perfused at constant flow. Similarly, Case and Greenberg (1976) reported that hypocapnia, produced locally in the left coronary bed, produced a substantial increase in coronary resistance when perfused at constant flow. However, Feinberg et al. (1960) reported that systemically administered carbon dioxide was a poor vasodilator in the left coronary artery when perfused at natural flow. This position was also supported by the work of Rooke and Sparks (1978), while Alella et al. (1955) had previously demonstrated that coronary sinus carbon dioxide tension does not rise to vasoactive levels during enhanced cardiac activity.

Data from the present study demonstrates that under constant flow conditions, systemic or local hypocapnia results in a significant increase in right coronary resistance without a measureable change in ventricular performance. During constant pressure perfusion, hypocapnia had a variable effect, producing coronary constriction in four out of seven animals studied. With hypocapnia, ventricular pressure was slightly but significantly decreased, which could, in part, explain the

rise in coronary resistance. However, no change in ventricular function was noted with hypocapnia during constant flow perfusion. Threfore, it seems more likely that changes in coronary resistance seen are related to the direct influences of changes in carbon dioxide tension.

Hypercapnia during constant pressure perfusion was associated with a significant degree of right coronary vasodilation. This coronary vasodilation was also associated with a significant decrease in dP/dT. It is more apparent in this case that the metabolic factors are not mediating the vascular response since a fall in dP/dT should cause a fall in myocardial oxygen consumption and a subsequent increase in coronary resistance. The fact that resistance decreased in response to hypercapnia again suggests that the vascular response is the result of direct effects of carbon dioxide tensions (or H^+ ion) on the coronary vasculature.

These results support the proposal that the vasoactivity associated with local changes in carbon dioxide are related to the direct effects of CO_2 on the right coronary vasculature. These results do not necessarily suggest that CO_2 is involved in the local regulation of blood flow. They do, however, support the work of Daugherty et al. (1967) and Case and Greenberg (1976) in which locally produced changes in carbon dioxide tensions were shown to be vasoactive in the left coronary vascular bed. The work of Feinberg (1960) and Rooke and Sparks (1978) would support the opposite view. However, in both of these studies (Feinberg, Rooke), CO_2 was administered systemically. This methodology greatly complicates the picture since CO_2 has many

systemic effects; such as, chemoreceptor reflex activation, catecholamine release, etc. Therefore, it is impossible to compare these studies with those in which carbon dioxide is introduced locally.

The response to the combination of local coronary hypoxia and hypocapnia was also determined for the right coronary vascular bed. Such a combination produced a substantial coronary vasodilation during constant flow perfusion. The degree of vasodilation seen during these conditions is not different from that which occurs during hypoxia alone, which further supports the concept that when hypoxia and hypocapnia are combined, the effects from hypoxia predominate and coronary vasodilation is seen.

It was also important to determine if changes in blood gas tensions altered the response of the right coronary circulation to adrenergic stimuli. It was hypothesized that perhaps the coronary vasoconstriction seen with sympathetic stimulation would be enhanced during hypocapnia conditions since Yasue et al. (1978) had shown that coronary vasospasm could be induced in patients with Prinzmetal's angina by hyperventilation and systemic alkalosis. It is also generally believed that the effect of catecholamines is enhanced in an alkalotic medium. Hence, the present study investigated the response to sympathetic stimulation with coronary hypoxia, hypocapnia, the combination of the two, as well as hypercapnia. During systemic or local hypocapnia, with constant flow perfusion, the effects of sympathetic stimulation were the same as those seen with normocapnic perfusion. Therefore, it appears that the degree of coronary vasoconstriction is not changed when the bed is rendered hypocapnic. However, the vasoconstrictor effects of hypocapnia and

sympathetic stimulation are additive such that the combination of the two produces a substantial degree of coronary vasoconstriction.

The results obtained with constant pressure perfusion are not as clear. As a group it appears that the sympathetic vasoconstriction on the coronary bed was prevented during hypocapnia. A closer examination of the results reveals that three out of the seven animals studied did not respond to stimulation during hypocapnic perfusion. Of the four that did respond, the coronary vasoconstriction seen with stimulation was not different in magnitude from that which occurred during control conditions. This suggests that the results from the constant pressure group may not be much different from those obtained with constant flow perfusion.

Sympathetic stimulation during hypoxic conditions with either constant flow or constant pressure perfusion had no effect on ventricular function or coronary resistance. Detar and Bohr (1972) demonstrated that isolated aortic strips showed a profound decrease in contractile response to epinephrine when exposed to a bath with a low oxygen tension. This suggests that the contractile machinery in vascular smooth muscle is substantially depressed by an oxygen lack. This finding is supported by the present study in that the ventricular and coronary response to stimulation were completely blocked during hypoxic perfusion. As previously mentioned, when hypoxia and hypocapnia are combined during constant flow perfusion, a coronary vasodilation is seen. With subsequent sympathetic stimulation, the enhanced ventricular performance and coronary vasoconstriction occur to a similar degree as seen during normoxic perfusion. The fact that sympathetic stimulation produces

coronary vasoconstriction when the coronary is perfused with hypoxic and hypocapnic blood does not support the previously mentioned hypothesis that the ability of a blood vessel to actively develop tension during hypoxic conditions is greatly attenuated. The fact that the ability of the vessel to constrict during hypoxic and hypocapnic conditions is preserved suggests that the interactions between sympathetic nerve activity and alterations in local blood gas tensions (in relation to their effects on coronary resistance) may occur on levels other than that simply predicted by the direct effects of blood gas tensions alone. For instance, changes in pH may be partially responsible for the modulation of the sympathetic response.

During constant pressure perfusion, hypercapnia produced a decrease in coronary resistance and dP/dT. Subsequent sympathetic stimulation resulted in an increase in ventricular performance as well as coronary resistance. This increase in resistance was slightly but significantly decreased in magnitude when compared to that which occurred during normoxic, normocapnic perfusion.

From these studies it appears that the response of the right ventricle and right coronary circulation to sympathetic stimulation is unaffected by local or systemic hypocapnia, or by the combination of hypoxia and hypocapnia. The response is slightly diminished by local hypercapnia and is completely abolished by local hypoxia. It can be concluded from these experiments that local changes in blood gas tensions may alter the response of the coronary circulation to nerve stimulation.

Norepinephrine (NE) is a mixed adrenergic agonist, exhibiting primarily alpha receptor affinity with some degree of beta receptor affinity (Goodman and Gilman, 1970). The effect of exogenously administered NE on coronary blood flow has been reported by several investigators. Hardin et al. (1961) demonstrated that infusion of NE resulted in a transient increase in total coronary resistance which precedes the increase in heart rate. This is followed by a prolonged decrease in coronary resistance. This observation was also made in an earlier report by Berne et al. (1958) in which NE was administered to the left coronary artery of the beating, intact dog heart. In a more recent study, Malinzak et al. (1978) demonstrated that intravenous injections of NE has a differential response, depending on the portion of the vascular segment in question. The large artery segment of the left coronary artery responds to NE with an increase in resistance on the order of 190%. This rise in resistance could be prevented with alpha receptor blockade. The vascular segment distal to the large artery segment responds to NE with a 53% decrease in resistance. Coronary blood flow increases 250% above control with aortic pressure increasing to a lesser extent indicating that total coronary resistance has also decreased. Following beta blockade with propranolol, NE causes small artery resistance to increase while large artery resistance is relatively unchanged. Large artery resistance is unchanged during these conditions because the administration of propranolol results in a near maximal coronary vasoconstriction in the large artery segment. Zuberbuhler and Bohr (1965) demonstrated that large vascular strips taken from the left coronary arteries in dogs responded to NE with an

increase in tension while strips taken from small coronary arteries responded to NE with a decrease in tension. These studies suggest that NE acts directly on coronary vessels to produce alpha mediated vasoconstriction which is primarily found in the large artery segment. The small coronary arteries apparently have a population of beta receptors which mediate coronary vasodilation. NE also has indirect vasodilatory effects which are primarily mediated through the enhanced metabolism seen with stimulation of the myocardial beta 1 receptor. The beta 2 receptors located in the small coronary vessels seem to directly mediate coronary vasodilation when stimulated by beta agonists (Klocke et al., 1965; Braunwald et al., 1976; McRaven et al., 1971). However, Hamilton and Feigl (1976) observed only slight coronary vascular responses in the left coronary bed which were attributable to vascular beta 2 receptors, and concluded that they are of little functional significance. To complicate the issue, Baron and Bohr (1972) using coronary strips reported that practolol (beta 1 blocker) abolished the coronary vascular response to a pure beta agonist (isoproterenol), suggesting that the vascular beta receptors may be of the beta 1 variety, the same as those found in the myocardium.

