ALPHA-ADRENERGIC MODULATION OF CORONARY

BLOOD FLOW AND CARDIAC FUNCTION

DURING EXERCISE IN DOGS

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ALPHA-ADRENERGIC MODULATION OF CORONARY BLOOD FLOW AND CARDIAC FUNCTION DURING EXERCISE IN DOGS

THESIS

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In the present study alpha-receptor modulation of coronary flow and cardiac function was examined in exercising dogs, chronically instrumented to measure: circumflex blood flow velocity (CFV), heart rate (HR), global left ventricular function (LVP and dP/dt_{max}) and regional left ventricular function (%SL and $dL/dt_{(s)max}$). During exercise, local adrenergic blockade was produced by intracoronary injection of 1.0 mg phentolamine (a non-specific alpha-antagonist) or 0.5 mg prazosin (a specific postsynaptic $alpha_1$-receptor blocker). Exercise significantly increased HR, LVP, dP/dt_{max}, CFV, %SL and $dL/dt_{(s)max}$. Neither alpha-antagonist produced changes in HR, LVP or %SL; however, both phentolamine and prazosin produced significant increases in dP/dt_{max}, CFV and $dL/dt_{(s)max}$ of the alpha-blocked region, when compared to their exercise level before alpha-blockade. It is suggested that an $alpha_1$-adrenergic vasoconstriction limits coronary vasodilation and, thereby, cardiac function during exercise.

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CHAPTER I

INTRODUCTION

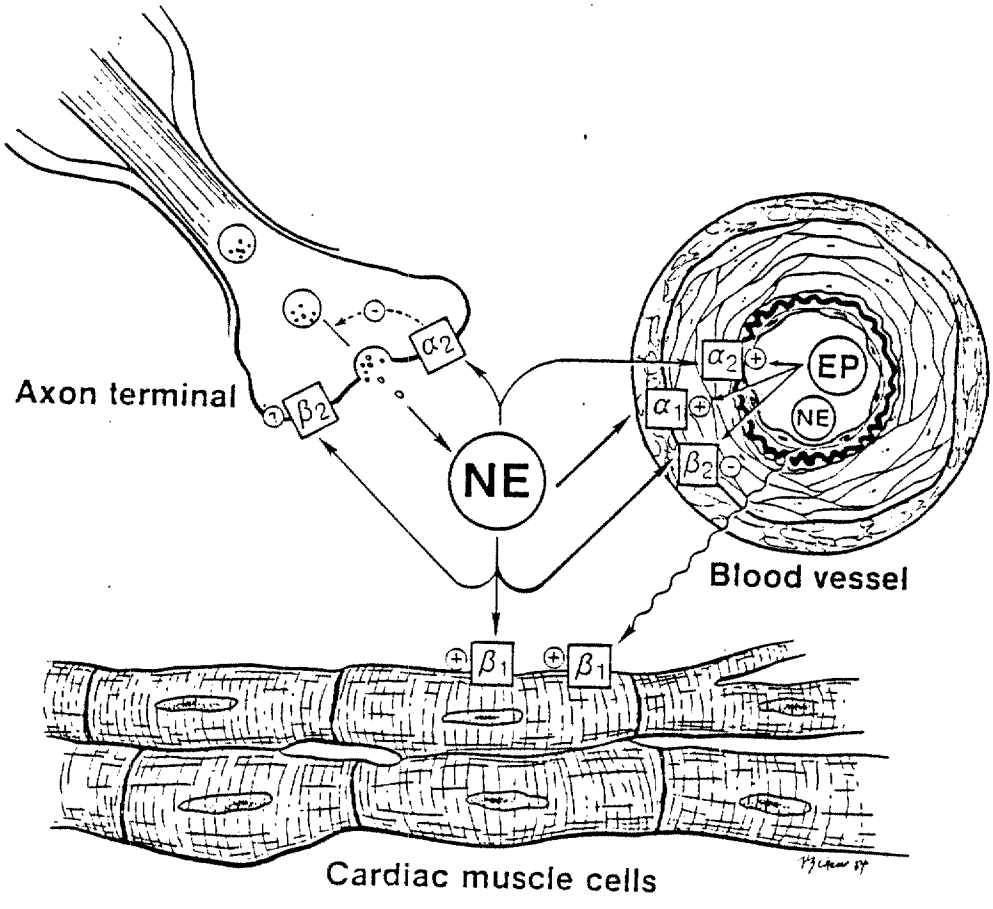
Introduction.--It has long been established that the myocardium can match an increased metabolic demand with an increase in coronary blood flow and that this balance between supply and demand could be attained solely by intrinsic mechanisms of the myocardium (9,45). For example, during periods of increased cardiac performance the working myocardial cells will accumulate and release vasoactive metabolic end products (such as adenosine and potassium) which act on the vascular smooth muscle of the coronary arteries causing them to dilate. This will result in an increase in coronary blood flow and oxygen availability to the myocardial cells . This local metabolic effect is the primary mechanism by which the myocardium maintains a balance between oxygen supply and oxygen demand. More recent studies in both conscious and anesthetized dogs suggest that the sympathetic nervous system may also exert a significant influence on the coronary circulation. Stimulation of cardiac $beta_1$-receptors by neurally released norepinephrine results in increased positive chronotropic and inotropic effects and, therefore, increased production of vasoactive metabolites, and an indirect vasodilation. Opposing this response is the direct sympathetic effect, an alpha-adrenergic mediated vasoconstriction. The full

physiological importance of these sympathetic effects on the coronary circulation is at present unclear. However, under conditions of physiological or pathological cardiac stress, when a substantial coronary vasodilatation is required to meet new metabolic demands of the cardiac tissue, a functional sympathetic constrictor tone may severely impede myocardial perfusion and oxygenation.

Below is presented a concise review of pertinent work addressing the existance of an alpha-adrenergic vasoconstriction in the coronary circulation and the nature of this constrictor effect.

Physiology of Myocardial and Coronary Adrenergic Receptors.--With the development of selective adrenergic receptor blockers and experimental methods, investigators have been able to examine the direct effect of cardiac nerve stimulation on coronary blood flow apart from the indirect effects of myocardial function. The heart and coronary blood vessels receive substantial sympathetic innervation (4,19,49). Figure 1 illustrates the myriad of adrenergic receptors which can be activated by the release of the endogenous neurotransmitter norepinephrine. Several studies have confirmed that alpha-receptors do not comprise a homogenous population. It has been observed that alpha-receptors which mediate inhibition of transmitter release from adrenergic neurons differ pharmacologically from those mediating contraction of smooth muscles. These receptors

Figure 1. A diagramatic representation of a cardiac adrenergic nerve terminal and the locations of both subtypes of adrenergic receptors. Norepinephrine released from adrenergic nerve terminals may act as an agonist postsynaptically on cardiac muscle or on coronary blood vessels as well as presynaptically on the axon terminal. Activation of $alpha_1$- and $alpha_2$-receptors on coronary vessels produces a vasoconstriction. Presynaptic $alpha_2$-receptors produce a negative feedback inhibition of norepinephrine release. Postsynaptic $beta_2$-receptors on coronary vessels produce vasodilitation. $Beta_1$-receptors are found on cardiac muscle and produce an increased chronotropic and inotropic state of that myocardium.


