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Muscle Metaboreflex Control Of Coronary Blood Flow And Ventricular Contractility During Dynamic Exercise In Normal And Heart Failure Conditions

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MUSCLE METABOREFLEX CONTROL OF CORONARY BLOOD FLOW AND VENTRICULAR CONTRACTILITY DURING DYNAMIC EXERCISE IN NORMAL AND HEART FAILURE CONDITIONS

by

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DISSERTATION

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DEDICATION

I would like to dedicate this dissertation to my family.

To my Father and Mother who have supported and nurtured my interest in science and human performance from a very early age. I remember the microscope kit you gave me for Christmas when I was just five years old. It all started there. Thank you. You pushed when I needed a push, and you gave perspective and direction when I had difficulty seeing the finish line. You have instilled dedication, perseverance and a work ethic when I was young. This is the reason I am here.

To my sister and brothers, from whom I have received much love and support over the years. Thank you. I am very thankful for our sibling bond.

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CHAPTER 1

Introduction

It is well known that the varying levels of metabolic requirements during exercise must be followed by changes in cardiovascular dynamics in order to meet the metabolic needs of the active skeletal muscle tissue. The cardiovascular system copes with an increase in metabolic need by increasing blood flow to the working skeletal muscle through either increasing the cardiac output of the heart, vascular resistance to the less metabolically demanding organs, or varying levels of both. There are several mechanisms that control these changes and are seen as feed forward and feed back in nature; though there are three main neural mechanisms known for cardiovascular homeostasis during exercise. One is central command (32), which is a feed forward mechanism; as well as the feedback mechanisms of the baroreceptor reflex (aka. baroreflex) (66), and the skeletal muscle afferents, composed of both the mechano- and metaboreflex (91; 109). For the purpose of this dissertation, the focus will be on the muscle metaboreflex.

The muscle metaboreflex is a negative feedback blood flow and blood pressure raising reflex. When blood flow to working muscles does not provide adequate oxygen and nutrients to maintain the metabolic level for the activity, the working muscles create metabolic by-products, also called metabolites. These metabolites stimulate group III and IV afferent nerve fibers (2; 6; 65; for review see 69). Activation of these afferent fibers elicits an increase in sympathetic tone. Increased sympathetic tone to the heart and vasculature brings forth an increase in cardiac output – known as the muscle metaboreflex.

Alam and Smirk (2) discovered the muscle metaboreflex serendipitously. They stumbled into this discovery after arresting circulation into and out of working muscles during a bout of static exercise (multiple sets of experiments were done: seated calf raises, and hand grip

exercises). They observed that during exercise, with the arrest of blood flow, there was a significant increase in blood pressure. Moreover, instead of blood pressure returning to near resting levels after the end of the exercise, blood pressure remained elevated while blood flow to the formerly working muscles was still under arrest. This increase in blood pressure was markedly greater than what was observed in similar experiments that did not include circulatory arrest.

Since their discovery, the idea disappeared until 1964 when Asmussen and Nielsen (6) used cycle ergometry and suggested that the reflexive nervous activity involved may be due to activation of mechanical and/or chemical receptors in the working skeletal muscle. Coote et al (19), furthered this idea by showing that, in cats, stimulation of skeletal muscle contraction along with occlusion of the iliac artery produced a much greater pressor response as opposed to stimulation alone. In this study it was also discussed that the afferent signals sent from metabolic receptors are likely transmitted through Group III and/or IV afferent fibers. McCloskey et al, (65) confirmed that Group III and IV afferent nerves are involved with the reflex; using two forms of nerve blockade to differentiate between large myelinated fibers (group III) versus small unmyelinated fibers (group IV). Since then, it has been shown that group IV afferent fibers are primarily chemo-sensitive, though possess some mechano-sensitive properties (1), and that group III afferent fibers are primarily mechano-sensitive, but possess some chemo-sensitive properties (1; 54). Following this, it has been determined that among the stimuli that activate these afferents are: lack of oxygen delivery (98), lactate (101), hydrogen ion concentration (H+), pH (99; 106), arachidonic acid (87), diprotonated phosphate (100), and adenosine (63).

Normal mild exercise does not elicit a muscle metaboreflex pressor response. As mentioned previously, the muscle metaboreflex is activated by accumulation of metabolites in

skeletal muscle (for review see 89). That is to say, one must either produce high levels of metabolites, as during higher intensity exercise, or produce a reduction of flow to the working muscles. When activated, the muscle metaboreflex causes, by increasing sympathetic activity, an increase in cardiac output through an increase in both heart rate and cardiac contractility (79; 95). Depending on the intensity of the exercise, there is also a degree of vasoconstriction to maintain proper blood pressure levels and thus an increase in central blood mobilization (97). It appears these processes all occur in order to increase blood pressure and flow to ischemic muscles. A study by Joyner (45) done in humans, and another by Mittelstadt et al. (70) have shown that even the vasculature of the working skeletal muscle is under vasoconstriction during exercise and muscle metaboreflex activation. These are the typical components of muscle metaboreflex activation, in mild to moderate exercise, but the manifestation of muscle metaboreflex activation can change in different circumstances.

What is observed during muscle metaboreflex activation in mild and moderate intensity exercise is somewhat different than what is seen during severe exercise. Augustyniak et al (8), performed a study using conscious dogs, and activated the muscle metaboreflex via partial reduction of blood flow at the terminal aorta. In that study they observed that while at mild and moderate levels of exercise, cardiac output increased significantly during muscle metaboreflex activation; yet there was no significant increase in cardiac output at severe exercise during muscle metaboreflex activation, though the pressor response still occurred. This shows an alteration in the mechanism of muscle metaboreflex activation, shifting the main manifestation of the muscle metaboreflex to be vasoconstriction rather than cardiac output. This allows for blood pressure to increase considerably, without a considerable increase in cardiac output. Joyner (45), suggests that this vasoconstriction may even impair flow to the muscles.

Heart failure is defined as a condition resulting from a myocardial dysfunction. This

abnormality causes a decrease in cardiac output, resulting in the inability of the heart to circulate enough oxygen rich blood throughout the body, to supply its metabolic needs. Therefore, one of the typical signs is a decreased cardiac output. Another sign is increased level of sympathetic activity (epinephrine and norepinephrine) in resting and exercise conditions. The increased sympathetic activity also results in high tachycardia, and a reduced tolerance to exercise (29; reviewed in 84).

A study conducted by Hammond et al (39), found that when dogs were in heart failure, muscle metaboreflex activation during exercise could not elicit a significant increase in cardiac output, leaving the pressor response entirely due to vasoconstriction. This effect of heart failure on muscle metaboreflex during exercise is very similar to what is observed during severe levels of exercise intensity, in normal conditions. Also found in heart failure dogs were increased levels of: vasopressin, norepinephrine, and renin. A study by O'Leary et al (81), found similar results, and also showed that the reason for a lack of a cardiac output increase was due to a significant decrease in stroke volume, (heart rate was higher in heart failure when compared to normal conditions). Ansorge et al (3), found similar results, as well as a decrease in the rate of ventricular contraction, measured with dL/dt (change in myocardial segment length with respect to time). It was also suggested that the increased sympathetic activity to the heart causes significant vasoconstriction of the coronary arteries, which may limit the heart's work capacity. Sala-Mercado et al (94), used the pressure volume relationship to illustrate a reduced ventricular contractility in dogs with heart failure while in exercise and muscle metaboreflex activation, as compared to when they were normal. More specifically, they showed that during heart failure, activation of the muscle metaboreflex did not further increase ventricular contractility when compared to exercise without activation of the muscle metaboreflex.

Examples of previously conventional measures of cardiac performance are: stroke

volume, ejection fraction, and maximal change of pressure (dP/dt_{max}), as well as maximal myocardial segment length shortening (dL/dt_{max}), with respect to time. While these measures are sensitive to contractile state, they are also influenced by changes in preload or afterload (48; 58), this is a major limitation in such techniques in measuring contractility. In order to take changes in preload and afterload into account, indexes using the pressure-volume relationship are used, preload recruitable stroke work (PRSW). The concept of preload recruitable stroke work is a modification of the Frank-Starling relationship, with the use of end diastolic volume instead of end diastolic pressure (30). Preload recruitable stroke work is a relationship of the stroke work with respect to the end diastolic volume. Stroke work is a product of stroke volume and the pressure change in the left ventricle throughout a cardiac cycle, i.e. the integral of the pressure-volume relationship during one cardiac cycle. When stroke work is plotted as a function of end diastolic volume, the slope of the resultant linear relationship is preload recruitable stroke work, which is measured in the $mmHg \cdot ml/ml$ also measured as $erg \cdot 10^3/cm^3$ (30). Preload recruitable stroke work however, is both insensitive to changes in loading conditions, and is not influenced by changes in ventricular size and structure (47).

Normally the muscle metaboreflex elicits an increase in cardiac performance (79). This in itself would increase cardiac output; and if there were no changes in the vascular dynamics, this would lead to a decrease in venous pressure, and subsequently a decrease in cardiac output. In order to maintain preload the muscle metaboreflex also elicits vaso and venocostriction to maintain right atrial pressure, coupled with the increase in cardiac output (97). But, this vasoconstriction may include vasoconstriction of the coronary vasculature. Gwirtz et al. (37) found that the increased α-adrenergic activation, from increased sympathetic tone, as a result of exercise, caused vasoconstriction in the coronary arteries. As well, it was suggested that this coronary vasoconstriction might modulate cardiac function. This was shown by a significant

vasodilation in the coronary vasculature, during exercise, following α-receptor blockade. Gwirtz, et al., not only showed an increase in blood flow, but also showed an increase in cardiovascular performance with α-blockade. O'Leary and Augustyniak (79) showed that increased sympathetic activation elicited by the muscle metaboreflex served to maintain or even increase stroke volume during tachycardia in exercise. The question remained as to whether the muscle metaboreflex would affect coronary blood flow. Following this, Ansorge et al. (4), discovered that during severe exercise, activation of the muscle metaboreflex significantly reduced the coronary vascular conductance. Furthermore, with dogs in heart failure, Ansorge et al. (3), found that this reduction in coronary vascular conductance was not only seen in moderate levels of exercise, but also mild levels of exercise, with activation of muscle metaboreflex. Sala-Mercado et al. (94), used the pressure-volume relationship to illustrate a reduced ventricular contractility in dogs with heart failure while in exercise and muscle metaboreflex activation, when compared to the control condition. During heart failure, it is known that there is a markedly high level of sympathetic activity; however no significant increases in cardiac output are observed during rest, mild, moderate or severe exercise conditions when compared to normal conditions with their corresponding intensities (39; 40). In fact, cardiac output is lower.