The current study presents data pertaining to the steady state response of the right coronary circulation to intracoronary infusions of NE. In virtually every animal (Tables 5, 6 and 9), NE increased heart rate, ventricular pressure during both constant pressure and constant flow perfusion. The infusion of NE was also associated in most instances with a decrease in right coronary vascular resistance. This coronary vascular response is different from that seen with sympathetic

stimulation. It is hypothesized that the reason nerve stimulation produces coronary constriction and NE produces coronary dilation may be the result of a greater stimulation of the myocardium with NE producing a significant metabolic influence on coronary resistance. The results in Figure 5 demonstrate that following beta-blockade with propranolol, the heart rate response to NE was completely blocked and NE produced a significant increase in coronary resistance during constant flow perfusion. This suggests that norepinephrine infusion results in coronary vasodilation in the control state due to an increased myocardial metabolism. However, it is uncertain in this series of experiments to what extent the vascular beta 2 receptors play in the vasodilatory response. While it is generally believed that vascular beta receptors do not play a large role in regulating vascular resistance, McRaven et al. (1971) suggested that as much as 70% of the left coronary vasodilation seen with isoproterenol infusion was due to stimulation of the vascular beta 2 receptors. In this regard, we have begun a study to try and understand the precise mechanism of the vasodilation seen with NE challenge in the present study. The responses to intracoronary bolus injections of NE and isoproterenol were obtained for the right coronary artery perfused at constant flow, before and after selective beta 1 receptor blockade with practolol (10 mg/kg), alpha receptor blockade with phentolamine (600 μg/min, intracoronary infusion) and beta 1 and 2 receptor blockade with propranolol (3 mg/kg). The results of this experiment for four animals is represented in Figure 18. Only the coronary resistance values are shown.

Figure 18. Effects of intracoronary bolus injections of isoproterenol (0.5 μg) and norepinephrine (1 μg) on right coronary vascular resistance before and after selective adrenergic receptor blockade with practolol (10 mg/Kg), propranolol (3 mg/Kg) and phentolamine (600 μg/min infusion) during constant flow perfusion.

N = 4
* = Significantly different from control at $P < 0.05$.

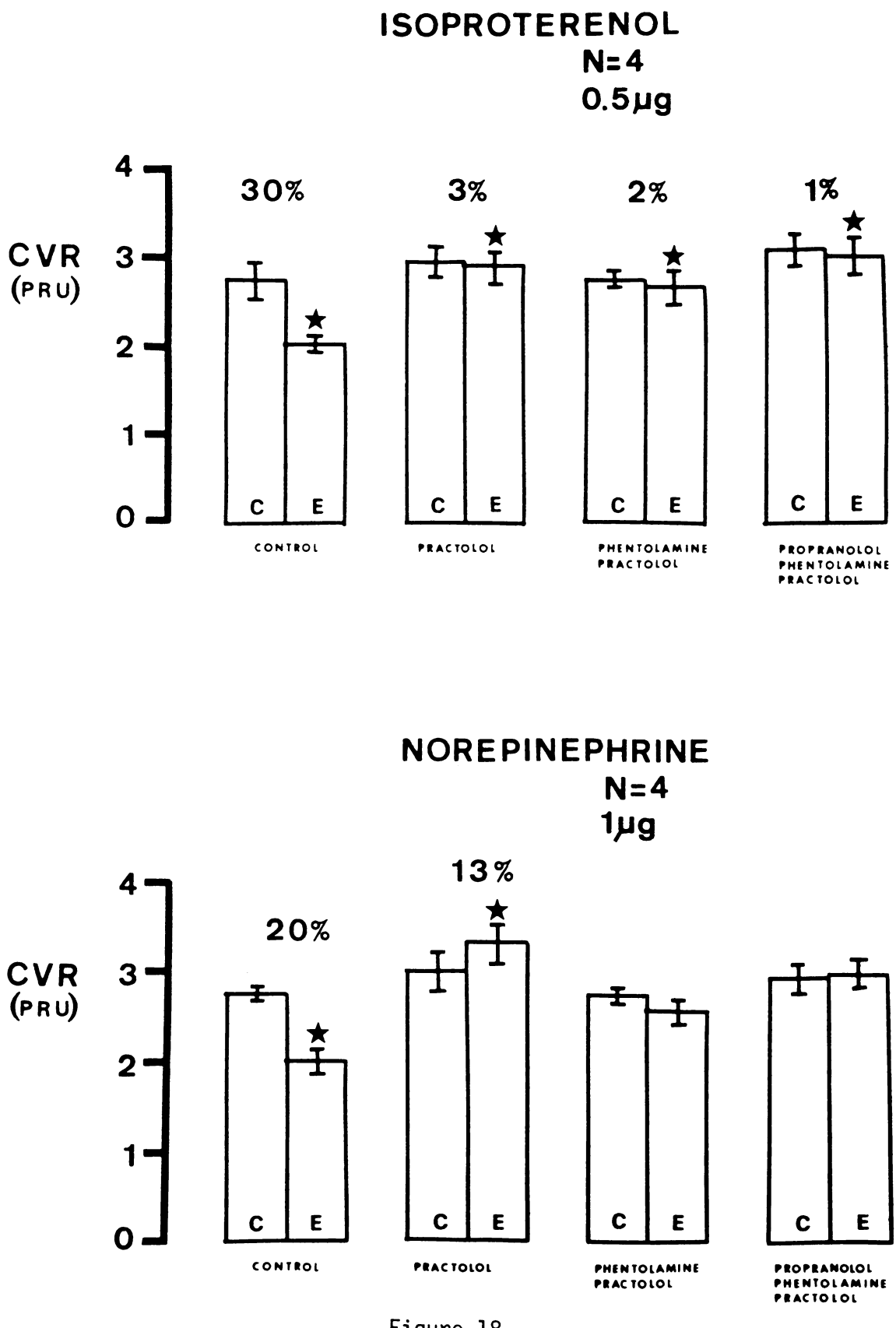

ISOPROTERENOL
N=4
0.5µg
CVR
(PRU)
4
3
2
1
0
30%
3%
2%
1%
C
E
CONTROL
PRACTOLOL
PHENTOLAMINE
PRACTOLOL
PROPRANOLOL
PHENTOLAMINE
PRACTOLOL
NOREPINEPHRINE
N=4
1µg
CVR
(PRU)
20%
13%
CONTROL
PRACTOLOL
PHENTOLAMINE
PRACTOLOL
PROPRANOLOL
PHENTOLAMINE
PRACTOLOL

Figure 18

Assuming that practolol blocks only the beta 1 receptor, these results demonstrate that following beta 1 blockade with practolol, isoproterenol causes a significant but very slight coronary vasodilation compared to the control response. This suggests that the vasodilation attributable to vascular beta 2 receptors is minimal. As for the results with NE injection, after beta 1 blockade with practolol, the vasodilation seen during control conditions is converted to a vasoconstriction. This finding supports the hypothesis that the vasodilation seen with intracoronary infusion of NE is indirect and due primarily to the fact that myocardial metabolism is increased through beta 1 receptor activation. The coronary vasoconstriction seen with NE and practolol is blocked when phentoalmine is infused into the coronary artery. These results attest to the fact that the response of the right coronary circulation to exogenous NE is dictated by the competition between alpha vasoconstrictor receptors and beta 1 myocardial receptors. The net effect of intracoronary NE infusion or injection is vasodilation primarily due to a greater influence of metabolic vasodilators. Vascular beta 2 receptors have little functional significance in this vascular bed.

The response of the coronary circulation to NE in conscious dogs is apparently somewhat different than that seen when the animals are anesthetized. Vatner et al. (1974) demonstrated that intravenous NE in the awake animal produced a brief fall in left coronary resistance followed by a sustained increase in coronary resistance. These responses were prevented by propranolol (early dilation) and phentolamine (late vasoconstriction), respectively. When the study was repeated

with the same animals anesthetized with sodium pentobarbital, only coronary dilation was seen. This phenomenon was also reported by Pitt et al. (1967). In order to try and relate the data obtained in the present study to the unanesthetized situation, two dogs were chronically instrumented for determination of right coronary blood flow and resistance in the awake state. In one animal, bolus injections of intracoronary NE resulted in a transient increase in coronary resistance followed by a prolonged decrease. The initial rise in resistance could be prevented to a great extent by alpha blockade (Figure 16). In the second animal, no transients were seen as NE resulted only in coronary vasodilation. These results support the data obtained in the present study with anesthetized animals except that no transient responses were seen. It is not entirely clear how this data relates to that published by other investigators since these responses were obtained in different vascular beds using different techniques.