Axon terminal
α2
β2
NE
α2
α1
β2
EP
NE
Blood vessel
β1
β1
Cardiac muscle cells

have been classified as pre- and postsynaptic alpha-receptors respectively. This classification is based on the anatomical location and pharmacological characteristics of these alpha-receptors. The alpha-adrenergic receptors are classified as $alpha_1$- and $alpha_2$-receptors. Postsynaptic $alpha_1$- and $alpha_2$-receptors are located on the surface of the myocardium and coronary vascular smooth muscle cells. These receptors mediate a direct coronary constriction (2,37,41,56,62). Presynaptic $alpha_2$-receptors are located on peripheral neurons. These receptors are part of a negative feedback mechanism which provides local modulation of norepinephrine release (2,37,62). Beta-adrenergic receptors have been subdivided into $beta_1$- and $beta_2$-subtypes, as well as pre- and postsynaptic receptors. The $beta_1$-receptor is located on the cardiac muscle cell and mediates the positive chronotropic and inotropic response to norepinephrine release (59). $Beta_2$-receptors are located on the coronary vascular smooth muscle and mediate a direct coronary vasodilation (59). The exact function of the presynaptic $beta_2$-receptors is unknown at the present time.

Many pharmacological agents show a high degree of specificity for one or several of these receptor sites. For example, phenylephrine is a specific $alpha_1$-agonist, prazosin is a specific $alpha_1$-antagonist, clonidine is reported as a selective $alpha_2$-agonist, and yohimbine and rauwolscine are both $alpha_2$-selective antagonists. Both

phentolamine and phenoxybenzamine are non-specific $alpha_1$- and $alpha_2$-receptor antagonists.

An Alpha-Adrenergic Constrictor Tone in the Coronary Circulation.--A sympathetic coronary vasoconstrictor tone has been demonstrated by several investigators, although the quantitative effect of this vasoconstriction on coronary blood flow has varied between studies. Thus, Brachfeld et al (12) reported that following left pericoronary neurectomy in dogs, left coronary blood flow was increased by 13%, while left ventricular oxygen extraction was reduced by 21%. The decrease in oxygen extraction indicates that neurectomy increases blood flow far above the metabolic demand of the tissue. Holtz et al (34) compared coronary perfusion in normal canine left ventricular myocardium to that in areas of the same ventricle that had been sympathectomized by regional intracoronary injection of 6-hydroxydopamine. These investigators reported that myocardial flow in the sympathectomized region was 64% greater than that in the control region. They also observed that propranolol did not alter flow in either region, but alpha-adrenergic blockade with phentolamine increased flow in the control region to a level equal to that in the sympathectomized region. These data strongly suggest that a substantial alpha-constrictor tone was operative in the control or innervated myocardium, and that the increased flow in the sympathectomized region

was a result of ablation of this constrictor tone.

The presence of a coronary alpha-receptor mediated constrictor tone has also been demonstrated in studies utilizing surgical or pharmacological removal of sympathetic nerves to the heart. Coronary reactive hyperemia is the increase in blood flow in response to a brief coronary occlusion. The amount of blood flow above normal during the hyperemic response is an indication of the amount of oxygen debt incured during the occlusion. This increase in flow is felt to be brought about by strictly local metabolic mechanisms. However, Schwartz and Stone (51) found that either removal of the left stellate ganglion or blockade of alpha-receptors by phentolamine caused an increase in coronary reactive hyperemia by 31%. In addition Drake et al (21) reported that left stellate ganglionectomy increased oxygen delivery during coronary reactive hyperemia by 30%, suggesting that the coronary vasoconstriction impeded both coronary flow and oxygen delivery despite the extremely high metabolic signals. In a recent study, Mohrman and Feigl (42) demonstrated that an alpha-adrenergic vasoconstrictor tone in the coronary circulation competes with metabolic vasodilatory signals during conditions of high cardiac sympathetic stimulation. They reported that during intracoronary infusion of norepinephrine in the anesthetized dog, the increase in coronary blood flow was approximately 30% higher following coronary alpha-adrenergic blockade with

phenoxybenzamine than under control conditions. These studies indicate that this tonic vasoconstriction is present even with strong vasodilatory metabolic signals.

Not only has it been demonstrated that an alpha-adrenergic constrictor tone exists in the coronary circulation, studies have suggested that coronary alpha-receptors are activated during reflex activation of the sympathetic nervous system. Thus, Powell et al (46) demonstrated that when sympathetic stimulation of the heart was increased by the baroreceptor reflex, the coronary alpha-vasoconstriction was increased. Similar studies have been reported by others (20,22,43,57).

The studies cited above were performed in the anesthetized animal, and in this preparation it is now clear that a sympathetic vasoconstrictor tone is operative. However, studies by Chilian et al (16) indicate that a coronary sympathetic vasoconstriction is negligable in the conscious resting dog. These investigators performed a regional myocardial sympathectomy by local application of phenol to the cardiac surface. No difference in blood flow between the control and sympathectomized regions was found, suggesting that a resting sympathetic coronary vasoconstriction was not substantial.

Alpha-Adrenergic Constrictor Tone in Pathologic Stress.--The studies cited above strongly indicate that a

coronary alpha-adrenergic vasoconstriction is present in the coronary circulation. Other studies have been directed at the question: Is this coronary vasoconstriction still present under conditions of pathologic cardiac stress, when metabolic vasodilatory signals are presumably very high?

Although local metabolic factors are considered to be the major determinant of coronary vascular tone, several studies indicate that an alpha-receptor mediated constrictor tone may contribute significantly to coronary vascular tone at rest and during various forms of stress. For example, work by Carlson (14), Bond et al (12), and Birinyi et al (10) have shown an increase in coronary blood flow secondary to systemic administation of nonspecific alpha-antagonists during severe hemorrhagic hypotension. More recent experiments by Jones et al (36) have also demonstrated that during hemorrhagic hypotension in anesthetized dogs, intracoronary administration of the nonspecific alpha-antagonist phenoxybenzamine increased both coronary blood flow and myocardial oxygen consumption.

Similar results have also been observed during partial coronary artery stenosis in the anesthetized dog. Thus, Buffington and Feigl (13) demonstrated that intracoronary administration of norepinephrine elicited a coronary vasoconstricion even during severe coronary artery stenosis. This constrictor effect of norepinephrine during severe stenosis was abolished by intracoronary administration of

the nonspecific alpha-antagonist phenoxybenzamine. Likewise, Heusch and Deussen (31) demonstrated a coronary vasoconstriction secondary to cardiac sympathetic nerve stimulation during partial coronary stenosis in anesthetized dogs. These investigators reported that an alpha-adrenergic blockade increased coronary blood flow during cardiac nerve stimulation and partial coronary stenosis, although they report that such vasodilatation was observed only during $alpha_2$-receptor blockade. Thus, these investigators feel the constrictor tone is mediated through stimulation of vascular $alpha_2$-receptors, while work reported in this thesis indicate that the alpha-vasoconstriction is mediated through stimulation of $alpha_1$-receptors.

Alpha-Adrenergic Constrictor Tone in Exercise.--In addition to a coronary alpha-vasoconstriction during conditions of pathologic cardiac stress, studies have indicated that an alpha-adrenergic constrictor tone is present in the coronary circulation during exercise. Physical exercise is a physiologically demanding activity resulting in a strong sympathoadrenal activation and an increase in cardiac output (stroke volume and heart rate). Studies utilizing selective sympathetic adrenergic blocking agents demonstrate that even though the coronary circulation is predominately regulated by metabolic vasodilator factors, it is also modulated by the alpha-adrenergic vasoconstrictor

mechanism during exercise. Thus, Murray and Vatner (44) demonstrated that systemic administration of the nonspecific alpha-receptor antagonist phentolamine, decreased diastolic coronary resistance by about 30% in the exercising dog. This increase in coronary blood flow caused by general alpha-blockade during exercise was not likely attributable to an increased myocardial metabolic demand since the effect was not altered by beta-receptor blockade with systemically administered propranolol. Results similar to those of Murray and Vatner (44) have also been observed by Gwirtz and Stone (27), Heyndrickx et al (32, 33), and Liang and Stone (38). The work by Gwirtz and Stone (27) also demonstrated that following systemic administration of phentolamine, the increase in coronary blood flow during exercise was greater per unit increase in myocardial oxygen consumption than in control conditions. This result suggests that the increase in blood flow was relatively independent of an increase in myocardial metabolic demand, i.e. independent of local metabolic dilation.