It is possible that one reason for this inability to increase cardiac output would be coronary vasoconstriction. O'Leary et al. (82) illustrated a significant increase in coronary vascular conductance after muscle metaboreflex activation in normal dogs during α_1-adrenergic blockade. In this study, a higher increase in cardiac output during muscle metaboreflex activation while under α_1-adrenergic blockade was also observed. Cardiac myocytes are able to increase their oxygen uptake up to five times during exercise. However, as depicted in Figure 1.1, even when the body is at rest the heart muscle extracts ~75% of the oxygen in arterial blood,

while the rest of the body (mostly skeletal muscle) extracts ~25%. As workload intensity increases, skeletal muscle is able to extract more oxygen from the blood. Since the heart muscle already extracts a large amount of oxygen when the body is at rest, it is unable to extract substantially more oxygen when workload increases. This leaves increasing coronary blood flow as the primary mechanism of delivering more oxygen to the cardiac myocytes (reviewed in 10; 105). In normal conditions, metabolic vasodilation facilitates an increase in coronary blood flow during heavy cardiac oxygen demand or ischemic situations. Factors that stimulate coronary vasodilation are adenosine, potassium channels, nitric oxide (reviewed in 105), low myocardial oxygen tension, or high myocardial carbon dioxide tension (11). The reduction in coronary vascular conductance during muscle metaboreflex activation suggests that the vasoconstriction caused by increased sympathetic tone, elicited by the muscle metaboreflex, is more powerful than the vasodilatory effects of the metabolic factors released with increase in cardiac work (eg. increased cardiac output). This vasoconstriction may limit coronary metabolic vasodilation, and could suppress increases in left ventricular performance: though this phenomenon has yet to be determined.

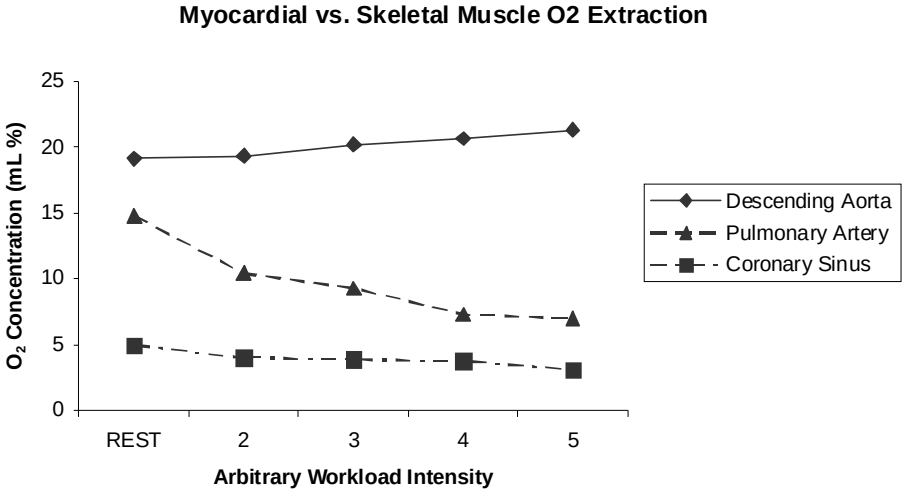


Figure 1.1. Illustration of cardiac muscle and somatic oxygen extraction, from arterial blood. The descending aorta contains oxygen rich blood. The pulmonary artery blood contains deoxygenated blood from throughout the body, while the coronary sinus contains deoxygenated blood specifically from the heart. (Adapted from 47; 75)

The purpose of this study was to determine if, during mild, dynamic exercise (2mph 10% grade), the α_1-adrenergic mediated vasoconstriction that occurs with muscle metaboreflex activation, results in a suppressed left ventricular contractility in normal and heart failure conditions. I hypothesized that:

1 – The muscle metaboreflex- induced increases in cardiac sympathetic activity functionally vasoconstricts the coronary vasculature and this limitation in raising coronary blood flow acts to limit the ability to raise ventricular contractility and therefore cardiac output in the normal animal.

2 – In animals with heart failure, the inability to raise ventricular contractility and cardiac output with metaboreflex activation is not simply due to the ventricular dysfunction, but is also attributable to this coronary vasoconstriction.

CHAPTER 2

Muscle Metaboreflex-Induced Coronary Vasoconstriction Functionally Limits Increases in Ventricular Contractility

Abstract

Muscle metaboreflex activation during dynamic exercise induces a substantial increase in cardiac work and oxygen demand via a significant increase in heart rate, ventricular contractility and afterload. This increase in cardiac work should cause coronary metabolic vasodilation. However, little if any coronary vasodilation is observed due to concomitant sympathetically induced coronary vasoconstriction. The purpose of the present study is to determine whether the restraint of coronary vasodilation functionally limits increases in left ventricular (LV) contractility. Using chronically instrumented, conscious dogs (n=9) we measured arterial pressure (MAP), cardiac output (CO), circumflex blood flow (CBF), and calculated coronary vascular conductance (CVC), maximal derivative of ventricular pressure (dp/dt), and preload recruitable stroke work (PRSW) at rest and during mild exercise (2mph) before and during activation of the muscle metaboreflex. Experiments were repeated after systemic alpha-1 adrenergic blockade (prazosin ~50 μg/kg). During prazosin we observed significantly greater increases in CVC (0.64 ±0.06 vs. 0.46 ±0.03 ml/min/mmHg, $p<0.05$), CBF (77.9 ±6.6 mL/min vs. 63.0 ±4.5 mL/min, $p<0.05$), CO (7.38 ±0.52 L/min vs. 6.02 ±0.42 L/min, $p<0.05$), dP/dt_{max} (5449 ±339 mmHg/s vs 3888 ±243 mmHg/s, $p<0.05$), and PRSW (160.1 ±10.3 erg·10^3/mL vs. 183.8 ±9.2 erg·10^3/mL, $p<0.05$), with metaboreflex activation vs. those seen in control experiments. We conclude that the sympathetic restraint of coronary vasodilation functionally limits further reflex increases in LV contractility.

Introduction

During exercise when oxygen demand by the active skeletal muscle is greater than

oxygen supply, metabolites accumulate stimulating chemosensitive afferents (62; 87; 98-100; 106) eliciting a pressor response termed the muscle metaboreflex (2; 6; 98). In contrast to other cardiovascular reflexes which raise arterial pressure primarily via peripheral vasoconstriction (e.g. the arterial and cardiopulmonary baroreflexes (17; 44; 85)), during submaximal exercise involving a large muscle mass the muscle metaboreflex-induced pressor response occurs virtually solely via increases in cardiac output (8; 39; 109). Raising the total flow available for perfusion is the only effective strategy to substantively increase skeletal muscle blood flow during exercise because the vast majority of cardiac output is already directed to this vascular bed (90). Vasoconstriction of inactive vascular beds has little potential to improve skeletal muscle blood flow in this setting (78). Thus, this reflex has been described as a flow-sensitive, flow-raising reflex (8; 88; 98). Muscle metaboreflex activation increases cardiac output (CO) by raising heart rate (HR) and ventricular contractility (22; 95). Left ventricular preload is sustained via substantial central blood volume mobilization (97) thereby allowing the chronotropic and inotropic responses to maintain steady-state increases in cardiac output. This substantial increase in cardiac work (large increases in cardiac output pumped against a much higher arterial pressure) would be expected to elicit marked metabolic coronary vasodilation (27; 49). Furthermore, the large increase in sympathetic activity could elicit significant β mediated feed-forward vasodilation (33; 34). However, the reflex rise in sympathetic activity to the heart may also activate vascular α_1 adrenergic receptors (37). Previous studies from our laboratory showed that despite the marked increase in cardiac work, no coronary vasodilation occurred when the reflex was activated during submaximal dynamic exercise (4). The potent vasoconstrictor impetus of this reflex was revealed when the marked increase in cardiac work did not or could not occur. In these settings actual coronary vasoconstriction was observed with metaboreflex activation (as seen in normal animals during severe exercise when cardiac output

is already maximal (4; 8), also during mild exercise after beta adrenergic blockade with acute ventricular pacing which causes acute ventricular dysfunction (4), as well as after induction of chronic heart failure (3)). In contrast, when the metaboreflex was activated after blockade of coronary vascular α_1 adrenergic receptors, substantial coronary vasodilation occurred with the large increases in cardiac work (82). Taken together, these studies support the concept that increases in cardiac sympathetic nerve activity simultaneously engender both coronary vasodilation (due to the substantial increase in cardiac work and possible β mediated feed-forward vasodilation) as well as neurogenic vasoconstriction (via activation of coronary α_1 adrenergic receptors) with the resulting level of coronary vasomotor tone dependant on the level of activation of each mechanism.

To what extent this functional metaboreflex-induced coronary vasoconstriction limits the ability to improve ventricular function and therefore ultimately limits the ability to increase cardiac output and improve oxygen delivery to the active muscle is unknown. Gwirtz et al, (37) have shown that α_1 adrenegic blockade accentuates the increase in coronary blood flow and left ventricular performance (dP/dt and myocardial segment dL/dt) observed during moderate exercise. These data indicate that even during moderate dynamic exercise the vasoconstrictor effects of increases in cardiac sympathetic nerve activity limits increases in myocardial performance. To what extent this change in segment performance translates into increases in global cardiac function is unclear. Previous to this, Heyndrickx et al, (42) showed no increase in left ventricular dP/dt during exercise after systemic infusion of prazosin. Notably Gwirtz et al, (37) used intracoronary infusion of prazosin resulting in unaltered loading conditions which may explain the different findings in dP/dt. O'Leary et al, (82) have shown that metaboreflex activation after systemic α_1 adrenergic blockade resulted in larger increases in CO. Whether the higher CO was due to an increased cardiac contractility brought about by the greater coronary

vasodilation vs. the lower left ventricular afterload caused by systemic vasodilation caused by the α_1 adrenergic blockade is unknown.

In the present study we tested whether this restraint of coronary vasodilation by the metaboreflex-induced increase in cardiac sympathetic nerve activity functionally limits the ability to increase left ventricular contractility. We assessed left ventricular contractility via analysis of changes in the pressure-volume relationship. We hypothesized that blockade of α_1 adrenergic receptors would now allow coronary vasodilation during metaboreflex activation and that the increase in coronary blood flow would further the reflex increase in left ventricular contractility.