The present study examined the effect of various flow rates on the right coronary response to NE. In the anesthetized dog, the response to NE was not different at any of the three flow rates studied. This result is different from that seen with sympathetic stimulation, in which the response was enhanced at low flow rates. With NE infusion, a greater release of vasodilator substances compared to nerve stimulation would be predicted. Hence, as flow is decreased, the washout of these vasodilators would be diminished. Therefore, it is not surprising that the response to NE at different flow rates is unaffected. This result is supported by the work of Hardin et al. (1961) in which flow

did not affect the response of the left coronary circulation to NE infusion.

In the anesthetized dog, the response to NE was not different at any of the three flow rates studied. However, in the unanesthetized preparation, NE was administered during myocardial ischemia, which was produced by inflation of a balloon cuff around the coronary artery. Coronary perfusion pressure was decreased by approximately 50% and coronary blood flow by approximately 20% by cuff inflation. Subsequent intracoronary bolus injection of NE produced a substantial (100%) increase in coronary resistance. This finding suggests that as flow is lowered, the response to NE is altered. This is supported by a preliminary report by Walinsky et al. (1978) who showed that NE caused an increase in left coronary blood flow during normal perfusion, but caused a significant decrease in blood flow when the coronary artery was stenotic.

There is a paucity of evidence in the literature relating the effect of changing blood gas tensions locally in the coronary bed on the response to catecholamines. As previously mentioned, Detar and Bohr (1972) showed that the contractile responses of aortic strips to epinephrine was drastically reduced when the oxygen tension of the bath was lowered to a level of 1mmHg. Since NE has been shown to be a good vasodilator through indirect mechanisms, during hypoxia (a condition which decreases resistance substantially) it might be expected that little further vasodilation would occur in response to NE.

It is also known that catecholamines exert a greater effect in an alkalotic medium as seen with hypocapnia blood, and less of an effect

with an acidotic medium as seen with hypercapnic blood. Therefore, NE may exert a greater vasodilator influence as the carbon dioxide tension of the coronary blood is lowered. The present study attempted to define the effects of NE during alterations in coronary blood gas tensions. The results suggest that coronary hypoxia diminishes the response to NE during constant flow perfusion, and completely prevents the response during constant pressure perfusion. No vasoconstrictor activity was seen with NE during hypoxia which suggests that the vascular bed is nearly maximally dilated, and is for the most part incapable of constricting in this situation. This result then gives *in vivo* support to the *in vitro* work of Detar and Bohr (1972) performed on left coronary vascular strips.

At low doses (0.25 μg/min) of NE, systemic or local hypocapnia prevented the dilation seen in response to the NE during constant flow perfusion. However, if the dose was doubled, the response was not prevented by hypocapnia. If the bed was perfused at constant pressure, local hypocapnia again did not alter the response to the low dose of NE, and the same degree of vasodilation was again seen. During constant flow hypocapnia, statistical analysis showed that there was no significant response to NE, however, four out of the six animals studied showed the same degree of vasodilation as seen with NE during control perfusion. Using the more physiological of the perfusion techniques (constant pressure perfusion), it appears that hypocapnia has little, if any, effect on the response of the right coronary circulation to NE infusion. The data obtained from the constant flow studies would also support this view.

The effects of NE during hypercapnic conditions were observed during constant pressure perfusion. Hypercapnia alone produced a significant coronary vasodilation, although not to the same extent as that seen with hypoxia. The infusion of NE during hypercapnia had no effect on coronary resistance; however, it did produce an increase in ventricular function as judged by dP/dT. While it was shown (Figure 1) that there is no correlation between initial resistance and the change in resistance in response to NE in our preparation, the initial resistances obtained with hypercapnia fell out of the range analyzed in Figure 1. At extremely low values of initial resistance, it is only reasonable to assume that a vasodilator would have less of an effect. This seems to be the case in the present study. The same result occurs when hypoxia and hypocapnia are combined during constant pressure perfusion. Such a combination results in a profound decrease in resistance, and subsequent NE infusion results in a diminished vasodilatory response at the high dose and no response at the low dose.

As one progresses from a hypercapnia to a hypocapnia medium, the concentration of hydrogen ions decreases. This causes increased binding of calcium ions to sites on contractile proteins in cardiac and vascular smooth muscle, which increases contractility or smooth muscle tension (Katz and Hecht, 1969). This may also result in a transient release of histamine and/or changes in hematocrit via changes in the size of red blood cells (Kontos et al., 1971). These effects could be responsible for enhanced cardiac contractility (histamine) and changes in vascular resistance through changes in viscosity (RBC size). In the present study, no increases in right ventricular contractility were appreciated

with hypocapnia; however, a substantial increase in coronary resistance was noted. Since it is generally believed that the effect of catecholamines is enhanced in an alkalotic medium, it was surprising that no greater response to NE infusion was seen in the presence of low levels of carbon dioxide tension. The same was true for sympathetic stimulation. However, the response to these stimuli were attenuated when the carbon dioxide tension of the blood was increased (hypercapnia).

Therefore, these results support the concept that changes in carbon dioxide tension may alter the vascular response to endogenous or exogenous NE in this vascular bed. While the response to catecholamines was not enhanced during hypocapnia, it was depressed by hypercapnia.

The role of the endogenous prostaglandins in the regulation of either left or right coronary blood flow is not well-defined. Investigators have proposed several hypotheses for participation of the prostaglandins in the regulation of coronary blood flow; however, due to differing experimental results, a general agreement among investigators has not been reached. Part of the disparity of beliefs may be due to different experimental models and techniques.

Several investigators believe that the prostaglandins participate in the coronary vascular response to hypoxia. Needleman et al. (1975) showed that hypoxia caused a transient release of prostaglandins from isolated perfused rabbit heart. Afonso et al. (1974) demonstrated that hypoxic coronary vasodilation was attenuated following blockade of prostaglandin synthesis with indomethacin in the closed-chest dog. However, Needleman et al. (1975) in the isolated perfused rabbit heart and Hintze and Kaley (1977) in the open-chest dog showed that

indomethacin had no effect on hypoxic coronary vasodilation. In vitro studies by Kalsner (1975,1976) demonstrated that hypoxia caused release of vasodilator prostaglandins from isolated bovine coronary artery strips. Alexander et al. (1975) proposed a role for prostaglandins in the genesis of coronary reactive hyperemia in a report that demonstrated the attenuation of the reactive hyperemia and prostaglandin (PGE) release from the left coronary bed of the dog following administration of indomethacin. In a report that contradicted these findings, Owen et al. (1975) reported that indomethacin had no effect of left coronary artery reactive hyperemia in the closed-chest dog. This was confirmed by Needleman (1975) and Hintze and Kaley (1977).

In the present study, indomethacin had no significant effect on resting right coronary resistance. However, resistance was increased in eight of nine animals by approximately 10%. It is possible that a baseline level of vasodilator prostaglandins is being released by these vessels; however, the data are not definitive on this point.

The effect of indomethacin on the response of the right coronary circulation to interruptions of flow was also determined. During constant flow perfusion, a 20 second interruption of flow produced a reactive dilation as seen in Figure 12. Following administration of indomethacin, the reactive dilation was significantly decreased in magnitude (area) and duration by 24% and 6%, respectively. The hypoxia which results from the flow deprivation may enhance the synthesis of vasodilator prostaglandins. This is supported by the observation that the attenuation in the magnitude of the response (area) is greater than that predicted by the effects of indomethacin alone on resting coronary

resistance. Indomethacin increased resting coronary resistance by approximately 10% in most animals, but decreased the magnitude of the reactive dilation by 24%. This suggests that the prostaglandins may be involved in the response to interruptions of flow in this preparation. In this series of experiments, the methodology involved perfusion of the coronary circulation by isolating the vessel, cutting through the wall of the vessel and inserting a cannula into the lumen. Damage to the wall of blood vessels is thought to enhance the synthesis of vasodilator prostaglandins (Sivakoff et al., 1979). This factor may be responsible for an enhanced baseline synthesis of vasodilator prostaglandins; however, it does not account for the enhanced magnitude of reactive dilation following administration of indomethacin seen in the present study.