While the studies cited above strongly suggest the presence of an alpha-vasoconstriction in the coronary circulation during exercise, the data are not completely convincing. Some continuing uncertainty arises from 1) the previous use of systemic administration of alpha-antagonists to demonstrate a coronary alpha-vasoconstriction, and 2) from an incomplete understanding of the distribution and

function of alpha-adrenergic receptors on the coronary vasculature and on sympathetic nerve terminals. For example, blockade of peripheral alpha-receptors may elicit peripheral circulatory reflexes which could indirectly effect coronary blood flow via effects on the inotropic and chronotropic state of the myocardium. In addition, the possibility of a central effect of systemic alpha-blockade could produce changes in coronary blood flow through changes in central sympathetic outflow. Furthermore, it can be seen that using only a nonspecific alpha-blocking agent could indirectly influence coronary blood flow through metabolic mechanisms and lead to a misinterpretation of results.

The present study was designed to overcome these problems in methodology associated with previous studies and to more precisely examine the role of a coronary alpha-mediated vasoconstrictor tone in the resting and exercising dog. First, in order to assure adequate and strictly regional alpha-receptor blockade, alpha-blocking agents were administered directly into the coronary circulation through an indwelling catheter in doses that have been shown to adequately produce total alpha-blockade in the circumflex perfusion territory, without causing any discernable peripheral effects (28). This preparation offers several advantages, including the ability to pharmacologically study and compare one region of the coronary vascular bed to

another region at a time when the whole left ventricle is under similar preload and afterload conditions. One region, perfused by the circumflex, will be under the influence of alpha-blockade while the other region, perfused by the left anterior descending artery, will serve as a control and a gauge for possible peripheral effects.

Also, to more precisely determine through which alpha-receptor this constrictor tone is mediated, both the nonspecific alpha-blocker phentolamine and the selective $alpha_1$-blocker prazosin were used. Prazosin is 200-1000 times more selective for $alpha_1$-receptors than it is for $alpha_2$-receptors (3, 18), and should remove the vasoconstrictor tone and decrease coronary resistance without interfering with the negative feedback inhibition of norepinephrine release as could be seen with phentolamine.

Specific Aims.--Work by other investigators have therefore suggested a coronary adrenergic vasoconstriction exists during hemorragic hypotension, partial coronary stenosis, and a more physiological stress, i.e. exercise. However, two major problems prevented a pure delineation between neural and local vasoactive events:

1) Previous studies examining the role of an alpha-adrenergic mediated vasoconstrictor tone employed systemic admnistration of alpha-antagonists. Certain problems prevent full interpretation of these results. For example, systemic administration of the alpha-antagonist does not

rule out the possibility that many effects seen are due to the actions in the peripheral circulation.

2) Previous use of nonspecific alpha-antagonists leaves the possibility that many of the effects seen were due to blockade of sympathetic presynaptic $alpha_2$-receptors. This may result in increased norepinephrine release with an increased betal-adrenergic stimulation of the heart and metabolic vasodilatation or direct dilitation through stimulation of $beta_2$-receptors.

To circumvent the problems associated with these earlier studies, direct intracoronary injections of all pharmacological agents will be used in these studies. The specific aims of this study were

1) To examine the possibility that an alpha-receptor mediated vasoconstrictor tone limits coronary blood flow during exercise;

2) To examine whether this constrictor tone is of physiological significance in the resting animal;

3) To determine the role of the $alpha_1$-adrenergic receptors mediating a coronary constrictor tone during exercise;

4) To determine whether the limitation of coronary blood flow imposed by a vasoconstrictor tone may also limit the increase in myocardial contractile function during strenuous exercise.

CHAPTER II

METHODS

Surgical Procedure.-- Mongrel dogs, of either sex (25-30 kg) were selected on the basis of general good health, mild temperament, willingness to run on a motor driven treadmill and being heartworm free prior to surgery. Norpace (150 mg O.D.) was given the day before surgery, the morning of surgery and the day after surgery for control of arrythmias during and after the surgical procedure. Dogs were presedated before surgery with Acepromazine (0.25 mg/lb), and anesthetized with sodium pentobarbital (30 mg/kg i.v.). The trachea was intubated, and the dog was ventilated with room air using a Harvard Apparatus respirator pump. Under sterile conditions, the left thorax was entered through the fifth intercostal space, and the heart was raised in a pericardial cradle.

Figure 2 diagramatically shows the manner in which the heart was instrumented during the surgical procedure. A solid state pressure transducer (Konigsberg P6.5) and a saline-heparin filled tygon catheter were inserted into the left ventricular chamber through a stab wound in the apex of the left ventricle. The left ventricular pressure transducer was calibrated in vitro before implantation in a 37 degree C water bath and again in vivo using the Tygon catheter which was attached to a Sorenson Microtrans I

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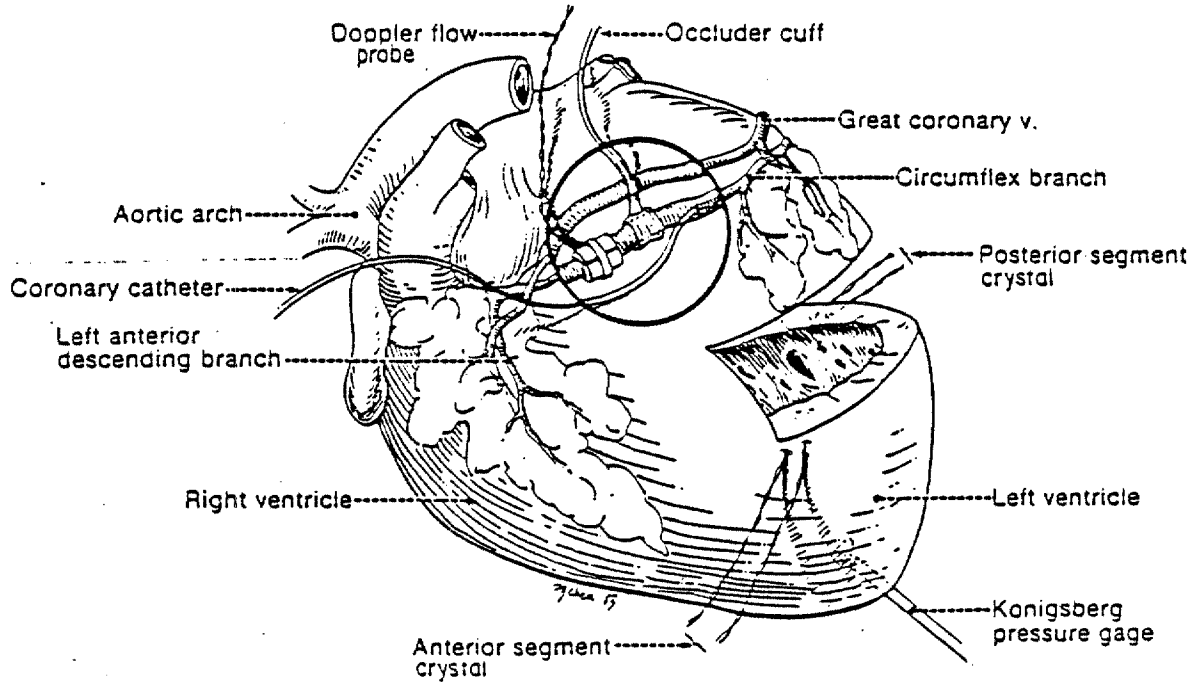
Figure 2. A diagramatic representation of the placement of the instrumentation used to measure circumflex blood flow velocity, regional segment length changes and left ventricular pressure. A catheter was also placed in the circumflex artery to administer all pharmacologic agents.