Methods

All of the methods and procedures were reviewed and approved by the Wayne State University Institutional Animal Care and Use Committee. The experiments were conducted on mongrel dogs (n=9), weighing 22.7 (± 2.02) kg. The dogs were selected for their willingness to exercise on a motor-driven treadmill. Although no selection was made for gender, by random availability of laboratory dogs, all animals were female. We have previously shown that gender has little or no effect on metaboreflex responses in dogs (55).

The medications and surgical preparations used have been described in detail previously (3; 4; 95). Briefly, a 20mm flow transducer was placed around the aortic root to assess cardiac output. Hydraulic vascular occluders were placed on the superior and inferior vena cavae to manipulate preload. Two pairs of sonomicrometry crystals were implanted in the endocardium of the left ventricle, to measure the long axis and the short axis which were used to estimate ventricular volume. A catheter was placed in the left ventricle and its telemeter-pressure transducer was implanted subcutaneously for left ventricular pressure. A 3 mm flow transducer was placed on the circumflex artery to assess coronary flow. Arterial and central venous

catheters were placed to measure systemic blood pressures. In a retroperitoneal abdominal approach, a vascular occluder was placed about the terminal aorta. Just proximal to this occluder, a 10mm flow transducer was placed about the aorta to measure hindlimb blood flow (HLBF). The animals were allowed at least 7 days for recovery prior to the experiments.

Experimental Protocol

Each dog was directed to stand on the treadmill for 10-15 minutes while all equipment was connected and adequacy of the signals verified. All data were recorded on digital recording systems.

We obtained 1 minute of steady-state resting data with the dog standing on the treadmill. Steady-state data and data during transient vena caval occlusions (for variably loaded pressure-volume loops) were recorded during the conditions of: rest, mild exercise (3.2 km/h), and mild exercise with muscle metaboreflex activation. The reflex was activated by partially inflating the vascular occluder on the terminal aorta to reduce hindlimb blood flow to approximately 50% of the normal value during mild exercise. The experiments were performed with and without α_1 blockade (prazosin; 20-50 μg/kg, i.v. 30 minutes prior to exercise). In each experiment, the dose of prazosin was sufficient to abolish any pressor response to 4 μg/kg of phenylephrine for the duration of the experiment.

Data Analysis

We calculated left ventricular volume using a modified ellipsoid equation: $LVV = (\pi/6)\times(SA)^2\times(LA)$: where LVV is the left ventricle volume, SA (short axis) represents the distance between the anterior and posterior crystals, and LA (long axis) represents the distance between the crystals placed on the base and apex of the left ventricle (58). The pressure-volume loops were plotted for each condition. Preload recruitable stroke work (PRSW), and ± dP/dt were calculated. PRSW is the slope of the relationship between stroke work and the LV end

diastolic volume (illustrated in figure 2.1). An increased slope reflects an increased contractility, as a decreased slope reflects a decrease in contractility (30; 47; 59). Cardiac power was calculated as the product of stroke work and heart rate. The integral of the cardiac output wave was calculated to give stroke volume. Coronary vascular conductance (CVC) was calculated as CBF/(MAP-CVP): where CBF is coronary blood flow, MAP is mean arterial pressure, and CVP is central venous pressure. Systemic vascular conductance to all non-ischemic areas (e.g. all areas except the hindlimbs) is termed non-ischemic vascular conductance (NIVC) and was calculated as (CO-HLBF)/ (MAP-CVP). A repeated measures factorial ANOVA, was used for the main effects analyses, and a pair-wise comparison was used for post-hoc analyses using the Test for Simple Effects. Statistical significance was defined as $P < 0.05$. Regression analyses were conducted with CVC with respect to cardiac power for each animal, and the slopes were compared between control and α_1 blockade by repeated measures one way ANOVA.

Results

Table 2.1 shows the levels of HLBF at rest, during exercise and during metaboreflex activation before and after α_1 adrenergic blockade. Prazosin caused a small, but significant increase in HLBF over control values during exercise. HLBF was reduced to the same values in both conditions for activation of the muscle metaboreflex.

Figure 2.2 shows the mean steady state values of MAP, HR, left ventricular end diastolic and end systolic volumes, CO, and NIVC, at rest, mild exercise, and during exercise with metaboreflex activation in control and after α_1 blockade. In control there was no change in MAP or stroke volume (SV) from rest to mild exercise, however HR, CO, and NIVC were increased. Imposed reductions in HLBF caused muscle metaboreflex-induced increases in MAP, HR, SV and CO. No significant change in NIVC occurred with metaboreflex activation. At rest, α_1 blockade caused a significant decrease in MAP, marked tachycardia and reduced SV,

due to a reduced end diastolic volume. Responses to mild exercise were similar to control with the exception that now SV slightly increased. Metaboreflex activation caused a significant though lesser increase in MAP, and a significant increase in SV. End diastolic volume was still reduced compared to control, however end systolic volume was also reduced, resulting with a comparable SV between control and α_1 blockade. A greater reflex increase in HR and CO as compared to control and a significant increase in NIVC occurred. LV end systolic volume was significantly different across workloads, but had no significant difference between conditions (control vs. α_1 blockade) and no significant interaction, so a pairwise comparison could not be calculated.

Figure 2.3 shows left ventricular hemodynamic and inotropic responses to mild exercise and metaboreflex activation before and after α_1 blockade. In control there was a significant increase from rest to mild exercise in CBF, CVC, dP/dt_{max}, and PRSW. Metaboreflex activation increased coronary blood flow and left ventricular contractility, however no vasodilation occurred in the coronary circulation as there was no significant increase in CVC, thus all of the increase in CBF was due to the increase in perfusion pressure. Under α_1 blockade there was also a significant increase in all illustrated parameters from rest to mild exercise, which were statistically greater in CVC and dP/dt_{max} compared to control. After α_1 blockade, activation of the muscle metaboreflex now elicited significantly greater increases in CBF. Although the rise in perfusion pressure was smaller, substantial coronary vasodilation occurred. Metaboreflex activation in this setting caused significantly greater increases in both indices of myocardial contractility.

After α_1 blockade the slope of the relationship between CVC and cardiac power (used as an index of myocardial O_2 consumption) was significantly increased. Further, this relationship was extended over a significantly greater range as both CVC and cardiac power were

significantly greater during muscle metaboreflex stimulation after α_1 blockade (Figure 2.4).

Figure 2.5 shows the relationship between PRSW and CBF. There was no difference between the slope of the relationship between control and after α_1 blockade therefore the data were combined into one regression. After α_1 blockade, greater increases in CBF occurred with metaboreflex activation which also elicited substantially greater increases in ventricular contractility.

Table 2.1. Hind-limb blood flow at rest, during exercise and during metaboreflex activation before and after α_1 adrenergic blockade

HLBF (L/min)	Rest	Ex.	Ex.+MMA
Control	0.58±0.05	1.00±0.09 †	0.52±0.04
α_1 blockade	0.61±0.06	1.07±0.09 * †	0.55±0.04

Levels of hindlimb blood flow at rest, during exercise (Ex) and during exercise with metaboreflex activation (Ex+MMA) before and after α_1 adrenergic blockade. During Ex+MMA, hindlimb blood flow was mechanically reduced to the same values in both conditions. An * above a specific setting signifies a significant pairwise comparison ($P < 0.05$). A † above a column signifies a significant increase from rest to mild exercise ($P < 0.05$).

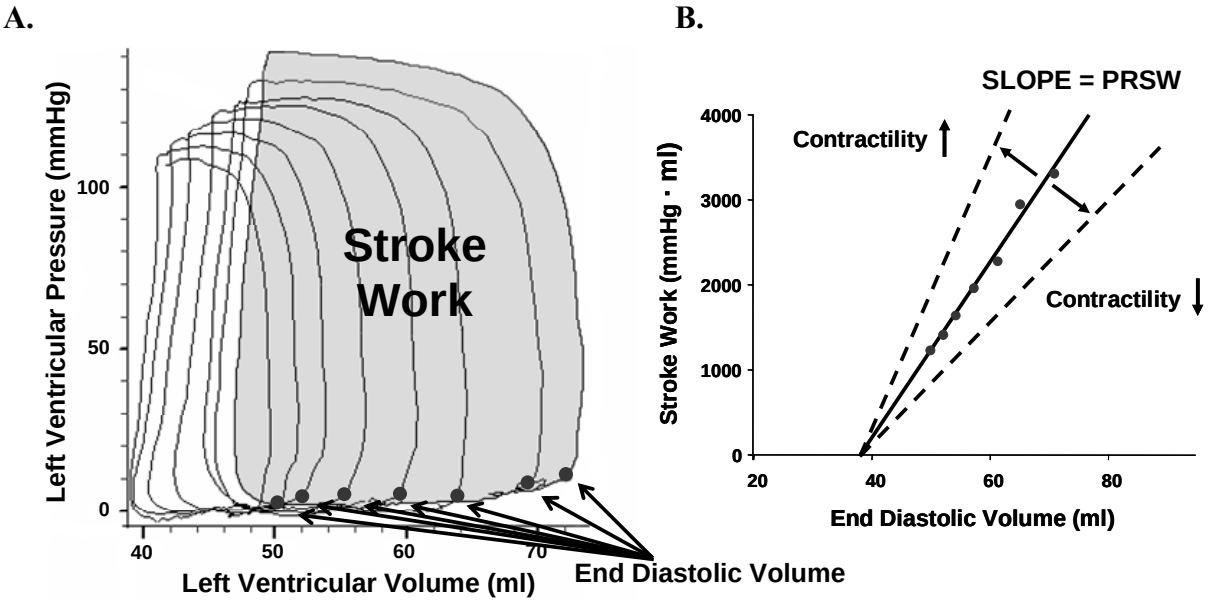


Figure 2.1: Example of pressure-volume loop during preload reduction (A), illustrating stroke work of a single loop (shaded) and the end diastolic volume point (●) for each loop. (B) Example of how the end diastolic points and corresponding stroke work for weach loop is used to illustrate preload recruitable stroke work and how it can be used to assess contractility.