In an additional study, the effect of brief occlusions of the right coronary artery in the conscious, intact animal instrumented for the measurement of right coronary blood flow was determined before and after administration of indomethacin. The results of this study are illustrated in Figure 14. The reactive hyperemic response to a 3 second occlusion was decreased in terms of peak flow and duration of the response following indomethacin. Indomethacin had no effect on the response to 5, 10, or 30 second occlusions. The conditions under which these observations were made were far more physiological than those with the anesthetized open-chest animal perfused at constant flow. However, this data represents only one animal, and therefore it is difficult to relate this result to the group of anesthetized animals. While these results are far from definitive, it appears that the

prostaglandins may play a minor role in the response of the right coronary circulation to periods of brief occlusions.

The issue of the involvement of prostaglandins in the regulation of coronary blood flow during enhanced cardiac activity is also controversial. Sunahara and Talesnik (1973) reported that the coronary flow response in isolated rat hearts to NE was enhanced following indomethacin administration while the contractile force response was unchanged. Talesnik and Sunahara (1974) later showed that prostaglandin E1 infusion (in doses which did not affect coronary resistance) also attenuated the coronary flow response to NE or isoproterenol. The coronary response to other direct vasodilators was unaffected. These investigators suggested that the prostaglandins may act as a brake on coronary metabolic vasodilation. Harlan et al. (1978) employed the use of an intact dog model to show that indomethacin had no effect on the relationship between left coronary blood flow and myocardial oxygen consumption in response to isoproterenol infusions. This study provides evidence to support the concept that the endogenous prostaglandins do not play a role in the regulation of coronary blood flow during enhanced metabolic activity, at least in the intact anesthetized dog.

In the present study, the effects of sympathetic stimulation and NE infusion were determined before and after the blockade of prostaglandin synthesis with indomethacin. These results (depicted in Figure 10) demonstrate that the coronary constriction seen with sympathetic stimulation following indomethacin is not different from that seen prior to indomethacin. NE prior to indomethacin produced a significant coronary vasodilation. Following indomethacin NE had no

no statistically significant effect on coronary resistance. However, six out of seven animals demonstrated a degree of coronary vasodilation in response to NE following indomethacin that was not different from that seen prior to indomethacin. One animal out of the group showed an increase in resistance with NE infusion following indomethacin administration. It is also noted that the coronary vascular response to systemic hypocapnia is not different following indomethacin administration as compared to before.

Therefore, it appears that the response to the right coronary circulation to adrenergic stimulation is not affected by the blockade of prostaglandin synthesis. These findings are in contrast to those reported for the left coronary circulation by Talesnik and Sunahara (1974) and Sunahara and Talesnik (1973) which provide good evidence for the participation of the prostaglandins in the left coronary flow response to norepinephrine or isoproterenol.

It has been reported by many investigators that the left coronary circulation demonstrates the ability to autoregulate its blood flow (Eckel et al., 1949; Fishback et al., 1959; Scott et al., 1960; Brandfonbrener, 1969; Driscoll, 1964). However, the autoregulatory ability of the right coronary circulation has never been described. In the present study, autoregulation was assessed by pump perfusing the right coronary artery and making stepwise changes in flow (constant flow) or pressure (constant pressure) and observing the resultant responses. The results of these maneuvers during constant flow perfusion are depicted in Figure 6. These data demonstrate that the pressure/flow relationships are virtually linear over the range of flow

studied. The relationship between flow and calculated resistance is such that resistance remains relatively constant as flow is decreased over the range of 60-10 ml/min. If this bed were autoregulating to any great extent, resistance would decrease over this range. At a flow of approximately 10 ml/min. resistance dramatically increases. This is probably due to the passive collapse of the vasculature. These data would suggest that the right coronary circulation does not demonstrate a great ability to autoregulate. In order to support this result, the ability of the right coronary circulation to autoregulate was assessed during constant pressure perfusion. Perfusion pressure was varied in a stepwise manner over the range of 50-175 mmHg and the flow response at each new level of pressure was recorded. These results are depicted in Figure 13. These data demonstrate that as pressure is increased over the range of 75-150 mmHg, flow is maintained relatively constant. The relationship between pressure and calculated resistance shows that resistance generally increases over the range of pressures studied. The data suggest that during constant pressure conditions, this vascular bed autoregulates to a much greater extent than suggested from the constant flow studies.

The pressure/flow relationships were also determined in one unanesthetized dog chronically instrumented for the determination of right coronary hemodynamics. A hydraulic occluder was inflated in a stepwise manner to lower pressure over a range of 90-20 mmHg, and the coronary flow response recorded. Over this range, pressure decreases out of proportion to flow such that flow appeared to be relatively well-maintained. As pressure falls, calculated resistance also falls in

order to maintain flow. This data obtained during natural flow conditions supports the results obtained during constant pressure perfusion in the anesthetized dog.

It therefore appears that this vascular bed demonstrates the ability to autoregulate much better during constant pressure, natural flow conditions, than during constant flow conditions. This conflicting result can be hypothetically explained on the basis of myocardial oxygen consumption. During constant pressure perfusion, flow is allowed to vary according to the needs of the myocardium. As pressure is increased, a myogenic response coupled with a change in the concentration of vasodilator metabolites may occur which limit the rise in blood flow through a rise in resistance.

During constant flow perfusion, flow is mechanically increased and held constant at the new level. Perfusion pressure increases which would again elicit a myogenic response. However, this would not limit the increase in flow since it is maintained at a constant level. This sustained higher flow rate will increase O_2 delivery and may raise oxygen consumption and hold it at higher steady state value. The increased oxygen consumption may result in elevated levels of vasodilator metabolites and thereby decrease resistance. The result is that as flow is increased in a stepwise manner, resistance does not increase, as seen during constant pressure perfusion. Instead, resistance is maintained at a relatively lower level, thereby producing the flat flow/resistance relationship as depicted in Figure 6. Scott *et al.* (1969) reported a virtually identical pressure/flow and flow/resistance relationship when

the total coronary bed was perfused at constant flow in the beating non-working dog heart.

The author is currently conducting experiments on the right coronary circulation of the pig in which pressure/flow/oxygen consumption determinations are made during constant flow and constant pressure perfusion in the same animal. The preliminary data support the hypothesis that for the same increase in pressure, a relatively greater increase in oxygen consumption is seen with constant flow perfusion compared to constant pressure perfusion. The pressure/flow curves are also similar for the pig and the dog with the two perfusion techniques. It, therefore, appears that for the normal heart under constant pressure, natural flow conditions, the right coronary circulation does exhibit the ability to autoregulate its blood flow. It is also possible that an experimental artifact influenced the results obtained during constant flow conditions. Perfusion during these studies at constant flow was accomplished with a Sigmamotor pump, an apparatus known to cause some hemolysis related to pump speed. Moreover, hemolyzed blood is known to cause coronary dilation. Therefore, as pump flow was increased, hemolysis increased and the concentration of dilator substance in the coronary blood increased which offset the autoregulatory response. This would not be as likely to occur during constant pressure perfusion as a roller pump was used, a device which is far less traumatic to the blood.

The metabolic hypothesis for the regulation of left coronary blood flow is currently the subject of intense investigation. It is also generally felt by most investigators to be the dominant mechanism

by which coronary blood flow is altered to meet the moment to moment oxygen demands of the tissue. In recent years, however, work by several investigators has shown that there is a direct neural component which antagonizes the metabolically mediate changes in coronary vascular resistance. Such work has led to the concept of competition between neurally mediated coronary vasoconstriction and metabolically mediated coronary vasodilation. The vast bulk of the evidence to support these concepts has been derived from experiments performed on the left coronary circulation. It is obvious that in this vascular bed, the metabolic component is normally the dominant factor in the moment to moment regulation of coronary blood flow.

The current study as well as the work of other investigators (Lowensohn et al., 1978; Murray and Vatner, 1979) indicate that the metabolic requirements of the myocardium supplied by the right coronary artery are much less with respect to the left ventricle. This is based on the observation that the reactive hyperemic responses to the same duration of coronary occlusions are less in the right coronary bed (Lowensohn et al., 1978) than for those reported for the left (Olsson and Gregg, 1975). Furthermore, the response of the right coronary circulation to baroreflex sympathetic activation produces a coronary constriction, which is not altered by beta blockade (Murray and Vatner, 1979). The present study confirmed this and also demonstrated that sympathetic stimulation following alpha receptor blockade produced no significant effect on right coronary resistance. This suggests that under these conditions, right ventricular metabolism is minimally affected. Similar stimulation produces a substantial decrease in left

coronary resistance which is prevented when the metabolic effects are blocked with propranolol (DiSalvo et al., 1971; Feigl, 1968).