Instrumentation



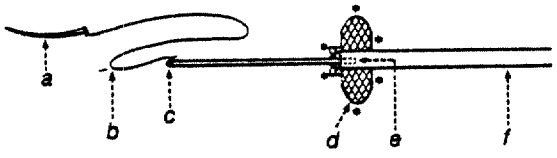
pressure transducer. The pressure transducer was calibrated to match the pressure against the catheter. The Sorenson transducer was calibrated with a mercury manometer. Fluid filled catheters tend to expand and contract with the high fluctuating ventricular pressures found during exercise and produce large errors in their signals. The Koningsberg solid state pressure transducer was used to insure an accurate recording of left ventricular pressure at high heart rates and high fluxuating pressures. This acurate measurement is crucial for accurate differentiation of this signal to obtain dP/dt. The dP/dt_{max} can be used as an index of global myocardial contractility.

The left atrium was then retracted, and the proximal left circumflex artery was disected free from the surrounding myocardium for approximatly 2.5-3 cm from its origin to the first major branch.

A 10 MHz Doppler ultrasonic flow probe, constructed in this laboratory, used to measure coronary blood flow velocity through the circumflex artery, and a Tygon vascular hydraulic occluder, constructed in this laboratory, used to occlude the circumflex artery and check the zero flow reference, were secured around the circumflex artery as close to its origin as possible. The Doppler ultrasonic flow technique has been shown to have a reliable zero reference (24) and the relationship between blood flow velocity and volume flow has been shown to be linear

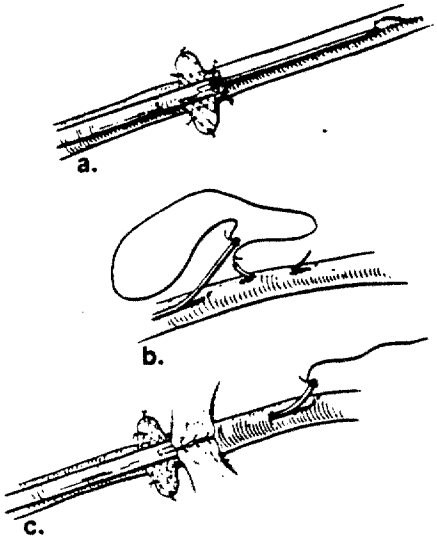
Figure 3. A diagramatic representation of the insertion of a coronary artery catheter into the left circumflex coronary artery. A: The wings of silastic sheeting were sutured to the myocardium on either side of the circumflex artery. The tip of the catheter is then tied with 5-0 suture afixed to a straightened needle. B: The catheter tip is then pulled into and out of the lumen of the artery through the holes made with the passage of the needle. The catheter tip is then cut very close to the distal exit hole in the artery. The catheter is then pulled backward until the tip re-enters the lumen of the vessel and the hole is covered until clot formation stops any bleeding.

A



a-Needle, V. Mueller #SN891, straightened
b-5-0 silk suture
c-Catheter tip
d-Wings, sew to myocardium at three points indicated by "*"
e-Joint between catheter tip and body
f-Body of catheter

B



provided the cross-sectional area of the blood vessel within the flow probe remains constant (58). Blood flow velocity may be converted to actual volume flow using the Doppler conversion equation. Fibrosis within the Doppler shell surounding the transmitting crystal, will prevent changes in diameter of the blood vessel or the angle of the crystal reletive to the blood vessel. At the time of autopsy the cross-sectional area of the coronary artery under the flow probe was determined.

A heparin filled silastic tipped catheter, constructed in this laboratory, was then inserted into the circumflex lumen before the first major branch as shown in Figure 2 . This indwelling catheter served as a route for administration of all pharmacological agents and for measurement of coronary blood pressure. The catheter is diagramatically illustrated in Figure 3. The tip of the catheter (0.6 mm O.D.) was bonded to a slightly larger silastic catheter with Dow-Corning silastic monomer (Dow-Corning #891). A 2.0 cm X 0.7 cmectangle of reinforced silastic sheeting (Dow-Corning #501-3) was bonded near the tip of the catheter and was used to fasten the catheter in place, using the surrounding tissue as an anchor as shown in Figure 3 (30). In five additional animals a catheter was positioned in the coronary sinus to allow sampling of coronary sinus blood (47).

Three sets of opposing 5MHz ultrasonic dimension

crystals, constructed in this laboratory, were then implanted 0.5-1.0 cm apart and 0.5-0.8 cm below the suface of the epicardium (50). Each set contains two round piezoelectric crystal heads, 2 mm diameter, soldered to 25 strand insulated silver wire. One crystal emits a 5 mHz ultrasonic sound wave to the receiver crystal which reflects the sound wave back to the original crystal. The time in usec required for the signal to be sent and received again depends on the distance between the two crystals. Since the sound waves are sent continuously at a 5 MHz interval, then the length of the myocardial muscle cells between the two crystals can be monitered continuously throughout the cardiac cycle. The time signal is converted to a length by multiplying by the speed of sound in tissue (1.58 usec/mm). This signal indicates the degree of shortening of the cardiac musculature between the crystal heads. Upon differentiation of the signal, dL/dt can be obtained to produce an index of regional contractility. Two sets of crystals were implanted in a region that was clearly perfused by the circumflex artery (posterior region), and the third set was implanted in a region clearly perfused by the left anterior descending artery (anterior region) and served as an internal control. Proper placement of the crystal heads was confirmed at autopsy.

All the catheters and lead wires were tunneled under

the skin dorsally until their exit between the animals scapuli. The ribs were then approximated, the chest was closed in layers and the thoracic cavity was evacuated with suction. Antibiotics (Penicillin G Procaine in dihydrostreptomycin sulfate solution, 400,000 U i.m.) were given the day before surgery, the day of surgery and again as needed. A recovery period of 14-21 days was alloted for the recovery from surgery before any experiments were performed. During this time each animal was familiarized with the labratory environment, and the motor-driven treadmill. All catheters were kept patent with a saline-heparin flush every other day and were flushed with Streptokinase (4 U/ml) as needed to prevent clot formation.

Measurements.--During all experiments simultaneous measurements of left ventricular pressure (LVP), circumflex blood flow velocity (CFV) and pressure (CBP), and segment length shortening (SL) were recorded on an 8-channel Coulbourn Instrument recorder and also on an analogue magnetic tape recorder (Hewlett-Packard 3968A instumentation recorder) for subsequent analysis of data. Upon electrical differentiation of the LVP signal, dP/dt can be determined, which served as an index of global left ventricular contractility. An Scheussler ultrasonic transit-time dimension gauge was used to measure regional myocardial segment length (SL). The ultrasonic crystals were used to asses regional contractility in their respective areas of

the left ventricle. Electrical differentiation of the signals from the segment length crystals produced the rate of segment length shortening (dL/dt) in their respective regions. The per cent shortening (%S) of the segment lengths could be determined by calculating: End Diastolic Length (EDL) - End Systolic Length (ESL) / EDL. Measurements of EDL and ESL were identified on the records at the time the velocity of shortening or lengthening crossed zero. CFV was recorded both as mean coronary flow velocity and as phasic flow velocity. Heart rate (HR) was recorded from a tachometer receiving its input from the ventricular pressure transducer.