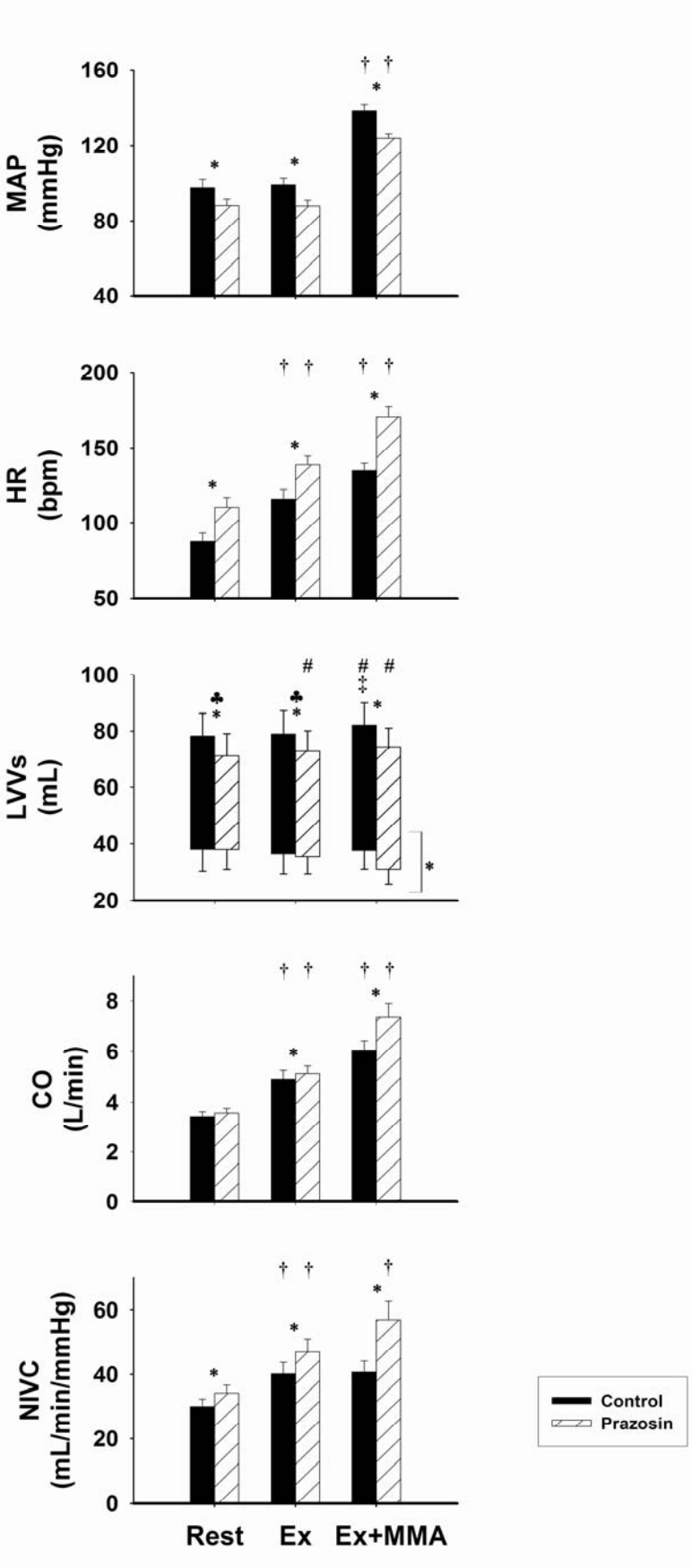


Figure 2.2: Hemodynamic responses: Mean arterial pressure (MAP), heart rate (HR), Left Ventricular Volumes (Left VVs), cardiac output (CO), and non-ischemic vascular conductance (NIVC); during rest, mild exercise (Ex), and mild exercise with MMA (Ex+MMA); in control (black bars) and α_1 blockade conditions (striped bars). All parameters showed a significance across workload settings, as well as significance between control and prazosin conditions ($P < 0.05$); with the exception of stroke volume and LV end systolic volume (which were only significant across workload settings). All parameters had a significant interaction between the two independent variables, with the exception of LV end systolic volume. * (between two bars) signifies a significant pairwise comparison ($P < 0.05$). † above a column signifies a significant increase from the previous workload. A ♣ above a specific setting signifies a significant pairwise comparison in left ventricle stroke volume ($P < 0.05$). A ‡ above a column signifies a significant increase in LV end diastolic volume from the previous workload while a # above a column indicates a significant increase in stoke volume from the previous workload ($P < 0.05$). An * next to the bracket indicates a significance between LV end systolic volume across workloads but not between control and α_1 blockade conditions.

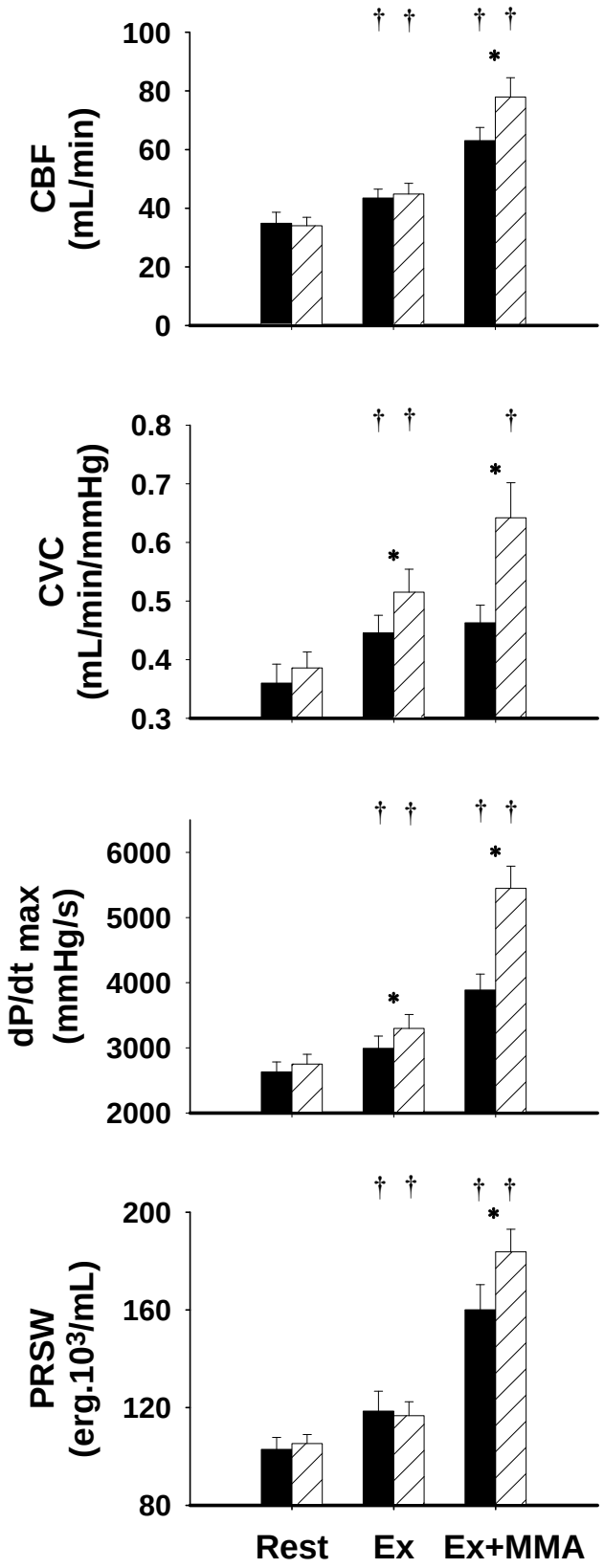


Figure 2.3: Left ventricular hemodynamic and function responses: Coronary blood flow (CBF), coronary vascular conductance (CVC), maximal rate of left ventricular pressure change (dP/dt_{max}), and preload recruitable stroke work (PRSW); during rest, mild exercise (Ex), and mild exercise with MMA (Ex+MMA); in control (black bars) and α_1 blockade conditions (striped bars). All parameters showed a significance across workload settings, as well as significance between control and prazosin conditions ($P < 0.05$). All parameters had a significant interaction between the two independent variables. An * above a specific setting signifies a significant pairwise comparison ($P < 0.05$). A † above a column signifies a significant increase from the previous workload ($P < 0.05$).

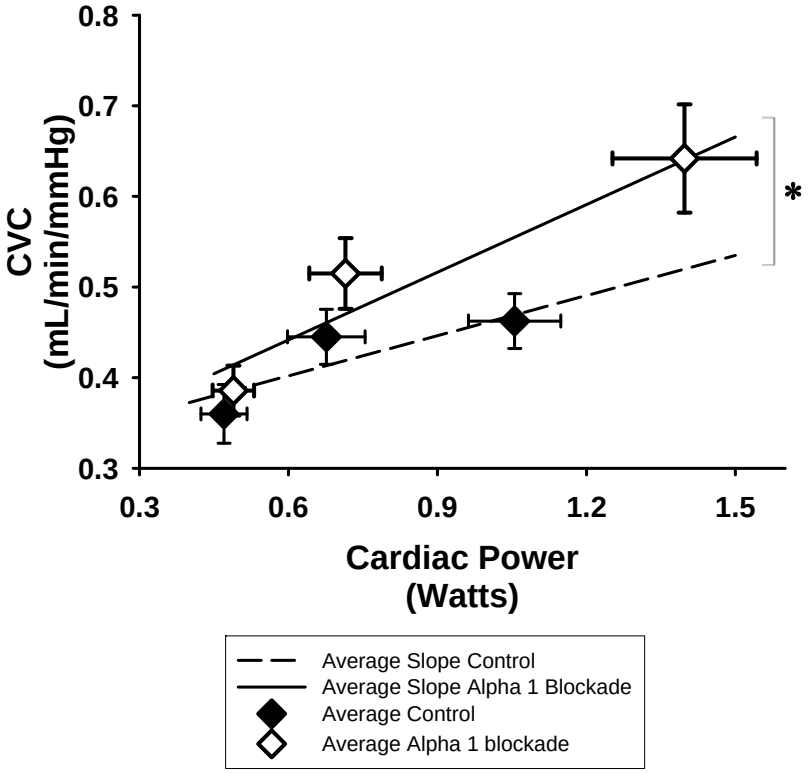
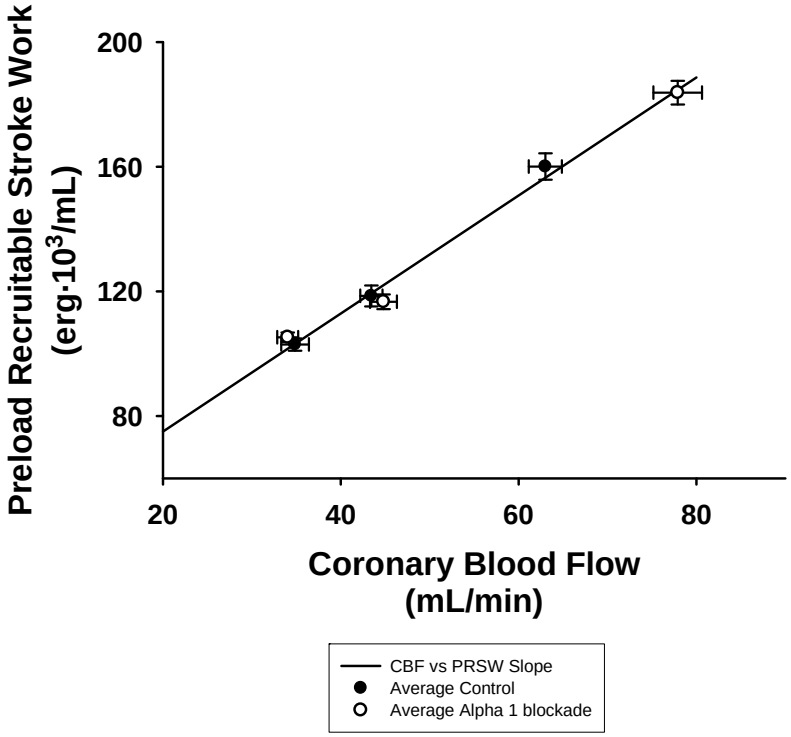


Figure 2.4: Coronary vascular conductance (CVC) plotted as a function of cardiac power. The broken regression line represents the average relationship between CVC and cardiac power in control while the solid regression line represents the corresponding average relationship during α_1 blockade. The averaged values in control are represented with black diamonds (♦) while averaged values during α_1 blockade are shown as open diamonds (◊). The bracket shown to the right with the * signifies the significant difference between the two slopes ($P < 0.05$).