Determinations of regional coronary blood flow for the left and right ventricles have been reported using the microsphere technique. Cobb et al. (1974) demonstrated that coronary blood flow in the left ventricle of the awake dog averaged 70-80 ml/min/100 g and increased to 100-110 ml/min/100 g under conditions of anesthesia. Using similar techniques, Murray et al. (1979) reported coronary blood flow in the right ventricle of the awake dog to be 63 ml/min/100 g, a value somewhat lower than that reported for the left. Manohar et al. (1979) reported values of 73 ml/min/100 g right ventricle in the awake calf also using the microsphere technique. This value closely approximates the reported flows for the left ventricle. The fact that this value is slightly higher than that reported by Murray could be a species difference. These results suggest that the coronary flow/gm of tissue may be somewhat lower for the right ventricular myocardium as compared to the left. This concept is also supported by the values reported for coronary resistances in the left versus the right coronary circulations. Murray et al. (1979) reported values for mean left coronary vascular resistances in the anesthetized dog perfused at constant flow to be on the order of 1.4 mmHg/ml/min/100 g LV. Using a similar preparation, Case and Greenberg (1976) obtained a value of 1.27 mmHg/ml/min/100 g LV. Mean values for left coronary resistance may give an inaccurately high estimate due to the substantial extravascular compressive forces which act on the left coronary vasculature during systole. Therefore, left coronary resistance obtained during the late disastolic phase of the

cardiac cycle gives a more accurate assessment of the resistance attributable to vascular smooth muscle activity of the left coronary vascular bed. Murray and Vatner (1979) reported left coronary diastolic resistance in resting, conscious dogs to be on the order of 0.8 mmHg/ml/min. In contrast, Lowensohn et al. (1976) demonstrated that mean right coronary resistance in the awake dog was 2.1-2.9 mmHg/ml/min/100 g RV, with diastolic resistance being only slightly less. These data also suggest that flow per gram of tissue is less in the right ventricle than the left.

The present study employed two perfusion techniques. Constant flow perfusion utilized a finger-type Sigmamotor pump. Initially, flow was set to produce a perfusion pressure of approximately 110 mmHg. Flow per 100 g right ventricle ranged from 60-85 ml/min/100 g and averaged 72 ml/min/100 g for all animals studied. These values are similar to those reported for the left ventricular myocardium. However, during constant pressure perfusion, values averaged 53 ml/min/100 g at a perfusion pressure of 100 mmHg. An explanation for the difference in values for right coronary blood flow using these two perfusion techniques may be found in the type of pumps used in each perfusion system. The Sigmamotor pump, used to provide perfusion at constant flow, is known to produce higher blood flows for the same perfusion pressure in skeletal muscle when compared to the flows seen under natural flow conditions. This may be accounted for by the hemolysis of red blood cells produced by the Sigmamotor pump, and subsequent release of vasodilator substances, such as adenine nucleotides. In the constant pressure system, a Holter roller pump was used to deliver blood to the

coronary artery. This type of pump is known to be less traumatic for red blood cells and hence hemolysis is not as big a factor. This could then account for the higher resting right coronary blood flows seen with constant flow perfusion. It is therefore assumed, that the flows obtained with the constant pressure perfusion apparatus are more representative of the coronary flows that are actually experienced by the normal right ventricle. This would suggest that the flow in the right ventricular myocardium may be less than that appreciated by the left ventricle. Certainly, the oxygen consumption of the right ventricle must be less than that of the left ventricle since the work performed by the right ventricle is 1/6 that of the left, and wall tension as predicted from the law of Laplace would also be less. These two factors are primary determinants of myocardial oxygen consumption. It would, therefore, stand to reason that while the flow to the right ventricle is somewhat less than to the left, the oxygen consumption of the right ventricle may be far less than that seen in the left. This would produce a greater flow/metabolic ratio that is much greater for the right ventricle. In this situation, oxygen delivery to the right ventricular myocardium may greatly exceed the oxygen demand relative to the left. The demands of increasing oxygen consumption, within certain limits, could therefore be theoretically met by increasing oxygen extraction. It is unfortunate that right coronary venous blood cannot be obtained in the dog. However, preliminary studies by the author in the right coronary circulation of the pig have provided several interesting observations that may support the aforementioned theories. First, the difference in right coronary arterio-venous oxygen content under resting

conditions is approximately 6 vols. percent, compared to the 15 vols. percent reported for the left ventricle of the dog and the pig. This indicates that the oxygen extraction by the right ventricle is far less than that of the left. Second, the oxygen consumption for the tissue supplied by the right coronary artery ranges from 3-5 ml 02/min/100 g RV., compared to 8-10 ml 02/min/100 g reported for the left ventricle.

These preliminary results obtained in the pig support the data presented in the current study. It is apparent that oxygen extraction in the left coronary circulation is nearly maximal. Therefore, increased oxygen demand through increased oxygen consumption must be met mainly by increases in left coronary blood flow. This, coupled with the fact that the left ventricle has a high rate of oxygen consumption supports the hypothesis that metabolic factors may serve to provide the dominant influence in the moment to moment regulation of left coronary blood flow. Theoretically, the flow to metabolism ratio in the right coronary circulation should be greater than in the left coronary circulation. Therefore, within limits, metabolic factors would not be expected to play as large a role in the control of right coronary blood flow.

The current studies support this hypothesis in that they demonstrate that the autoregulatory response in the right coronary circulation is less effective than in the left, and that the right coronary vascular bed responds differently in the steady state to sympathetic stimulation. Moreover, sympathetic stimulation following alpha blockade does not decrease right coronary vascular resistance.

SUMMARY AND CONCLUSIONS

1. Local coronary hypoxia, hypercapnia, and the combination of hypoxia and hypocapnia produce significant right coronary vasodilation without an associated change in ventricular function as judged by right ventricular systolic pressure and dP/dT. Local or systemic hypocapnia produce a substantial increase in right coronary resistance. From these studies it appears that alterations in local oxygen or carbon dioxide tensions are capable of producing changes in right coronary resistance. The effects of carbon dioxide (hydrogen ion concentration) are most likely mediated through direct effects on the coronary vasculature while it is unclear whether the vasoactivity associated with low oxygen tensions are mediated through direct or indirect mechanisms.

2. Sympathetic (baroreflex) stimulation produces an elevated right ventricular pressure, dP/dT, and right coronary vascular resistance. This effect is not enhanced by beta blockade, but is prevented by alpha blockade. Stimulation after alpha blockade produces no significant effect on right coronary resistance. These data suggest that the response of the right coronary circulation to sympathetic stimulation is dominated by alpha mediated coronary vasoconstriction. Apparently, stimulation has little influence on metabolic vasodilator production.

3. The response of the right coronary circulation to sympathetic stimulation was determined under a variety of background conditions

to attempt to determine if there are conditions which alter the response of this bed to stimulation. The present study demonstrates that decreasing flow to this vascular bed results in an enhanced coronary vasoconstriction when the sympathetic nervous system is activated. The response to stimulation is not altered during systemic or local hypocapnia; however, the vasoconstrictor effects of these two stimuli are additive. Local hypercapnia attenuates the coronary vasoconstriction seen with stimulation and local hypoxia prevents the response altogether. Therefore, decreases in flow, oxygen or carbon dioxide tensions may serve to modulate the response of this vascular bed to sympathetic nerve activity.

4. Intracoronary infusion of NE produced an increase in right ventricular systolic pressure, dP/dT, and a pronounced fall in right coronary vascular resistance. Following beta receptor blockade with propranolol or practolol, NE produced a significant increase in right coronary resistance. This rise in resistance could be prevented with alpha receptor blockade. These data suggest that NE produces dilation of the right coronary vascular bed primarily through a stimulation of myocardial metabolism through beta 1 receptor activation. Blockade of the beta receptors cause an unmasking of the alpha receptor mediated coronary vasoconstriction.

5. It was also determined whether or not the response of the right coronary circulation to NE was altered by changes in flow, oxygen or carbon dioxide tensions in the coronary blood. These data suggest that the response of this vascular bed to NE infusion was unaltered with the changes in flow. Furthermore, the response to NE was unaltered

during local or systemic hypocapnia, but was attenuated during local hypoxia or hypercapnia.

6. In order to determine if locally synthesized prostaglandins were involved in the regulation of blood flow in the right coronary vascular bed, the responses to brief interruptions of coronary blood flow, sympathetic stimulation and NE infusion were obtained before and after the administration of indomethacin. These data suggest that the prostaglandins may be involved in the reactive dilation associated with 20 second interruptions of flow. The coronary vascular response to sympathetic stimulation or NE infusion was apparently unaffected by the blockade of prostaglandin synthesis. Therefore, the prostaglandins do not appear to be involved in the response of the right coronary circulation to adrenergic stimulation.