Experimental Protocol.--After initial control readings from each animal while lying quietly on the floor and again while standing on the treadmill, the animals were subjected to a standardized submaximal exercise test developed by Tipton (54) using a Quinton model 18-60 motor driven treadmill. The submaximal test, illustrated in Figure 4, consists of increasing the treadmill speed from 4.8 km/hr during the first three minutes to 6.4 km/hr at the sixth minute. Speed then remains constant for the duration of the experiment. The percent grade of the treadmill was elevated progressivly during the experiment to encompass 0, 4, 8, 12 and 16% incline starting at the sixth minute. At a workload of 6.4 km/hr and 16% grade an injection of either saline

Figure 4. The protocol for exercise stressing dogs. Either treadmill elevation or treadmill speed was increased at 3 minute intervals until a level of 6.4 km/hr and 16% incline was attained. At this work load an intracoronary injection of either saline, phentolamine or prazosin was introduced into the left circumflex coronary artery.

(1.0 ml), which served as the vehicle for all agents injected, phentolamine (1.0 mg i.c.), or prazosin (0.5 mg, i.c.) was injected into the circumflex artery using the indwelling artery catheter. These doses were selected on the basis of adequately blocking the vasoconstrictor response to intracoronary injection of 20 ug phenylephrine, while showing no discernable peripheral effects (28).

Also to insure that beta-receptor activation did not lead to a direct vasodilatation or an indirect metabolic vasodilatation and lead to a misinterpretation of the results, atenolol or propranolol were used in conjunction with the alpha-blockers. Atenolol, a selective $beta_1$-blocker, and propranolol, a nonselective beta-blocker, were used to insure any increase in norepinephrine released from the nerve terminal after nonspecific alpha-blockade could not produce a metabolic vasodilatation through activation of beta-receptors. In five animals atenolol (1.0 mg i.c.) was administered while the animal was standing quietly on the treadmill prior to the exercise test. In two animals propranolol (1.0 mg, i.c.) was used. Since the half-lives of atenolol and propranolol is greater than 30 min (15), adequate blockade of beta-receptors was insured at the time of administration of alpha-blocking agents.

In five dogs, mean arterial blood pressure, coronary flow velocity, and heart rate were measured. Blood samples were taken from the coronary sinus and left ventricle at

rest, at 6.4 kph and 16% incline and after intracoronary injection of prazosin (0.5 mg, i.c.) during exercise. Oxygen saturation and hemoglobin (Hb) content were determined using a co-oximeter (Instrumentation Laboratory Inc., Lexington, MA, model). An index of myocardial oxygen consumption was calculated using the following formula: MVO_2 (ml O_2/min) = (arterial-venous oxygen content, ml O_2) X Hb (gm/100 ml) X 1.34 ml O_2/gm of Hb X CBF (ml/min).

In addition to an examination of the effects of alpha-adrenergic blockade during exercise, the response to intracoronary administration of either phentolamine and prazosin was tested at least twice in each animal while the animal was lying quietly in a lateral recumbent position. It has been reported that in the resting dog, an alpha-adrenergic vasoconstrictor tone is negligable in the coronary circulation (16). Therefore, it is felt that if any effects of alpha-adrenergic blockade on either the coronary circulation or myocardial contractile function during exercise were due only to abolition of a coronary constrictor tone, rather than to a direct action of the antagonist on the coronary circulation or myocardium, an attenuated effect of these agents would be observed when administered in the resting dog.

The animals chosen for each experiment were chosen at random and subject to just one submaximal exercise test per

day.

Data Analysis.--Data were analyzed from the magnetic tape recorder using a computer program which sampled the data for 10 consecutive beats at a sampling rate of 2 msec and then averaged the data. The response to either saline, phentolamine, or prazosin during exercise was determined twice in each animal, and the two tests using a given agent were averaged. The response to prazosin and phentolamine were also obtained in each animal while the animal was lying quietly. It was noted that after injection of an antagonist during treadmill exercise, the changes in CFV began within 5-10 sec, reached stable values after approximately 30 sec, and the response was stable for several minutes. To quantitate the response to an agent, data for mean CBF, HR, mean CBP, systolic LVP, dP/dt_{max}, posterior and anterior EDL and %SL, as well as posterior and anterior $dL/dt_{(s)max}$ during the peak response were compared to those values immediately before administration of the agent using both a one-way analysis of variance and Student's paired t-test. In addition, the change in $dL/dt_{(s)max}$ from exercise to exercise plus alpha-adrenergic blockade in the anterior region was compared to that in the posterior region. All values are expressed as mean $\pm$S.E., and statistical significance of a response was accepted at $P < 0.05$.

CHAPTER III

RESULTS

Effectiveness of Alpha-Blockade.--One major objective in this study was to test the hypothesis that an alpha-mediated vasoconstrictor tone exists on coronary arteries and limits the increase in coronary flow during exercise. For this purpose, regional alpha-adrenergic blockade of the circumflex bed was employed. To demonstrate an adequate alpha-blockade, with the doses used, the blocking action of phentolamine and prazosin were challenged with 20 ug phenylephrine, an alpha-receptor agonist. Figure 5 shows the effectiveness of alpha-blockade with phentolamine on the electrocardiogram, or the electrical conduction system of the heart, mean coronary blood flow, phasic coronary blood flow and heart rate in one animal. Note in the first panel that a 20 ug injection of phenylephrine produced a decrease in mean CBF. Following 1.0 mg phentolamine, phenylephrine failed to produce a fall in mean CBF. Similar results were observed in all animals studied, thus providing sufficient evidence to prove adequate alpha-receptor blockade. Similar results were obtained upon administration of 0.5 mg prazosin followed by 20 ug phenylephrine.

Alpha-Blockade in the Resting Conscious Dog.--There is a controversy in the literature as to whether a tonic alpha-mediated vasoconstriction exists at rest in the normal

Figure 5. The response, from one dog, to a 1.0 mg intracoronary phenylephrine challenge on ECG, mean CBF, phasic CBF and HR in both the control, unblocked state, and then after 1.0 mg intracoronary phentolamine. The phentolamine abolished the reduction in CBF produced by the alpha-agonist phenylephrine. This proves adequate blockade of coronary alpha-receptors with a 1.0 mg intracoronary dose of phentolamine. Similar attenuated responses were produced with 0.5 mg intracoronary prazosin when challenged with phenylephrine.

conscious dog. To examine this possibility in the preparation used, phentolamine was injected into the circumflex in all 12 dogs during resting conditions (ie, when heart rate was between 60-90 bpm). Figure 6 shows the results from one dog. There was no change in LVP, dP/dt, HR, %S of either the posterior (circumflex) region or the anterior (control) region, dL/dt of either the posterior or anterior regions, CBF, or mean CBF after intracoronary injection of 1 mg phentolamine. Injection of prazosin under similar conditions produced the same results as shown in Figure 7. These data illustates that there is no discernable tonic alpha-mediated vasoconstriction at rest, suggesting that the level of sympathetic outflow occuring at rest in these dogs is insufficiant to produce a discerable vasoconstrictor tone.

Hemodynamic Response to Exercise and Saline Injection.--To determine if the saline used as both the vehicle and to flush the catheter after every injection was responsible for the responses observed after alpha-blockade (i.e. if there was a volume or vehicle effect of an intra-coronary injection) saline was injected during exercise in all 12 dogs. Figure 8 shows a typical tracing of saline injection during exercise in one dog. Posterior SL and dL/dt, LVP, dP/dt and mean CFV were monitered during control conditions, and while the dog was running at an exercise level of 6.4 km/hr and 16% incline. At this exercise

Figure 6. The response of LVP, dP/dt, posterior SL, posterior dL/dt, phasic CBF, mean CBF and HR to a 1.0 mg intracoronary injection of phentolamine in one resting (HR between 60-90 bpm) dog. Phentolamine administered at rest produced no change in any of the parameters measured.

Figure 7. The response of LVP, dP/dt, posterior SL, posterior dL/dt, CBF, mean CBF and HR to a 0.5 mg intracoronary injection of prazosin in a resting (HR between 60-90 bpm) dog. Prazosin, like phentolamine, administered at rest produced no change in any of the parameters measured.