Figure 2.5: Contractility indicated by preload recruitable stroke work (PRSW) with respect to coronary blood flow (CBF). As no significant difference between control and α_1 blockade was found ($P > 0.05$), a single relationship is represented by a single line. The averaged values in control are represented with black circles (●) while averaged values during α_1 blockade are shown as open circles (○).



Discussion

This is the first study to show that during dynamic exercise the sympathetically-induced restraint of coronary vasodilation during muscle metaboreflex activation impairs increases in left ventricular contractility. During metaboreflex activation a "push-pull" situation likely exists as a result of the increase in sympathetic activity to the heart. The increase in metabolic vasodilation coupled with possible vascular β-mediated feed forward vasodilation is opposed by direct α-mediated vasoconstriction. The direct vasoconstrictor drive limits vasodilation and the restrained increase in blood flow limits increases in ventricular performance. Suppressing the increase in ventricular contractility likely limits the ability to raise cardiac output and thereby functionally limits the ability of the muscle metaboreflex to improve blood flow to the active skeletal muscles.

Coronary perfusion/dilation and ventricular performance: cause and effect:

The complex relationship between coronary perfusion and ventricular performance can make it difficult to discern the difference between cause and effect. Changes in flow can elicit changes in function and changes in function can elicit metabolic coronary vasodilation. Since flow will vary with changes in both vessel caliber and perfusion pressure, vasodilation can only be assessed via changes in conductance (or resistance, we prefer conductance (78)). Ventricular function is likely limited by blood flow (or O_2 delivery (77)) rather than vasodilation per se (e.g. flow can change solely due to changes in perfusion pressure (3; 4)). We addressed this in two distinct ways. Figure 2.4 shows that the relationship between cardiac power and coronary vascular conductance was shifted upwards with a significantly steeper slope after α_1 adrenergic blockade. This shows that with metaboreflex activation greater vasodilation occurs after α_1 adrenergic blockade at any level of metabolic stimuli for vasodilation (as indexed by cardiac power). We based this analysis on that done by Huang and Feigl (43), who showed that the

relationship between coronary blood flow and myocardial O_2 consumption is linear but that the slope of the relationship during exercise increases after regional α_1 receptor blockade. In that study (43), perfusion pressure was not different with coronary α receptor blockade therefore changes in blood flow will be proportionally equivalent to changes in conductance and therefore flow is a valid index of vasodilation/vasoconstriction. In our study, perfusion pressure was different both before and after α_1 receptor blockade and markedly so between exercise and metaboreflex activation therefore differences in vasomotor tone must be addressed via changes in conductance (78). For example, in the control experiments large increases in coronary blood flow occurred with metaboreflex activation yet this was not due to vasodilation inasmuch as conductance remained unchanged. All of the increase in flow was due to an increase in perfusion pressure.

Whether due to increased perfusion pressure or vasodilation, increases in blood flow may allow increases in ventricular function by providing more O_2 delivery (77). O_2 extraction in the coronary circulation is already near maximal under basal conditions, therefore increases in myocardial O_2 consumption with exercise occur predominately via increases in coronary blood flow (49). In addition, mild exercise and metaboreflex activation in this model elicit minimal increases in arterial O_2 content (~ 5%) (80) therefore increases in O_2 delivery occur via increases in blood flow. We found that the relationship between ventricular contractility (PRSW) and blood flow was exceedingly linear. α_1 adrenergic blockade only extended the range of this relationship and did not affect the slope. With metaboreflex activation in the control experiments, all of the increase in coronary blood flow and therefore O_2 delivery occurred via the increase in perfusion pressure, no vasodilation occurred (no significant increase in conductance) as we have previously observed (4; 82). In contrast, after prazosin much larger increases coronary blood flow occurred due to the combined effect of substantial vasodilation

coupled with increased perfusion pressure and the increases in PRSW were much greater. Collectively, we interpret these data as indicating that during metaboreflex activation, the increases in sympathetic activity prevents coronary vasodilation and therefore restrains increases in coronary blood flow to only that which occurs via increases in perfusion pressure (4; 82). α_1 adrenergic blockade revealed substantial coronary vasodilation during metaboreflex activation which now coupled with the rise in perfusion pressure provided for much greater increases in coronary blood flow. The increased blood flow and O_2 delivery thereby elicited a greater increase in ventricular contractility. Gwirtz and colleagues (36; 37; 52) showed that blockade of coronary α_1 adrenergic receptors increased coronary blood flow during moderate exercise in dogs. This was also accompanied by higher myocardial O_2 consumption and regional ventricular dynamics (increased maximal velocity of segment shortening). Thus the rise in sympathetic activity that normally occurs with moderate exercise likely functionally restrains coronary vasodilation and ventricular function. One possible beneficial effect of this vasoconstriction may be to preserve endocardial blood flow (43), inasmuch as the epicardium is vasoconstricted to a greater extent than the endocardium, which would act to redistribute coronary blood flow towards the inner layers of the ventricle. This greater vasodilation with α_1 blockade could be revealing both metabolic vasodilation as well as β mediated feed-forward vasodilation (34).

Muscle metaboreflex activation either during exercise or during post-exercise circulatory occlusion causes marked increases in cardiac work, yet, little if any coronary vasodilation is observed (4; 72; 82). Similar results are observed with strong static muscle contractions (61; 73). Previous studies from our laboratory have shown that metaboreflex activation during sub-maximal dynamic exercise caused no coronary vasodilation despite marked increases in heart rate and ventricular contractility. Cardiac output increased substantially and was pumped

against a much higher afterload, yet all of the increase in coronary blood flow occurred via increases in perfusion pressure rather than vasodilation (4). These results indicated that a "push-pull" situation exists between the vasodilatory drives and the vasoconstrictor effects of the increased sympathetic activity. If the increase in cardiac work during metaboreflex activation is reduced, actual coronary vasoconstriction is seen (4). Similarly, during maximal exercise when heart rate and cardiac output are already at maximal levels and little further steady-state increase in ventricular work occurs, metaboreflex activation causes coronary vasoconstriction (4). Finally, in heart failure little or no metaboreflex increases in contractility occur and the reflex increase in cardiac sympathetic activity causes frank coronary vasoconstriction (3). To what extent this actual coronary vasoconstriction contributes to the inability to raise ventricular contractility and cardiac output during metaboreflex activation in heart failure is unknown.

Baroreflex vs. Metaboreflex

We used systemic α adrenergic blockade rather than injection into a coronary artery because we wanted to assess the effects on total ventricular function rather than only an individual ventricular segment which is more susceptible to changes in loading conditions (48; 58). After prazosin, MAP was lower due to the peripheral vasodilation which raises the question as to what extent the enhanced increases in CO and ventricular contractility reflect baroreflex responses. We feel this is unlikely for several reasons. Heyndrickx et al. (42) previously showed that during exercise after systemic infusion of prazosin, whereas arterial plasma levels of norepinephrine were increased, there was no increase in norepinephrine release at the heart itself despite a large decrease in MAP. After prazosin in the present study, neither at rest, nor during mild exercise were cardiac output or preload recruitable stroke work higher than control levels (a small rise in dP/dt did occur which may reflect changes in preload and/or

afterload, (48)). In addition coronary blood flow was unchanged; the small increase in coronary conductance was offset by the small reduction in perfusion pressure. Thus, whereas MAP was lower after α_1 blockade which would elicit a baroreflex response (tachycardia), this resulted in no significant increase in cardiac output or ventricular contractility as stroke volume fell with the rise in heart rate. The fall in stroke volume with this rise in rate is very similar to that observed with merely increasing pacing rate within this range which also elicits little if any increase in CO (107). We have recently shown that this increase in rate by itself would have very little direct effects on ventricular contractility (Treppe effect) in this model (15). In contrast, a similar tachycardia induced by activation of the muscle metaboreflex causes large increases in CO and ventricular contractility (95). Further, in both dogs (17) and humans (85), carotid baroreceptor unloading during exercise causes little steady state increase in CO. The baroreflex pressor response is mediated via increases in peripheral resistance (17; 85). After α_1 adrenergic blockade, only when the metaboreflex was activated did cardiac output, ventricular contractility, coronary vascular conductance and coronary blood flow all rise above levels observed during the control experiments whereas the difference in MAP was similar to that at rest and during mild exercise. We feel this is compelling evidence that the response was indeed metaboreflex in nature as the major effects on CO and PRSW were only observed when the metaboreflex was activated and not at rest or during exercise when pressure was similarly lowered with α_1 blockade.

The arterial baroreflex normally acts to buffer the metaboreflex (51). Whether the rise in sympathetic activity which occurred with metaboreflex activation was greater after α_1 blockade because MAP did not rise to the same extent cannot be discounted. However, we recently showed that after removal of the buffering effects of the arterial baroreflex (sino-aortic arterial baroreflex denervation), the much larger metaboreflex pressor response occurs via

increased peripheral vasoconstriction. Indeed, the rise in CO is if anything slightly smaller after baroreceptor denervation (50). Further, the higher slope of the relationship between coronary conductance and cardiac power indicates that greater vasodilation occurs with α_1 blockade as power increases during metaboreflex activation. Thus, even at the same cardiac power, larger coronary vasodilation occurs. Similarly, the overlap of the data relating PRSW to coronary blood flow indicates that if the rise in coronary blood flow was the same after α_1 blockade, then ventricular contractility would have risen to the same extent.