7. The ability of this vascular bed to autoregulate was assessed using constant flow and constant pressure perfusion techniques. During constant flow perfusion stepwise changes in right coronary flow produced a virtually linear pressure/flow relationship over the pressure range of 25-180 mmHg. As flow was decreased, calculated resistance remained constant until pressure falls below 30 mmHg at which point resistance increases substantially. This suggests that the bed is autoregulating but only to a minor extent. During constant pressure perfusion, pressure was varied in a stepwise fashion over this range of 50-175 mmHg. As pressure increases over the range of 75-150 mmHg, flow remains relatively constant. Calculated resistance generally increases over this same range of pressures. These data suggest that the right coronary bed demonstrates much better autoregulation with constant pressure

perfusion, although not to the same extent as that reported for the left coronary vascular bed.

In conclusion, this study suggests that the right coronary vascular bed is capable of exhibiting some degree of local regulation. However, within limits, the influence of metabolic factors do not appear to play as large a role in regulation of blood flow through this vascular bed as compared to the left coronary circulation. The regulation of the right coronary circulation is apparently more substantially influenced by neural and/or myogenic factors.

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APPENDIX

APPENDIX

The tables represented on the following pages contain raw resistance values for each series of experiments conducted in this study. This data is presented as a representative example of the statistical method employed (Student's t test modified for paired replicates) to determine significance of the effect seen with experimental intervention on each measured variable. The resistance values are presented as they are the focal point of this study. The difference (ΔR) between control (C) and experimental (E) values are presented, as are the means ($\bar{x}$) and standard error of the means ($\pm$ SEM) for each respective group. The paired t statistic is also reported for each analysis.

PRU = peripheral resistance unit mmHg/ml/min

PRU_{100} = peripheral resistance unit mmHg/ml/min/100 g

* = significantly different from control at $P < 0.05$

SERIES I

	PRU			
	C	E	ΔR	
Sympathetic stimulation at normal flow	5.90	6.36	-.46	
	4.21	4.84	-.63	
	6.38	6.94	-.56	
	5.75	8.0	-2.25	
	12.5	14.3	-1.80	
	11.66	13.33	-1.67	
	6.25	7.25	-1.00	
	4.54	4.68	-.14	
	9.09	9.36	-.27	
$\bar{x}$ ± SEM	7.35±1.12	8.34±1.14	-0.97±.25	t=-3.88*
Sympathetic stimulation at low flow	11.66	11.66	0	
	7.14	9.28	-2.14	
	6.0	7.6	-1.6	
	8.75	9.50	-.75	
	8.75	10.5	-1.75	
	18.33	21.66	-3.33	
	11.0	13.6	-2.6	
	13.46	15.38	-1.92	
	7.77	8.44	-.67	
$\bar{x}$ ± SEM	10.31±1.27	11.95±1.46	-1.64±.34	t=-4.76*
Sympathetic stimulation at high flow	8.43	8.75	-.32	
	4.16	4.71	-.55	
	5.31	5.40	-.15	
	5.66	6.40	-.74	
	11.0	12.5	-1.5	
	12.33	13.33	-1.0	
	5.78	5.93	-.15	
	5.00	5.23	-.23	
	5.48	5.87	-.39	
$\bar{x}$ ± SEM	7.01±.96	7.57±1.07	-.55±1.5	t=-3.70*
1 μg NE infusion at normal flow	5.45	5.90	-.45	
	3.90	3.12	.78	
	6.38	3.05	3.33	
	5.50	6.25	-.75	
	13.75	8.75	5.0	
	12.22	13.88	-1.66	
	7.00	6.75	.25	
	4.54	3.40	1.14	
	9.09	5.45	3.64	
$\bar{x}$ ± SEM	7.53±1.15	6.28±1.14	1.25±.75	t=1.66

continued

SERIES I--continued

	PRU			
	C	E	ΔR	
1 μg NE infusion at low flow	11.66	10.0	1.66	
	7.85	5.71	2.14	
	6.00	4.66	1.34	
	9.75	9.25	.50	
	8.75	9.00	-.25	
	18.33	23.33	-5.0	
	11.0	12.0	-1.0	
	13.46	13.84	-.38	
	7.77	7.55	.22	
$\bar{x}$ ± SEM	10.50±1.23	10.59±1.85	-0.08±.7	t=-0.12
1 μg NE infusion at high flow	7.81	5.62	2.19	
	4.28	3.45	.83	
	5.06	2.96	2.10	
	6.33	7.00	-.67	
	12.5	9.28	3.22	
	13.33	14.66	-1.33	
	6.18	6.09	.09	
	5.14	3.08	2.06	
	5.64	5.32	.32	
$\bar{x}$ ± SEM	7.36±1.1	6.38±1.23	0.97±.5	t=1.94
Sympathetic stimulation at normal flow after beta-blockade	9.09	10.45	-1.36	
	8.05	8.33	-.28	
	7.22	7.77	-.55	
	7.25	7.65	-.40	
	20.00	20.00	-.60	
	11.66	13.33	-1.67	
	8.75	9.00	-.25	
	6.25	6.56	-.31	
	14.00	15.20	-1.20	
$\bar{x}$ ± SEM	10.25±1.46	10.98±1.52	-.73±.17	t=-4.14*
Sympathetic stimulation at low flow after beta-blockade	11.66	12.33	-.67	
	8.57	9.28	-.71	
	8.00	8.93	-.93	
	22.50	23.75	-1.25	
	12.50	14.25	-1.75	
	18.33	21.66	-3.33	
	15.00	15.20	-.20	
	13.46	15.38	-1.92	
	17.50	19.00	-1.50	
$\bar{x}$ ± SEM	14.16±1.54	15.53±1.77	-1.36±.3	t=-4.43*

continued

SERIES I--continued

	PRU			
	C	E	ΔR	
Sympathetic stimulation at high flow after beta-blockade	7.81	8.43	-.62	
	5.93	6.25	-.32	
	5.31	5.59	-.28	
	8.16	8.66	-.50	
	14.28	15.00	-.72	
	12.33	13.33	-1.00	
	7.50	7.65	-.15	
	5.66	5.83	-.17	
	15.90	16.72	-.82	
$\bar{x}$ ± SEM	9.20±1.31	9.71±1.4	-.50±.1	t=-5.06*
1 µg NE infusion at normal flow after beta-blockade	10.45	11.36	-.91	
	7.22	8.88	-1.66	
	7.50	8.33	-.83	
	7.65	8.15	-.50	
	20.00	21.25	-1.25	
	17.77	18.33	-.56	
	8.75	9.25	-.50	
	6.56	6.62	-.06	
	13.75	14.37	-.62	
$\bar{x}$ ± SEM	11.07±1.65	11.83±1.69	-.76±.15	t=-4.89*
1 µg NE infusion at low flow after beta-blockade	11.66	13.33	-1.67	
	8.57	9.00	-.43	
	9.33	11.33	-2.00	
	23.75	27.50	-3.75	
	12.50	13.75	-1.25	
	31.66	35.00	-3.34	
	15.00	17.40	-2.40	
	13.46	14.61	-1.15	
	17.50	20.00	-2.50	
$\bar{x}$ ± SEM	15.93±2.48	17.99±2.79	-2.05±.35	t=-5.77*
1 µg NE infusion at high flow after beta-blockade	9.06	10.00	-.94	
	6.56	6.87	-.31	
	5.46	5.93	-.47	
	8.66	9.00	-.34	
	14.28	15.35	-1.07	
	14.66	14.66	0	
	7.50	7.81	-.31	
	5.73	6.06	-.33	
	15.90	16.36	-.46	
$\bar{x}$ ± SEM	9.75±1.36	10.22±1.36	-.47±.11	t=-4.22*