Figure 8. The effect of the exercise stress and intracoronary saline on LVP, dP/dt, posterior SL, posterior dL/dt, mean CBF and HR. Exercise produced increases in all parameters measured as expected with a strong sympathoadrenal activation. The 1.0 ml of saline injected intracoronarily during exercise produced no change in any of the parameters both during injection and one minute after injection.

workload saline was injected into the circumflex. Recordings were obtained during saline injection and one minute after saline injection. The first panel shows typical tracings of LVP, dP/dt, SL, dL/dt, HR and mean CFV recorded during control conditions with the animal standing on the treadmill. The next panal shows the increases in these signals associated with the exercise stress, an increased LVP, dP/dt, SL, dL/dt, HR and mean CFV. It is important to note there were no changes in these parameters during saline injection or one minute after saline administration, as shown in the next two panals. Similar results were obtained in all animals. These data indicates there was no volume or vehicle effect with an intracoronary injection and saline itself had no effect.

Response to Phentolamine During Exercise.--Figure 9 shows the response of LVP, dP/dt, posterior SL and dL/dt, anteior SL and dL/dt and mean left circumflex blood flow to phentolamine injection during exercise. When all signals had reached a new steady state following their increases due to the exercise stress, further significant increases were seen in CFV, posterior dL/dt, and dP/dt following phentolamine injection. It is important to note that the %S and dL/dt of the control anterior region did not change. Table I shows the mean $\pm$ SE for the above parameters in 15 dogs at rest, during exercise at 6.4 Km/hr and 16% incline and during exercise one minute after intracoronary

Figure 9. The effect intracoronary phentolamine has on LVP, dP/dt, posterior SL, posterior dL/dt, anterior SL, anterior dL/dt, mean CBF and HR during exercise. Phentolamine administered during exercise produced significant increases in dP/dt, CBF and dL/dt of the posterior region, when compared to exercise without nonspecific alpha-blockade.

TABLE I

EFFECTS OF PHENTOLAMINE ON CARDIAC FUNCTION AND CORONARY FLOW DURING EXERCISE

	RESTING	EXERCISE	EX+PHENT	%CHANGE
LVESP (mmHg)	132 ± 4	148 ± 5	155 ± 3	6 ± 3
LVEDP (mmHg)	3 ± 2	4 ± 1	3 ± 1	
dP/dt_{max} (mmHg/sec)	3467 ± 248	5473 ± 446	7280 ± 684*	33 ± 6
mean CBP (mmHg)	95 ± 5	97 ± 3	100 ± 5	
HR (bpm)	125 ± 7	213 ± 8	230 ± 8	9 ± 2
CBF (ml/min)	33 ± 6	55 ± 10	71 ± 13*	30 ± 3
Posterior Segment				
EDL (mm)	123 ± 0.5	12.7 ± 0.6	12.5 ± 0.6	-1 ± 1
%SL	15.9 ± 1	20.6 ± 2	21.6 ± 2	5 ± 2
$dL/dt_{(s)max}$ (mm/sec)	23.1 ± 3	48.2 ± 9	58.7 ± 8*	40 ± 13
Anterior Segment				
EDL (mm)	11.2 ± 0.6	11.3 ± 0.7	11.1 ± 0.6	-1 ± 1
%SL	18.4 ± 4	21.5 ± 5	22.2 ± 5	10 ± 9
$dL/dt_{(s)max}$ (mm/sec)	22.8 ± 3	38.6 ± 10	42.2 ± 10	13 ± 5

Data are mean ± S.E. N=15
*$p<0.05$ exercise vs. exercise with alpha-blockade
Abbreviations: LVESP = Left Ventricular End Systolic Pressure; LVEDP = Left Ventricular End Diastolic Pressure; dP/dt_{max} = maximum rate of change of LVP; CBP = Coronary Blood Pressure; HR = Heart Rate; EDL = End Diastolic Length; %SL = Segment Length Shortening; $dL/dt_{(s)max}$ = maximum rate of segment length shortening; CBF = Circumflex Blood Flow; %CHANGE = change in the parameter from exercise to exercise plus alpha-blockade; EX-PHENT = the parameter measured during exercise after intracoronary phentolamine.

phentolamine injection. The values for dP/dt_{max}, CBF and $dL/dt_{(s)max}$ of the posterior segment showed a further statistically significant rise from the exercise level after phentolamine.

Response to Prazosin During Exercise.--Similar responses were seen following prazosin injection during exercise as shown in Figure 10. The effect of a 0.5 mg injection of prazosin on LVP, dP/dt, SL, and dL/dt of the circumflex and control regions, along with CBF during exercise can be seen in a typical tracing from one dog. Table II shows the mean values, in 15 dogs, for each parameter during control, during exercise and during exercise after injection of prazosin. Once again the values for dP/dt_{max}, CBF and $dL/dt_{(s)max}$ for the posterior segments showed statistically significant increase in these values above the exercise level following prazosin administration.

Response to Alpha-Blockade After Beta-Blockade During Exercise.--To eliminate the possibility that phentolamine was producing a coronary vasodilitation through metabolic mechanisms, experiments were repeated in 5 dogs following $beta_1$-blockade with atenolol and in 2 dogs following combined $beta_1$- and $beta_2$-blockade with propranolol. Beta-blockade was produced prior to the exercise test.

A typical tracing of the effect of alpha-blockade during exercise after beta-blockade with atenolol is shown in Figure 11. In the presence of atenolol after

Figure 10. The effect intracoronary prazosin has on LVP, dP/dt, posterior SL, posterior dL/dt, anterior SL, anterior dL/dt, mean CBF and HR during exercise. As with phentolamine, prazosin produced significant increases in dP/dt, CBF and dL/dt of the posterior region during exercise, when compared to exercise without $alpha_1$-blockade.

TABLE II

EFFECTS OF PRAZOSIN ON CARDIAC FUNCTION AND CORONARY FLOW DURING EXERCISE

	RESTING	EXERCISE	EX+PRAZ	%CHANGE
LVESP (mmHg)	139 ± 7	153 ± 6	158 ± 7	4 ± 2
LVEDP (mmHg)	2 ± 2	1 ± 2	0.5 ± 1	
dP/dt_{max} (mmHg/sec)	3455 ± 206	5757 ± 346	7001 ± 534*	21 ± 4
mean CBP (mmHg)	95 ± 5	97 ± 3	100 ± 5	
HR (bpm)	127 ± 9	213 ± 8	220 ± 7	4 ± 1
CBF (ml/min)	32 ± 6	53 ± 10	63 ± 11*	21 ± 3
Posterior Segment				
EDL (mm)	12.0 ± 0.6	12.3 ± 0.6	12.2 ± 0.6	-1 ± 0.4
%SL	14.6 ± 1	18.6 ± 1	18.9 ± 1	3 ± 5
$dL/dt_{(s)max}$ (mm/sec)	20.7 ± 2	34.3 ± 4	45.8 ± 4*	37 ± 6
Anterior Segment				
EDL (mm)	10.8 ± 0.5	10.9 ± 0.6	10.9 ± 0.6	-0.2 ± 0.3
%SL	15.7 ± 2	19.5 ± 0.6	10.9 ± 0.6	11 ± 5
$dL/dt_{(s)max}$ (mm/sec)	24.5 ± 3	32.8 ± 4	33.7 ± 4	4 ± 4

Data are mean ± S.E. N=15.
*$p<0.05$ exercise vs. exercise with $alpha_1$-blockade
Abbreviations: LVESP = Left Ventricular End Systolic Pressure; LVEDP = Left Ventricular End Diastolic Pressure; dP/dt_{max} = maximum rate of change of LVP; CBP = Coronary Blood Pressure; HR = Heart Rate; EDL = End Diastolic Length; %SL = Segment Length Shortening; $dL/dt_{(s)max}$ = maximum rate of segment length shortening; CBF = Circumflex Blood Flow; %CHANGE = change in the parameter from exercise to exercise plus alpha-blockade; EX-PRAZ = the parameter measured during exercise after intracoronary prazosin.