Limitations:

Cardiac power is a relatively novel measure of cardiac function (28; 67), and in the present study was used as an index of myocardial oxygen consumption. Previous studies performed in humans used cardiac power calculated as product of cardiac output and mean arterial pressure. Khouri et al. (49) previously used a similar calculation and they referred to it as cardiac work or left ventricular work. However, power is work performed over time so we feel cardiac power is the correct term, especially so as we calculated cardiac power as stroke work (work/beat) times heart rate (beats/minute), therefore resulting in work/minute. Khouri et al. (49) showed an excellent correlation between this and myocardial O_2 consumption. Cardiac power has been shown to be a strong indicator of prognosis in chronic heart failure (108), and a strong predictor of mortality due to cardiogenic shock (28). Most recently there has been evidence to suggest that cardiac power can be a very useful prognostic tool in across a broad spectrum of acute cardiac diseases (67).

PRSW has been shown to be a very robust index of cardiac contractility (47). However our technique used to estimate left ventricular volume has limitations. On average, the left ventricular volume values calculated from the sonomicrometry crystals underestimated the SV obtained by integrating the signal from cardiac output flow probe placed on the ascending aorta.

We showed previously that this underestimation is highly linear within each animal (95). Similarly low SV values for dogs of this size were reported by others using sonomicrometery (58; 94; 95). To our knowledge, our studies are the only in which SV was measured simultaneously via these two techniques. This discrepancy between the SV values calculated using sonomicrometry vs. CO likely occurred due to the number of crystals used and their placement on the left ventricle. In our study, only two pairs of crystals were used, in order to limit any damage made to the myocardium. In two animals we simultaneously measured left ventricular volumes via sonomicrometry as well as echocardiography while also monitoring CO via the implanted blood flow transducer. As we suspected, values for end diastolic volume for echocardiography and sonomicrometry were very similar whereas the values for stroke volume were very similar between echocardiography and that calculated from the ascending aortic flow probe. Therefore, we believe that the error in the sonomicrometry value for stroke volume resides in over estimating end systolic volume. Therefore, for the volume data shown in figure 2.2 we used the end diastolic volume obtained from sonomicrometry and stroke volume from the aortic flow signal. These calculations yield reasonable estimates of other parameters such as ejection fraction.

In the present study, systemic vascular conductance to all areas except the hindlimbs (NIVC) also increased with metaboreflex activation after α_1 receptor blockade. In a limited number of previous experiments, this systemic vasodilation was abolished by propranolol (82). NIVC reflects mostly skeletal muscle (51). Thus, this vasodilation likely is within skeletal muscle and may occur via epinephrine release from the adrenal glands (53). This may explain why with metaboreflex activation vasoconstriction is seen in select vascular beds, but no global change in NIVC is observed (7; 8; 39; 70; 71). It is possible that a portion of the coronary vasodilation seen after α_1 adrenergic blockade was due to β_2 adrenergic receptor stimulation via

an increase in circulating epinephrine in addition to the marked increase in ventricular work(41).

In summary, muscle metaboreflex activation increases sympathetic tone to α_1 adrenergic receptors, and functionally restricts coronary vasodilation. This impedes blood flow to the myocardium and limits the increase in left ventricular performance. This likely limits the ability of the reflex to raise cardiac output and therefore restore blood flow to the ischemic muscles.

CHAPTER 3

Muscle Metaboreflex-Induced Coronary Vasoconstriction Limits Ventricular Contractility during Dynamic Exercise in Heart Failure

Abstract

Muscle metaboreflex activation (MMA) during dynamic exercise increases cardiac work and O_2 demand via increases in heart rate, ventricular contractility and afterload. This increase in cardiac work should lead to metabolic coronary vasodilation. However, no change in coronary vascular conductance is seen, indicating that the increased sympathetic activity which increased contractility also caused vasoconstriction. In heart failure, cardiac output does not increase with MMA presumably due to impaired left ventricular contractility, and large decreases in coronary vascular conductance are observed. We tested whether this coronary vasoconstriction could explain in part, the reduced ability to increase cardiac performance during MMA. In conscious, chronically instrumented dogs after pacing induced heart failure, MMA responses during mild exercise were observed before and after α_1 adrenergic blockade (prazosin 50-100μg/kg). During MMA, the increases in coronary blood flow, coronary vascular conductance, cardiac output, and $+dP/dt_{max}$ were significantly greater after α_1 adrenergic blockade. We conclude that during heart failure the coronary vasoconstriction limits the ability of muscle metaboreflex to increase left ventricular contractility.

Introduction

During exercise, metabolite sensitive afferent neurons within the skeletal muscle may be stimulated and evoke a reflex increase in sympathetic nerve activity to the heart and vasculature, known as the muscle metaboreflex (3; 8; 39; 62; 70; 87; 98-101; 106). In normal subjects during submaximal exercise the metaboreflex elicits an increase in blood pressure mainly via a marked increase in cardiac output (CO) (2; 6; 8; 22; 39; 98; 109). This increase in flow serves

to partially restore blood flow and oxygen delivery to the ischemic muscle (80; 83).

However, in heart failure, this reflex increase in blood pressure occurs mainly due to peripheral vasoconstriction, as little or no increase in CO occurs (3; 39; 81; 93). Despite tachycardia, the metaboreflex does not increase CO, due to a marked drop in stroke volume (SV) (21; 39; 93). This is likely due to an inability to increase left ventricular contractility which is an important component of the cardiac response allowing SV to be maintained or even increased slightly in the face of increased afterload (79; 81; 95). The inability to increase contractility in heart failure can be attributed to several factors. Structurally, the ventricle is enlarged with no increase in wall thickness, leading to elongated myocytes (reviewed in 29; 35), disorganization of myofilaments (96; 102; 103), transverse tubule and mitochondrial swelling, as well as mitochondrial rupture and consequently decreased mitochondrial density (96; 103).

Another factor that may play a role in the reduced cardiac function during exercise and metaboreflex activation is a limited oxygen supply to the myocardium. In humans (23; 74) and animals (76), heart failure has been shown to increase myocardial oxygen consumption. Coronary blood flow also increases during heart failure (74). However coronary flow reserve is impaired during heart failure, indicating a possible restraint of coronary blood flow during high oxygen demand situations such as exercise. This restraint may occur via sympathetic vasoconstriction of the coronary vasculature. Even in normal subjects during exercise the left ventricle is functionally vasoconstricted inasmuch as coronary vasodilation increases with α_1 adrenergic blockade (20; 37; 43) and with the increase in blood flow, significant increases in left ventricular contractility occur (20; 37).

In normal subjects, muscle metaboreflex activation markedly increases ventricular work, and while coronary blood flow rises with the substantial increase in arterial pressure, little or no coronary vasodilation is seen (4; 20; 72; 82). With metaboreflex activation in heart failure,

frank coronary vasoconstriction occurs (3). To what extent this functional metaboreflex-induced coronary vasoconstriction in heart failure limits the ability to improve ventricular function and therefore ultimately limits the ability to increase cardiac output and improve oxygen delivery to the active muscle is unknown.

Methods

All of the methods and procedures were reviewed and approved by the Wayne State University Institutional Animal Care and Use Committee. The experiments were conducted on mongrel dogs (N=7), weighing 22.7 (+/- 2.02) kg. The dogs were selected for their willingness to walk/run on a motor-driven treadmill. There was no intended selection was made for gender, however by random all animals were female. No dogs were in the proestrus phase of the menstrual cycle during the experiments. Previously this laboratory has shown that gender has little or no effect on metaboreflex responses in dogs (55).

The medications and surgical preparations used have been described in detail previously (95), (3; 4; 84). Briefly, a 20mm flow transducer was placed around the aortic root to measure cardiac output. Hydraulic vascular occluders were placed on the superior and inferior vena cavae to manipulate preload. Two pairs of sonomicrometry crystals were implanted in the endocardium of the left ventricle on the short axis and long axis to estimate ventricular volume. A catheter was placed in the left ventricle for left ventricular pressure and its telemeter-pressure transducer was implanted subcutaneously. A 3 mm flow transducer was placed on the circumflex artery to assess coronary blood flow (CBF). Three ventricular pacing wires (0-Flexon) were sutured to the free wall of the right ventricle for subsequent ventricular pacing to induce HF. Arterial and central venous catheters were placed to measure systemic blood pressures. In the retroperitoneal region, a vascular occluder was placed about the terminal aorta. Just proximal to this occluder, a 10mm flow transducer was placed about the aorta to measure

hind-limb blood flow (HLBF).

Experimental Protocol

Each dog was directed to stand on the treadmill for 10-15 minutes while all equipment was connected and adequacy of the signals verified. All data were recorded on digital recording systems (Windaq, and Sonometrics).

We obtained 1 minute of steady-state resting data with the dog standing on the treadmill. Steady-state data and data during transient vena caval occlusions (for variably loaded pressure-volume (PV) loops) were recorded during the conditions of: rest, mild exercise (3.2 km/h), and mild exercise with muscle metaborelex activation. The reflex was activated by partially inflating the vascular occluder on the terminal aorta to reduce hindlimb blood flow to approximately 50% of the normal value during mild exercise. The experiments were performed with and without α_1-blockade (prazosin; 20-50 μg/kg, i.v. 30 minutes prior to exercise). In each experiment, the dose of prazosin was sufficient to abolish any pressor response to 4 μg/kg of phenylephrine for the duration of the experiment. After completion of the control and α_1-blockade experiments, congestive heart failure was induced via rapid ventricular pacing. This technique has been widely accepted to create chronic model of left ventricular failure (39; 40). Briefly, the right ventricular pacing electrodes were connected to a pacemaker set at 200 - 220 beats/minute for ~ 30 days. When signs of congestive heart failure appear, such as: anorexia, decreased cardiac output, stroke volume reduction > 30%, increased left ventricular end diastolic pressure, and increased heart rate; the experiments were repeated. The pacemaker was disconnected during the experiments.