SERIES II

	PRU_{100}			
	C	E	ΔR	
Sympathetic stimulation at normal flow	1.28	1.41	-.13	
	1.36	1.43	-.07	
	1.47	1.54	-.07	
	1.39	1.51	-.12	
	1.79	1.87	-.08	
	2.00	2.08	-.08	
	3.67	3.82	-.15	
	3.23	3.38	-.15	
$\bar{x}$ ± SEM	2.02±.32	2.13±.33	-.10±.01	t=-8.58*
Phentolamine infusion at normal flow	1.34	1.28	.06	
	1.36	1.36	0	
	1.47	1.44	.03	
	1.36	1.30	.06	
	2.10	1.95	.15	
	2.33	1.01	.42	
	3.90	2.20	1.70	
	4.41	3.97	.44	
$\bar{x}$ ± SEM	2.28±.43	1.92±.31	0.35±.2	t=1.77
Sympathetic stimulation during phentolamine infusion at normal flow	1.28	1.30	-.02	
	1.36	1.36	0	
	1.47	1.47	0	
	1.30	1.31	-.01	
	1.95	1.95	0	
	1.91	1.91	0	
	2.20	2.23	-.03	
$\bar{x}$ ± SEM	1.93±.3	1.91±.2	-.008±.004	t=-1.86
1 μg NE infusion at normal flow	1.30	0.96	.34	
	1.39	1.02	.37	
	1.47	1.13	.34	
	1.42	1.19	.23	
	1.79	1.01	.78	
	2.08	1.16	.92	
	3.67	2.05	1.62	
	3.25	1.61	1.64	
$\bar{x}$ ± SEM	2.04±.32	1.26±.13	.78±.2	t=3.83*

continued

SERIES II--continued

	PRU_{100}			
	C	E	ΔR	
1 μg NE infusion with phentolamine at normal flow	1.28	0.89	.39	
	1.36	0.95	.41	
	1.47	1.02	.45	
	1.30	1.07	.23	
	1.87	1.32	.55	
	1.91	1.08	.83	
	2.35	1.47	.88	
	4.41	3.38	1.03	
$\bar{x}$ ± SEM	1.99±.36	1.39±.29	.59±.09	t=5.97*
Sympathetic stimulation at high flow	1.02	1.08	-.06	
	0.82	0.88	-.06	
	1.60	1.67	-.07	
	0.91	0.95	-.04	
$\bar{x}$ ± SEM	1.08±.17	1.14±.17	-.05±.006	t=-9.13*
Sympathetic stimulation with phentolamine at high flow	1.01	1.01	0	
	0.82	0.83	-.01	
	1.60	1.61	-.01	
	0.91	0.91	0	
$\bar{x}$ ± SEM	1.08±.17	1.09±.17	-.005±.002	t=-1.73
Sympathetic stimulation at low flow	0.97	1.11	-.14	
	1.16	1.26	-.10	
	3.88	4.44	-.56	
	0.94	1.02	-.08	
$\bar{x}$ ± SEM	1.73±.71	1.95±.80	-.22±.11	t=-1.92
Sympathetic stimulation with phentolamine at low flow	0.97	0.97	0	
	1.16	1.16	0	
	3.88	3.88	0	
	0.94	0.94	0	
$\bar{x}$ ± SEM	1.73±.71	1.73±.71	0±0	t=0
1 μg NE influsion at high flow	1.04	0.83	.21	
	0.84	0.77	.07	
	1.65	1.36	.29	
	0.92	0.81	.11	
$\bar{x}$ ± SEM	1.11±.18	0.94±.13	.17±.04	t=3.42*

continued

SERIES II--continued

	PRU_{100}			
	C	E	ΔR	
1 µg NE infusion with phentolamine at high flow	1.01	0.80	.21	
	0.82	0.75	.07	
	1.60	1.32	.28	
	0.91	0.75	.16	
$\bar{x}$ ± SEM	1.08±.17	0.90±.13	.18±.04	t=4.07*
1 µg NE infusion at low flow	1.00	0.83	.17	
	1.16	1.13	.03	
	3.88	3.77	.11	
	0.94	0.91	.03	
$\bar{x}$ ± SEM	1.74±,71	1.66±.70	.08±.03	t=2.49
1 µg NE infusion with phentolamine at low flow	0.97	0.83	.14	
	1.16	1.10	.06	
	3.88	3.77	.11	
	0.94	0.81	.13	
$\bar{x}$ ± SEM	1.73±.71	1.62±.71	.11±.01	t=6.18*

SERIES III

	PRU_{100}			
	C	E	ΔR	
Sympathetic stimulation	1.11	1.30	-.19	
	1.03	1.11	-.08	
	1.21	1.30	-.09	
	0.89	0.98	-.09	
	1.30	1.42	-.12	
	2.18	2.45	-.27	
	2.87	3.19	-.32	
$\bar{x}$ ± SEM	1.51±.27	1.72±.09	-.16±.03	t=-4.53*
Systemic hypocapnia	1.33	1.46	-.13	
	1.03	1.08	-.05	
	1.16	1.16	0	
	0.82	0.89	-.07	
	1.30	1.48	-.18	
	2.09	2.36	-.27	
	2.44	2.65	-.21	
$\bar{x}$ ± SEM	1.45±.15	1.58±.25	-.13±.03	t=-3.57*
Sympathetic stimulation during hypocapnia	1.46	1.61	-.15	
	1.08	1.11	-.03	
	1.16	1.19	-.03	
	0.89	1.07	-.18	
	1.48	1.54	-.06	
	2.36	2.54	-.18	
	2.65	2.87	-.22	
$\bar{x}$ ± SEM	1.58±.25	1.70±.27	-.12±.03	t=-4.04*
0.25 µg NE infusion	1.27	1.33	-.06	
	1.08	0.82	.26	
	1.21	0.75	.46	
	0.93	0.66	.27	
	1.36	1.25	.11	
	2.27	2.18	.09	
	2.87	2.76	.11	
$\bar{x}$ ± SEM	1.57±.27	1.39±.30	0.17±.06	t=2.79*
0.25 µg NE infusion during hypocapnia	1.55	1.66	-.11	
	1.03	0.82	.21	
	1.16	0.87	.29	
	1.07	0.89	.18	
	1.42	1.30	.12	
	2.36	2.27	.09	
	2.65	2.02	.63	
$\bar{x}$ ± SEM	1.60±.24	1.40±.22	0.20±.08	t=2.35

continued

SERIES III--continued

	PRU_{100}			
	C	E	ΔR	
0.25 μg NE after indomethacin	2.00	2.00	0	
	0.67	0.61	.06	
	1.39	1.45	-.06	
	1.25	1.11	.14	
	1.42	1.19	.23	
	2.36	2.32	.04	
	2.97	1.70	1.27	
$\bar{x}$ ± SEM	1.72±.29	1.48±.21	0.24±.17	t-1.36
Indomethacin	0.95	1.17	-.22	
	0.88	1.00	-.12	
	1.72	1.91	-.19	
	1.03	0.67	.36	
	1.16	1.51	-.35	
	0.89	1.02	-.13	
	1.30	1.48	-.18	
	1.81	2.27	-.46	
	2.44	2.65	-.21	
$\bar{x}$ ± SEM	1.35±.17	1.52±.21	-.16±.07	t=-2.21
Sympathetic stimulation after indomethacin	1.17	1.22	-.05	
	1.00	1.22	-.22	
	1.91	2.00	-.09	
	0.67	0.69	-.02	
	1.27	1.39	-.12	
	1.02	1.25	-.23	
	1.42	1.52	-.10	
	2.27	2.45	-.18	
	2.97	3.08	-.11	
$\bar{x}$ ± SEM	1.52±.24	1.64±.24	-.12±.02	t=-5.16*
Hypocapnia after indomethacin	0.67	0.72	-.05	
	1.29	1.56	-.27	
	1.42	1.54	-.12	
	2.09	2.36	-.27	
	2.97	3.29	0.32	
$\bar{x}$ ± SEM	1.68±.39	1.89±.43	-.20±.05	t=-4.00*
Sympathetic stimulation during hypocapnia and after indomethacin	0.72	0.71	.01	
	1.56	1.62	-.06	
	1.54	1.57	-.03	
	2.36	2.69	-.33	
	2.97	3.08	-.11	
$\bar{x}$ ± SEM	1.83±.38	1.93±.42	-.10±.05	t=-1.73

continued

SERIES III--continued

	PRU_{100}			
	C	E	ΔR	
0.25 µg NE infusion during hypocapnia and after indomethacin	0.72	0.67	.05	
	1.56	1.33	.23	
	1.54	1.19	.35	
	2.69	2.60	.09	
	2.97	2.55	.42	
$\bar{x}$ ± SEM	1.89±.41	1.66±.38	.22±.07	t=3.18*