Figure 11. The response of LVP, dP/dt, psterior SL, posterior dL/dt, anterior SL, anterior dL/dt, mean CBF and HR to beta-blockade, exercise and exercise plus alpha- and beta-blockade. Beta-blockade produced reductions in all parameters at rest. Alpha- and beta-blockade during exercise produced further increases in dP/dt, CBF and dL/dt of the posterior region, when compared to exercise with beta-blockade alone.

TABLE III

EFFECTS OF NON-SPECIFIC ALPHA-BLOCKADE ON CARDIAC FUNCTION AND CORONARY FLOW AFTER $BETA_1$-BLOCKADE IN EXERCISE

	RESTING	ATENOLOL	EXERCISE	EX+PHENT
LVESP (mmHg)	118 ± 6	116 ± 3	134 ± 7	142 ± 11
dP/dt_{max} (mmHg/sec)	2600 ± 447	2144 ± 362	3398 ± 386	4106 ± 675*
CBP (mmHg)	95 ± 5	95 ± 5	100 ± 3	105 ± 5
HR (bpm)	100 ± 8	85 ± 15	163 ± 3	181 ± 7
CBF (ml/min)	27 ± 5	25 ± 5	33 ± 5	42 ± 7*
Posterior Segment				
%SL	18.0 ± 1.3	16.7 ± 2.1	21.1 ± 1.6	25.1 ± 2.3
$dL/dt_{(s)max}$ (mm/sec)	20.0 ± 0.2	19.3 ± 1.2	27.1 ± 3.8	39.4 ± 1.7*
Anterior Segment				
%SL	11.7 ± 0.6	12.8 ± 3.8	14.7 ± 0.9	15.9 ± 1.7
$dL/dt_{(s)max}$ (mm/sec)	15.2 ± 3.9	16.6 ± 2.8	23.3 ± 2.9	26.3 ± 3.3

Data are mean ± S.E. N=15
*$p<0.05$ exercise after atenolol vs. exercise with alpha-blockade. Abbreviations: LVESP = Left Ventricular End Systolic Pressure; dP/dt_{max} = maximum rate of change of LVP; CBP = Coronary Blood Pressure; HR = Heart Rate; %SL = Segment Length Shortening; CBF = Circumflex Blood Flow; $dL/dt_{(s)max}$ = maximum rate of segment length shortening.

phentolamine and prazosin injection, as before, increases in CBF, posterior dL/dt and dP/dt were observed. Table III shows the mean values for 5 animals, for all parameters at resting control, after $beta_1$-receptor blockade with atenolol, during exercise and after prazosin and phentolamine injection during exercise. Since these responses were similar to the response to phentolamine in the absence of $beta_1$-blockade, $beta_1$-activation was determined to have no significant role in the coronary flow response of phentolamine. Similar effects on CFV, posterior dL/dt and dP/dt were observed following intracoronary phentolamine in the presence of beta-receptor blockade with propranolol. This once again implies no significant effect of $beta_1$- or now $beta_2$-receptor activation in the flow response of phentolamine.

Effect of Alpha-Blockade on Myocardial Oxygen Consumption.--Left ventricular oxygen extraction (%E) and an index of myocardial oxygen consumption (MVO_2-I) were estimated by using the arteriovenous oxygen content difference $(A-V)O_2$ and mean CBF. The data obtained in 5 dogs is summarized in Table IV. Oxygen extraction and MVO_2-I increased with exercise. The increase in MVO_2-I was met by an increase in CBF. After prazosin was injected into the circumflex artery, MVO_2-I increased an additional 26 $\pm$ 11% and CBF increased 26 $\pm$ 4%. It should be noted, however, that %E tended to decrease after prazosin.

TABLE IV

CORONARY BLOOD FLOW AND LEFT VENTRICULAR OXYGEN CONSUMPTION DURING EXERCISE

	RESTING	EXERCISE	EX+PRAZOSIN
HR (bpm)	95 ± 2	206 ± 9	210 ± 10
MAP (mmHg)	111 ± 4	147 ± 7	147 ± 7
CBF (ml/min)	31 ± 2	49 ± 3	61* ± 4
%E	63 ± 2	80 ± 3	78 ± 3
MVO_2-I	4.22 ± .42	10.08 ± .78	12.81* ± 1.92

Data are mean ± S.E. N=5
*$p<0.05$ exercise vs. exercise with prazosin
Abbreviations: HR = Heart Rate; MAP = Mean Arterial Pressure; CBF = Circumflex Blood Flow; %E = arterial-venous oxygen extraction; MVO_2-I = index of myocardial oxygen cosumption.

CHAPTER IV

DISCUSSION

Previous studies suggest that an alpha-adrenergic constrictor tone is present in the coronary vasculature and limits the extent of coronary dilation during exercise (27,32,33,44). In these studies, systemic administration of an alpha-adrenergic antagonist during exercise was associated with an increase in coronary blood flow. While these data indeed suggest the existence of a coronary alpha-adrenergic constrictor tone, interpretation of the data is impeded by the systemic route of administration of the antagonist as well as by the use of the non-specific antagonist phentolamine. The present experiments further examine the presence of a coronary alpha-adrenergic constriction in exercise as well as the possible influence of such constriction on myocardial function. These experiments were designed to avoid the problems associated with previous studies. As antagonists, both the relatively specific $alpha_1$-adrenergic blocker prazosin as well as the non-specific alpha-adrenergic blocker phentolamine were employed. Furthermore, to avoid confusion in the interpretation of results due to presynaptic blockade of $alpha_2$-adrenergic receptors by phentolamine with a resulting increase in the release of norepinephrine, the experiments with phentolamine were also performed in the presence of

either specific $beta_1$-adrenergic blocker or non-specific beta-blockade. Finally, to minimize misinterpretation of results secondary to peripheral circulatory reflexes, both alpha-adrenergic antagonists were administered directly into the circumflex coronary artery. Following coronary administration of either antagonist, there was no significant change in mean coronary blood pressure, arterial blood pressure, HR, or LVEDP. This observation suggests that intracoronary administration of the antagonists in the doses employed did not cause peripheral circulatory dilation with a reduction in mean aretrial blood pressure. The preparation itself permitted measurement of any change in blood flow to the circumflex bed as well as any change in contractile function in the circumflex perfusion territory and in the perfusion territory of the non-injected left anterior descending artery. Since both regions were subjected to the same afterload and preload pressures as well as to any reflexes arising from the peripheral circulation or from centrally mediated reflexes, it could be assumed that any change in contractile function observed only in the circumflex territory was due to a local effect of the agent injected, and not to reflex-induced changes or to significant recirculation of the agent.

During exercise, both prazosin and phentolamine elicited substantial increases in cicumflex blood flow, and the increases elicited by both agents were nearly identical.