Data Analysis

We calculated left ventricular volume using a modified ellipsoid equation. [$LVV = (\pi/6)x(SA)^2x(LA)$]. Where LVV is the left ventricle volume, SA (short axis) represents the

distance between the anterior and posterior crystals, and LA (long axis) represents the distance between the crystals placed on the base and apex of the left ventricle. The pressure-volume loops were plotted for each condition. Preload recruitable stroke work (PRSW), and +/- dP/dt were calculated. PRSW is the slope of the relationship between stroke work and the LVV. An increased slope reflects an increased contractility and vice-versa (30; 47; 60). Cardiac power was calculated as the product of stroke work and heart rate. The integral of the cardiac output wave was calculated to give stroke volume. Left ventricular volume data were corrected using the end diastolic volume obtained from sonomicrometry and stroke volume from the aortic flow signal, as discussed in a previous study (20). Coronary vascular conductance (CVC) was calculated as CBF/(MAP-CVP). Systemic vascular conductance to all non-ischemic areas (e.g. all areas except the hindlimbs) is termed non-ischemic vascular conductance (NIVC) and was calculated as (CO-HLBF)/ (MAP-CVP). A repeated measures factorial ANOVA, was used for the main effects analyses, and a pair-wise comparison was used for post-hoc analyses using the Test for Simple Effects. Statistical significance was defined as $P < 0.05$.

Results

The expected hemodynamic changes due to heart failure, such as attenuated arterial pressure, stroke volume, cardiac output, and elevated heart rate were observed (Table 3.1)..

Table 3.1. Haemodynamics (MAP, HR, SV, CO) observed in normal animals and after induction of heart failure.

	Normal	Heart Failure
MAP (mmHg)	97 ± 4.4	76 ± 1.4 †
HR (bpm)	88 ± 5.7	117 ± 5.2 †
SV (mL)	40 ± 3.0	25 ± 2.1 †
CO (L/min)	3.5 ± 0.2	2.8 ± 0.2 †

Hemodynamic parameters during normal and heart failure conditions, † signifies a difference between the two conditions ($P < 0.05$).

In heart failure, prazosin caused a small, but significant increase in HLBF over the heart failure values at rest and during exercise without prazosin. In all conditions: control, control α_1 blockade, heart failure, and heart failure α_1 blockade, HLBF rose from rest to mild exercise. HLBF was reduced to the same values for activation of the muscle metaboreflex in all conditions (Table 3.2).

Figure 3.1 shows the mean steady state values of MAP, HR, left ventricular end diastolic and end systolic volumes, CO, and NIVC, at rest, mild exercise, and during exercise with metaboreflex activation in control and after α_1 blockade (panel A). In control there was no change in MAP from rest to mild exercise, however SV, CO, and NIVC were increased. Imposed reductions in HLBF caused muscle metaboreflex-induced increases in MAP, SV and CO. No significant change in NIVC occurred with metaboreflex activation. At rest, α_1 blockade caused a significant decrease in MAP, marked tachycardia and reduced SV, due to a reduced end diastolic volume. Responses to mild exercise were similar to control. Metaboreflex activation caused a significant though lesser increase in MAP, and a significant increase in SV. End diastolic volume was still reduced compared to control, however end systolic volume was also reduced, resulting with a comparable SV between control and α_1 blockade. A greater reflex increase in CO as compared to control and a significant increase in NIVC occurred. HR was significantly different across workloads, and significantly different between conditions (control vs. α_1 blockade) but no significant interaction, so a pairwise comparison could not be calculated.

After induction of heart failure (panel B) there was no change in MAP or SV from rest to mild exercise, however HR, CO, and NIVC were increased. Imposed reductions in HLBF caused muscle metaboreflex-induced increases in MAP and HR, but a decrease in SV and NIVC. There was no change in CO with metaboreflex activation. Thus, the mechanisms of the

reflex shifted from increased CO in the normal animal to increased peripheral vasoconstriction in HF. At rest, α_1 blockade did not affect MAP, or HR. SV increased, due to an increased end diastolic volume. During mild exercise LV end systolic volume decreased, which resulted in an increased stroke volume. CO and NIVC also increased greater than observed prior to α_1 blockade. Metaboreflex activation caused a similar increase in MAP as that without α_1 blockade, however the mechanisms of the pressor response were markedly different. End systolic volume decreased, resulting in an increase in SV with α_1 blockade in HF. End diastolic volume was not significantly different across workloads, or between conditions (control vs. α_1 blockade), so a pairwise comparison could not be calculated. The rise in SV coupled with the tachycardia now caused a significant increase in CO. Rather than a decrease in NIVC, a small increase was observed as was also seen in the normal animal during meatboreflex activation after α_1 blockade. Thus, after α_1 blockade in HF the metaboreflex pressor response returned to a cardiac output based response as seen prior to induction of HF.

Figure 3.2 shows left ventricular hemodynamic and performance responses to mild exercise and metaboreflex activation in control and after α_1 blockade (panel A) as well as heart failure, and heart failure with α_1 blockade (panel B). In control there were significant increases from rest to mild exercise in CBF, CVC, dP/dt_{max}, and PRSW. Metaboreflex activation increased coronary blood flow and left ventricular contractility, however no vasodilation occurred in the coronary circulation as there was no significant increase in CVC, thus all of the increase in CBF was due to the increase in perfusion pressure. Under α_1 blockade there was also a significant increase in all parameters from rest to mild exercise, which were statistically greater in CVC and dP/dt_{max} compared to control. After α_1 blockade, activation of the muscle metaboreflex now elicited significantly greater increases in CBF. Although the rise in perfusion

pressure was smaller, substantial coronary vasodilation occurred. Metaboreflex activation in this setting caused significantly greater increases in both indices of myocardial contractility.

CBF and CVC were higher at rest in heart failure compared to control, while dP/dt_{max} and PRSW were reduced. CBF, CVC, and dP/dt_{max} all increased from rest to mild exercise. Metaboreflex activation increased coronary blood flow and dP/dt_{max}, however vasoconstriction occurred in the coronary circulation as CVC decreased significantly. Under α_1 blockade there was also a significant increase in all illustrated parameters from rest to mild exercise, which were statistically greater in CBF, CVC and dP/dt_{max} compared to control. After α_1 blockade, activation of the muscle metaboreflex now elicited significantly greater increases in CBF, CVC and dP/dt_{max}. In this case PRSW was assessed in a smaller sample (N=3). PRSW was significantly different across workloads, and significantly different between conditions (control vs. α_1 blockade) however no significant interaction occurred, so a pairwise comparison could not be calculated.

Figure 3.3 illustrates the relationship between coronary vascular conductance and cardiac power following heart failure (A), as well as the changes in CVC with respect to the changes in cardiac power (ΔCVC:ΔCP ratio), from rest to mild exercise, and from mild exercise to MMA in control (B) and after the induction of HF (C). From rest to mild exercise there is a positive relationship both with and without α_1 blockade. That is, as cardiac power increased, coronary vasodilation occurred and this relationship was unaffected by α_1 blockade. With metaboreflex activation whereas cardiac power increased, little vasodilation occurred and this ratio fell. With α_1 blockade, increases in both cardiac power and CVC occurred with metaboreflex activation and this ratio increased significantly. After the induction of HF, whereas with the transition from rest to exercise both CVC and cardiac power rose (therefore positive value for this ratio), with metaboreflex activation since CVC decreased despite a very

small increased cardiac power this ratio became markedly negative. α_1 blockade reversed this ratio back to a positive value as now vasodilation did occur with increased cardiac power.

Figure 3.4 shows the relationship between dP/dt_{max} and CBF (panel A, $R^2 = 0.98$) and between PRSW and CBF (panel B, $R^2 = 0.97$, N=3). In both panels all 6 points in control (with and without α_1 blockade) were combined into one regression, as were all six points in heart failure. After α_1 blockade, greater increases in CBF occurred with metaboreflex activation which also elicited substantially greater increases in ventricular contractility. A similar linear response was observed in heart failure; however the slope of the relationship is much lower.

Table 3.2. Hind limb blood flow (L/min ± SE) at rest, during mild exercise, and metaboreflex activation, in control and heart failure conditions, before and after α_1 adrenergic blockade.

	Rest	Ex.	Ex.+MMA
Control	0.58±0.05	1.00±0.09 †	0.52±0.04
α_1-blockade	0.61±0.06	1.07±0.09 †	0.55±0.04
Heart Failure	0.46±0.05	0.86±0.11 †	0.51±0.06
α_1-blockade	0.57±0.07 *	1.16±0.119 *†	0.51±0.06

Levels of hindlimb blood flow before and after α_1 adrenergic blockade, shown with control, heart failure & their corresponding α_1 blockade conditions. During Ex+MMA, hindlimb blood flow was mechanically reduced to the same values in both conditions. * signifies a significant pairwise comparison ($P < 0.05$). † signifies a significant increase from rest to mild exercise ($P < 0.05$)).