SERIES IV

	PRU_{100}			
	C	E	ΔR	
Sympathetic stimulation during normoxia	1.80	2.13	-.33	
	3.15	3.26	-.11	
	1.92	2.19	-.27	
	1.28	1.39	-.11	
	1.93	2.01	-.08	
	1.50	1.61	-.11	
$\bar{x}$ ± SEM	1.93±.26	2.09±.26	-.16±.04	t=-3.95*
0.25 μg NE infusion during normoxia	2.13	2.21	-.08	
	3.21	3.47	-.26	
	2.19	1.31	.88	
	1.28	0.51	.77	
	1.96	1.13	.83	
	1.44	0.72	.72	
$\bar{x}$ ± SEM	2.03±.27	1.55±.45	.47±.20	t=2.60*
Hypoxia	2.04	1.88	.16	
	2.60	0.97	1.63	
	1.92	0.87	1.05	
	1.28	0.46	.82	
	1.59	0.60	.99	
	1.33	0.50	.83	
$\bar{x}$ ± SEM	1.79±.20	0.88±.21	.91±.19	t=4.72*
Sympathetic stimulation during hypoxia	1.31	1.31	0	
	0.97	0.97	0	
	0.87	0.87	0	
	0.46	0.46	0	
	0.60	0.60	0	
	0.44	0.50	-.06	
$\bar{x}$ ± SEM	0.77±.13	0.78±.13	-.01±.01	t=-1.0
0.25 μg NE infusion during hypoxia	1.31	1.22	.09	
	0.97	0.97	0	
	0.87	0.87	0	
	0.41	0.36	.05	
	0.60	0.53	.07	
	0.44	0.38	.06	
$\bar{x}$ ± SEM	0.76±.14	0.74±.14	.04±.01	t=2.95*

continued

SERIES IV--continued

	PRU_{100}			
	C	E	ΔR	
Hypocapnia	2.04	2.45	-.41	
	2.60	3.91	-1.31	
	1.92	3.50	-1.58	
	1.13	1.34	-.21	
	1.74	2.12	-.38	
	1.38	1.44	-.06	
$\bar{x}$ ± SEM	1.80±.21	2.46±.43	-.65±.25	t=-2.56*
Sympathetic stimulation during hypocapnia	2.45	2.54	-.09	
	3.91	5.13	-.22	
	3.50	3.59	-.09	
	1.34	1.42	-.08	
	2.12	2.27	-.15	
	1.44	1.50	-.06	
$\bar{x}$ ± SEM	2.45±.43	2.57±.44	-.11±.02	t=-.472*
0.25 µg NE infusion during hypocapnia	2.45	2.45	0	
	4.13	4.19	-.06	
	3.50	3.24	.26	
	1.28	0.97	.31	
	2.12	1.59	.53	
	1.38	0.66	.72	
$\bar{x}$ ± SEM	2.47±.46	2.18±.55	.29±.12	t=2.39
Hypoxia and hypocapnia	2.45	1.31	1.14	
	2.71	1.30	1.41	
	1.75	1.05	.70	
	1.39	0.46	.93	
	1.59	0.60	.99	
	1.61	0.55	1.06	
$\bar{x}$ ± SEM	1.91±.21	0.87±.15	1.03±.09	t=10.79*
Sympathetic stimulation during hypoxia and hypocapnia	1.31	1.31	0	
	1.30	1.30	0	
	1.05	1.14	-.09	
	0.46	0.51	-.05	
	0.60	0.68	-.08	
	0.55	0.66	-.11	
$\bar{x}$ ± SEM	0.87±.15	0.93±.14	-.05±.01	t=-2.87*

continued

SERIES IV--continued

	PRU_{100}			
	C	E	ΔR	
0.25 µg NE infusion during hypoxia and hypocapnia	1.22	1.22	0	
	1.30	1.41	-.11	
	1.14	1.05	.09	
	0.46	0.41	.05	
	0.60	0.57	.03	
	0.55	0.47	.08	
$\bar{x}$ ± SEM	0.87±.15	0.85±.17	.02±.02	t=0.78
0.50 µg NE infusion during normoxia	2.13	2.04	.09	
	3.21	2.93	.28	
	2.19	1.05	1.14	
	1.28	0.41	.87	
	1.96	1.06	.90	
$\bar{x}$ ± SEM	2.15±.30	1.49±.44	.65±.20	t=3.27*
0.5 µg NE infusion during hypoxia	1.31	1.22	.09	
	0.97	0.97	0	
	0.87	0.78	.09	
	0.41	0.36	.05	
	0.60	0.53	.07	
$\bar{x}$ ± SEM	0.83±.15	0.77±.15	.06±.01	t=3.58*
0.5 µg NE infusion during hypocapnia	2.45	2.29	.16	
	4.13	3.80	.33	
	3.50	3.07	.43	
	1.28	0.77	.51	
	2.12	1.51	.61	
$\bar{x}$ ± SEM	2.69±.50	2.28±.52	.40±.07	t=5.28*
0.5 µg NE infusion during hypoxia and hypocapnia	1.22	1.14	.08	
	1.41	1.30	.11	
	1.14	0.87	.27	
	0.46	0.41	.05	
	0.60	0.53	.07	
$\bar{x}$ ± SEM	0.96±.18	0.85±.17	.11±.03	t=2.92*

SERIES V

	PRU_{100}			
	C	E	ΔR	
Sympathetic	2.77	2.93	-.16	
	2.85	3.12	-.27	
	1.81	2.12	-.31	
	1.66	1.71	-.05	
	1.42	1.61	-.19	
	2.38	2.56	-.18	
	1.66	1.81	-.15	
	1.53	1.69	-.16	
$\bar{x}$ ± SEM	2.03±.21	2.21±.22	-.18±.02	t=-6.58*
0.25 µg NE	2.77	2.21	.56	
	2.38	1.90	.48	
	1.81	1.17	.64	
	1.78	1.13	.65	
	1.42	0.95	.47	
	2.38	1.42	.96	
	1.66	1.42	.24	
	1.53	0.98	.55	
$\bar{x}$ ± SEM	1.98±.18	1.41±.19	.59±.07	t=7.89*
Hypoxia	2.90	0.58	2.32	
	2.05	0.43	1.62	
	1.81	0.50	1.31	
	1.78	0.48	1.28	
	1.07	0.53	0.54	
	2.38	0.39	1.99	
	1.66	0.60	1.06	
	1.53	0.39	1.14	
$\bar{x}$ ± SEM	1.89±.19	0.48±.02	1.40±.19	t=7.12*
Sympathetic stimulation during hypoxia	0.58	0.58	0	
	0.43	0.44	-.01	
	0.53	0.53	0	
	0.39	0.42	-.03	
$\bar{x}$ ± SEM	0.48	0.49	-.01±.007	t=-1.41
0.25 µg NE during hypoxia	1.10	0.77	.33	
	0.42	0.45	-.03	
	0.53	0.53	0	
	0.35	0.38	-.03	
$\bar{x}$ ± SEM	0.60±.17	0.53±.08	.06±.08	t=.76

continued

SERIES V--continued

	PRU_{100}			
	C	E	ΔR	
Hypercapnia	1.23	0.73	.50	
	1.58	2.54	1.09	
	1.31	1.00	.31	
	1.42	0.78	.64	
	2.04	1.02	1.02	
	1.66	0.95	.71	
	1.53	0.63	.90	
$\bar{x}$ ± SEM	1.53±.09	0.81±.07	.73±.10	t=7.09*
Sympathetic stimulation during hypercapnia	0.71	0.73	-.02	
	0.78	0.95	-.17	
	1.02	1.07	-.05	
	0.86	0.90	-.04	
	0.63	0.67	-.04	
$\bar{x}$ ± SEM	0.80±.06	0.86±.07	-.06±.02	t=-2.37*
0.25 µg/min NE during hypercapnia	0.73	0.75	-.02	
	0.86	0.90	-.04	
	1.02	0.95	.07	
	0.95	0.90	.05	
	0.63	0.67	-.04	
$\bar{x}$ ± SEM	0.83±.07	0.84±.06	.004±.02	t=0.17
Hypocapnia	2.32	3.32	-1.0	
	1.51	1.72	-0.21	
	1.47	0.96	0.51	
	0.81	0.88	-0.07	
	2.04	2.85	-0.81	
	1.66	1.75	-0.09	
	1.53	2.27	-0.74	
$\bar{x}$ ± SEM	1.62±.18	1.96±.34	-0.34±.20	t=-1.71
Sympathetic stimulation during hypocapnia	3.32	3.88	-0.56	
	1.72	1.81	-0.09	
	0.96	1.00	-0.04	
	1.88	1.88	0	
	2.85	2.85	0	
	1.66	1.66	0	
	2.27	2.38	-0.11	
$\bar{x}$ ± SEM	2.09±.29	2.20±.35	-0.11±.07	t=-1.49

continued

SERIES V--continued

	PRU_{100}			
	C	E	ΔR	
0.25 μg NE during hypocapnia	3.32	1.94	1.38	
	1.72	1.58	0.14	
	1.00	0.80	0.20	
	1.88	0.86	1.02	
	2.85	1.29	1.56	
	1.66	1.53	0.13	
	2.27	1.78	0.49	
$\bar{x}$ ± SEM	2.10±.29	1.39±.16	0.70±.23	t=3.04*