Furthermore, it is noteworthy that the increase in coronary flow elicited by the non-specific $alpha_1$- and $alpha_2$-adrenergic antagonist phentolamine was not affected by either $beta_1$- or $beta_2$-adrenergic blockade. The experiments using the specific $alpha_1$-adrenergic antagonist prazosin and the experiments using phentolamine in the presence of beta-blockade imply that the increase in coronary flow observed cannot be attributed to a presynaptic $alpha_2$-adrenergic blockade with increase of norepinephrine from the sympathetic nerve terminal. If such an increase in norepinephrine release had occurred with phentolamine, it would be expected to cause an increased myocardial $beta_1$-receptor stimulation with secondary metabolic vasodilation (39) or an increased coronary $beta_2$-receptor stimulation with direct vasodilation (29). Also, since prazosin and phentolamine elicited similar increases in coronary blood flow during exercise, it is reasonable to suggest that the effects of these antagonists were not dependant on the blockade of postsynaptic $alpha_2$-adrenergic receptors which have been reported to mediate a coronary vascular constrictor tone (13,35). With this line of reasoning, it may be proposed that the coronary dilation seen with prazosin and phentolamine was due either to a direct vasodilatory effect of the two agents or to blockade of an $alpha_1$-adrenergic constrictor tone. In this regard, it

should be noted that a direct vasodilatory action of the two agents seems unlikely because neither antagonist elicited an increase in coronary blood flow in the resting recumbent animal. It is also unlikely that alpha-adrenergic blockade resulted in release of neuropeptides, leukotrienes, prostaglandins or electrolytes which may have an inotropic and/or coronary dilating effects. Since in the resting dog, sympathetic stimulation of the coronary circulation may be negligible (16), the present data are more compatable with the proposal that during exercise, sympathetic stimulation of the heart is substantially increased, and the increase in blood flow seen with prazosin and phentolamine under these conditions is due to ablation of an $alpha_1$-adrenergic constriction.

The results of the present experiments strongly indicate the presence of a coronary $alpha_1$-adrenergic constrictor tone in exercise. The results also suggest that the effect of an $alpha_2$-adrenergic constriction is not additive to that of the $alpha_1$-adrenergic constriction since phentolamine and prazosin caused similar increases in coronary flow. However, these results do not necessarily discount the presence of a coronary $alpha_2$-adrenergic influence because of the heretofore unconfirmed possibility that a combined activation of both $alpha_1$- and $alpha_2$-receptors is necessary for exertion of the vasoconstriction. In this case, inhibition of either receptor type would cause

the same dilation as would inhibition of both. Nevertheless, it should be noted that the results of the present experiments in the exercising dog are not in agreement with the recent report by Heusch and Deussen (31) that during partial coronary stenosis in the anesthetized dog, a sympathetic coronary constriction is entirely mediated by $alpha_2$-adrenergic receptors. Observations by Heyndrickx et al (32,33) also indicate that presynaptic $alpha_2$-receptor activation and concomitant release of norepinephrine is responsible for any increase in myocardial function and MVO_2 after systemic phentolamine in exercising dogs. In this regard, it may also be noted that these reports are in contrast to other more directly related work from the present labratory demonstrating that following a reduction in coronary perfusion pressure to 50 mmHg in the anesthetized dog, intracoronary administration of prazosin elicited a significant increase in coronary blood flow (52).

The increase in circumflex blood flow caused by administration of either prazosin or phentolamine during exercise was associated with a significantly increased contractile performance of myocardium within the circumflex perfusion territory as indicated by an increased rate of segment length shortening (53,55). Contractile performance within the left anterior descending region (which was subjected to the same preload and afterload pressures) was

not significantly changed. The precise basis for the increased contractile performance is not certain. This effect cannot be attributed to increased $alpha_1$-receptor stimulation since experiments with phentolamine showed that the effect was not altered by $beta_1$-receptor blockade, and in the doses employed, prazosin presumably does not cause increased norepinephrine release (2,33,35). Likewise, the increased performance cannot be attributed to inhibition of postsynaptic myocardial alpha-adrenergic receptors. Thus, if these receptors exist and are of functional importance, their inhibition would be expected to cause myocardial depression (17,39,40). Furthermore, it is felt the increased performance is not due to a direct inotropic effect of the alpha-adrenergic antagonists used, but is dependent on a high sympathetic drive to the heart. Thus, neither alpha-adrenergic antagonist elicited the effect in the resting recumbent dog. It is attractive to propose that the increased contractile performance of myocardium in the circumflex region was a direct result of the increase in blood flow. This proposal implies that during moderate to heavy exercise, with increased cardiac sympathetic stimulation and consequently increased inotropic state and heart rate, at least the deeper myocardial layers (in which the segment length crystals were implanted) become flow limited. A contributing factor to this flow-limitation is the alpha-adrenergic vasoconstriction, and abolition of this

vasoconstriction reduces the flow-limitation and permits an increase in contractile performance. This proposal is consistant with the "Gregg Phenomenon" first described in 1957 (23,26), which suggests that an increase in in coronary perfusion results in an increase in myocardial oxygen consumption. In other words, Gregg proposed that the strength of myocardial contraction is modulated by coronary perfusion. This idea is the inverse of the more commonly accepted idea that coronary flow is determined by myocardial oxygen demand via local mechanisms. Gregg's phenomenon has been observed in working, well perfused hearts, with the coronary autoregulation intact (1). It is possible, however, that local hypoperfusion, especially in the subendocardium, is responsible and that the increase in myocardial function and oxygen consumption is secondary to the increase in coronary blood flow. In the present study, oxygen extraction tended to decrease after prazosin, which indicates that the increase in oxygen consumption was actually due to the increase in coronary blood flow.

Previous results regarding a myocardial flow-limitation in dynamic exercise are controversial and inconclusive. Thus, it has been proposed that at high heart rates, the the reduction in diastolic coronary perfusion time may make the subendocardial myocardium especially vulnerable to ischemia (23). Certain investigators have indeed reported a

substantial reduction in the subendocardial to subepicardial flow ratio during exercise or pacing tachycardia (51,60). Whether or not this reduction in the transmural flow ratio indicates an actual deficiency of subendocardial flow is less certain. Heyndrickx et al (32) reported that systemic administration of phentolamine in running dogs elicited not only an increase in coronary blood flow, but also an increase in left ventricular oxygen consumption, which may suggest that the left ventricular myocardium becomes ischemic during moderate to high levels of exercise and that abolition of a coronary alpha-adrenergic constrictor tone results in an improved oxygen delivery to the myocardium. On the other hand, Barnard et al (6) observed a reduced subendocardial to subepicardial flow ratio in dogs subjected to near maximal exercise, but were unable to detect electrocardiographic evidence of myocardial ischemia. These investigators also observed that administration of the coronary vasodilator adenosine during exercise caused a further increase in subendocardial perfusion, indicating that the subendocardial vasodilatory reserve was not exceeded druing exercise. However, Aversano and Becker (5) demonstrated in anesthetized dogs that some vasodilatory reserve was still present when coronary perfusion pressure was reduced to 35 mmHg. Myocardal contractile performance was significantly reduced at this time. In other words, despite a functionally significant flow reduction, some

coronary reserve was still present, which may have been due to the presence of an alpha-adrenergic coronary vasoconstrictor tone.

Studies performed in humans have also been inconclusive. Thus, Gibbons et al (25) reported that in heavy treadmill exercise in trained runners, there was a consistant ST-segment depression indicative of myocardial ischemia. The runners showed no evidence of left ventricular hypertrophy. Barnard et al (7) observed that sudden onset of strenuous treadmill exercise caused transient electrocardiographic evidence of myocardial ischemia which was not present when the strenuous exercise was preceded by a warm-up. Also, Rose et al (48) observed that strenuous dynamic exercise in humans when preceded by a warm up was not associated with electrocardiographic changes generally accepted as indices of myocardial ischemia. In regard to these studies in humans, it should be recognized that overt electrocardiographic changes may not be adequately sensitive for detection of a flow-deficiency of sufficient magnitude to limit the increase in subendocardial contractile performance in exercise (8).

In summary, the present experiments provide strong evidence for $alpha_1$-adrenergic vasoconstriction in the coronary circulation in the running dog. The results suggest that abolition of this vasoconstrictior tone results

not only in an increase in coronary blood flow, but also an increase in myocardial contractile function. These results are compatible with the concept that the coronary vasoconstrictor tone during exercise limits both the increase in coronary blood flow and the increase in myocardial performance.

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