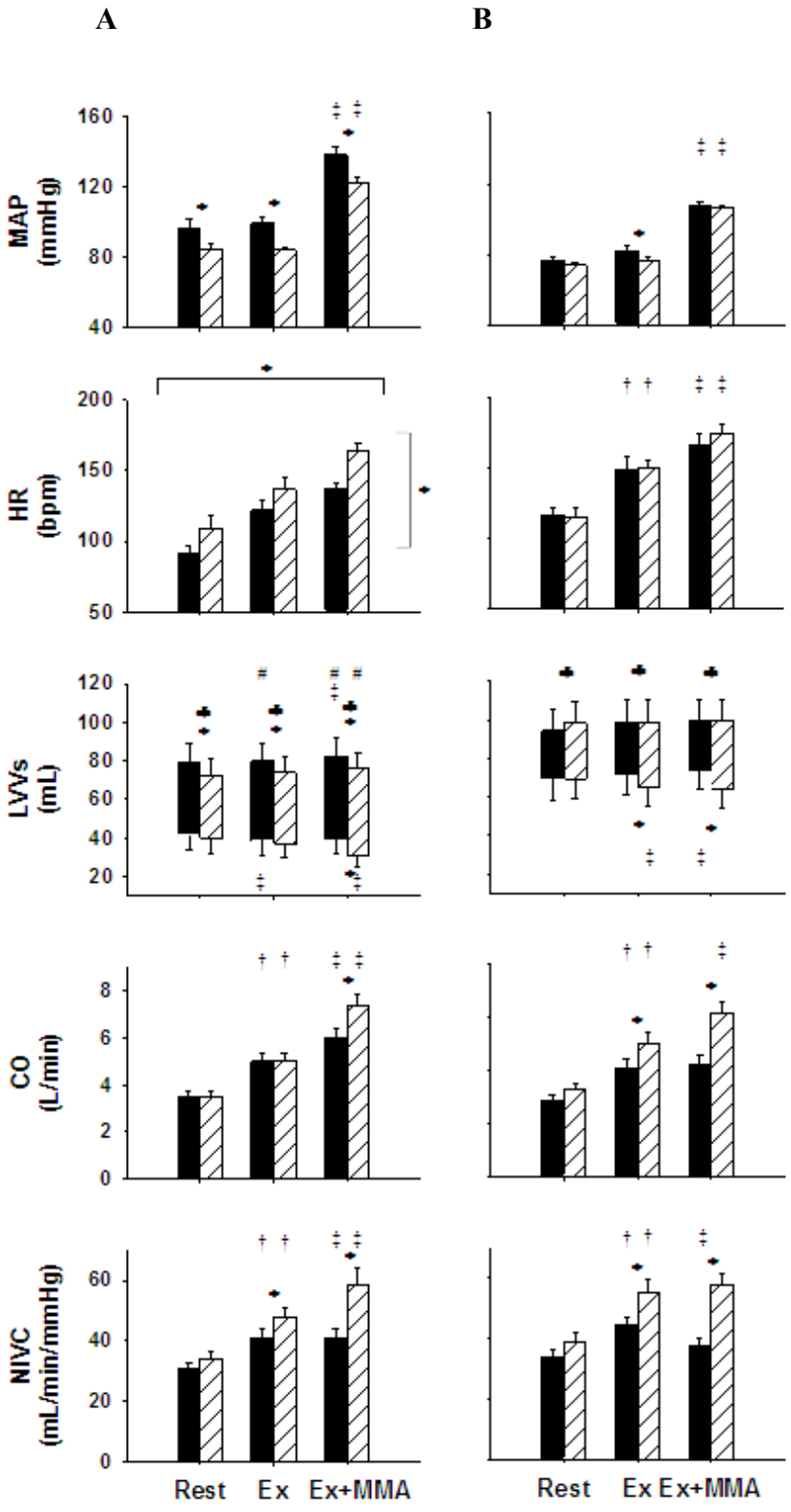


Figure 3.1: Hemodynamic responses: Mean arterial pressure (MAP), heart rate (HR), Left Ventricular Volumes (Left VVs), cardiac output (CO), and non-ischemic vascular conductance (NIVC); during rest, mild exercise (Ex), and mild exercise with MMA (Ex+MMA); in control (Panel A) and heart failure (panel B) (black bars) and the corresponding α_1 blockade conditions (striped bars). All parameters showed significance across workload settings, as well as significance between control and prazosin conditions ($P < 0.05$). All parameters had a significant interaction between the two independent variables, with the exception of hear rate in control and control after α_1 blockade. ***(column)** signifies a significant pairwise comparison ($P<0.05$). †signifies a significant increase from the previous workload. ♣signifies a significant pairwise comparison in left ventricle stroke volume ($P < 0.05$). ‡ signifies a significant increase in LV end diastolic volume while # indicates a significant increase in stoke volume from the previous workload ($P < 0.05$). ***(bracket)** indicates a significance between LV end systolic volume across workloads but not between control and α_1 blockade conditions.

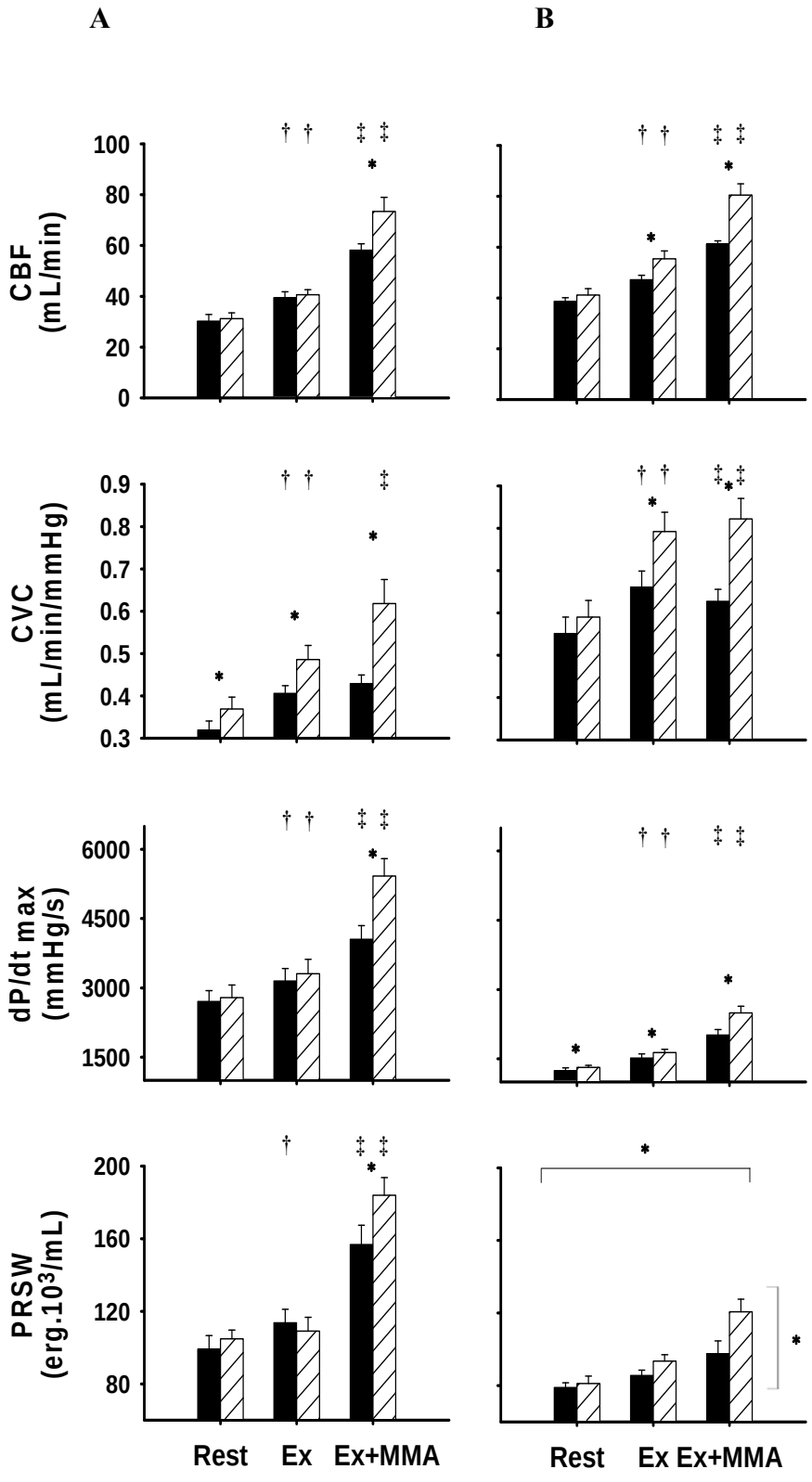


Figure 3.2: Left ventricular hemodynamic and function responses: Coronary blood flow (CBF), coronary vascular conductance (CVC), maximal rate of left ventricular pressure change (dP/dt_{max}), and preload recruitable stroke work (PRSW); during rest, mild exercise (Ex), and mild exercise with MMA (Ex+MMA); in control (Panel A) and heart failure (panel B) (black bars) and the corresponding α_1 blockade conditions (striped bars). All parameters showed a significance across workload settings, as well as significance between control and prazosin conditions ($P < 0.05$). All parameters had a significant interaction between the two independent variables, with the exception of PRSW in panel B, (N=3). An * above a specific setting signifies a significant pairwise comparison ($P < 0.05$). A † above a column signifies a significant increase from the previous workload ($P < 0.05$).

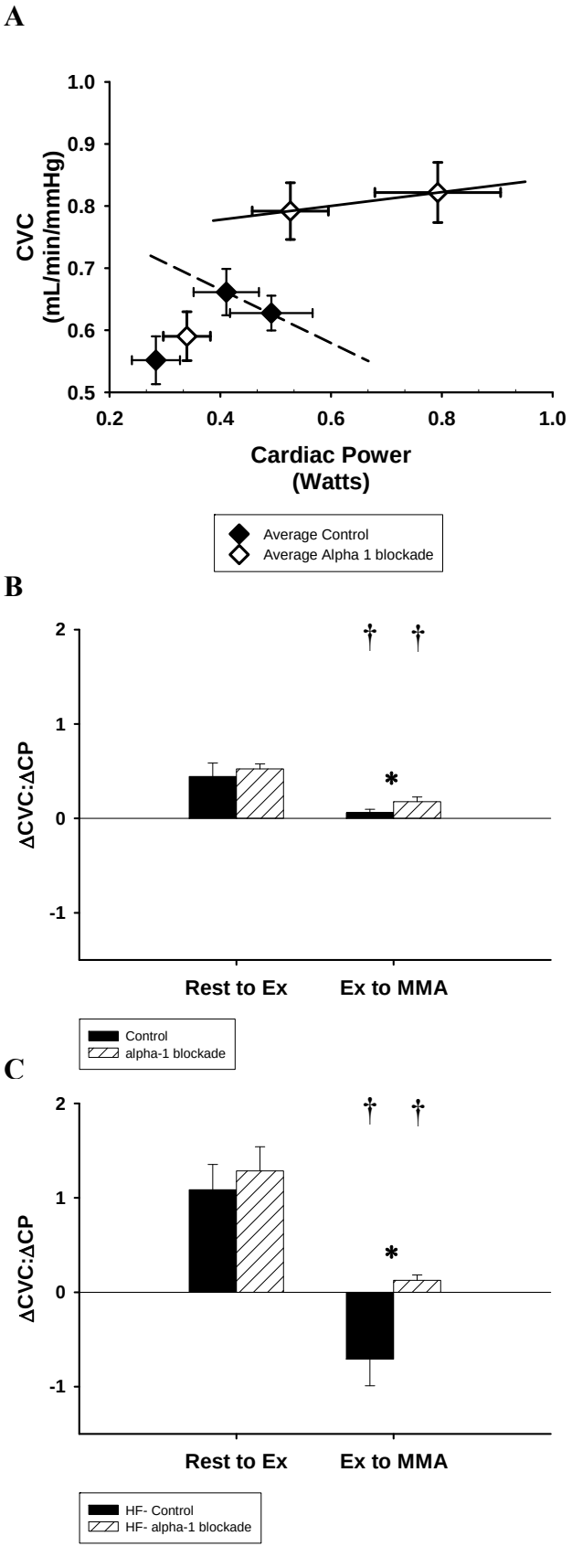


Figure 3.3: Coronary vascular conductance (CVC) plotted as a function of cardiac power (A). Ratio between change in coronary vascular conductance (ΔCVC) change in cardiac power (ΔCP) in control (B) and heart failure (C). The black bars represent control while the striped bars represent the corresponding α_1 blockade. Both are compared across rest to mild exercise (Rest to Ex.) and mild exercise to muscle metaboreflex activation (Ex. to MMA). An * above a specific setting signifies a significant pairwise comparison ($P < 0.05$). A † above a column signifies a significant increase from the previous setting ($P < 0.05$).

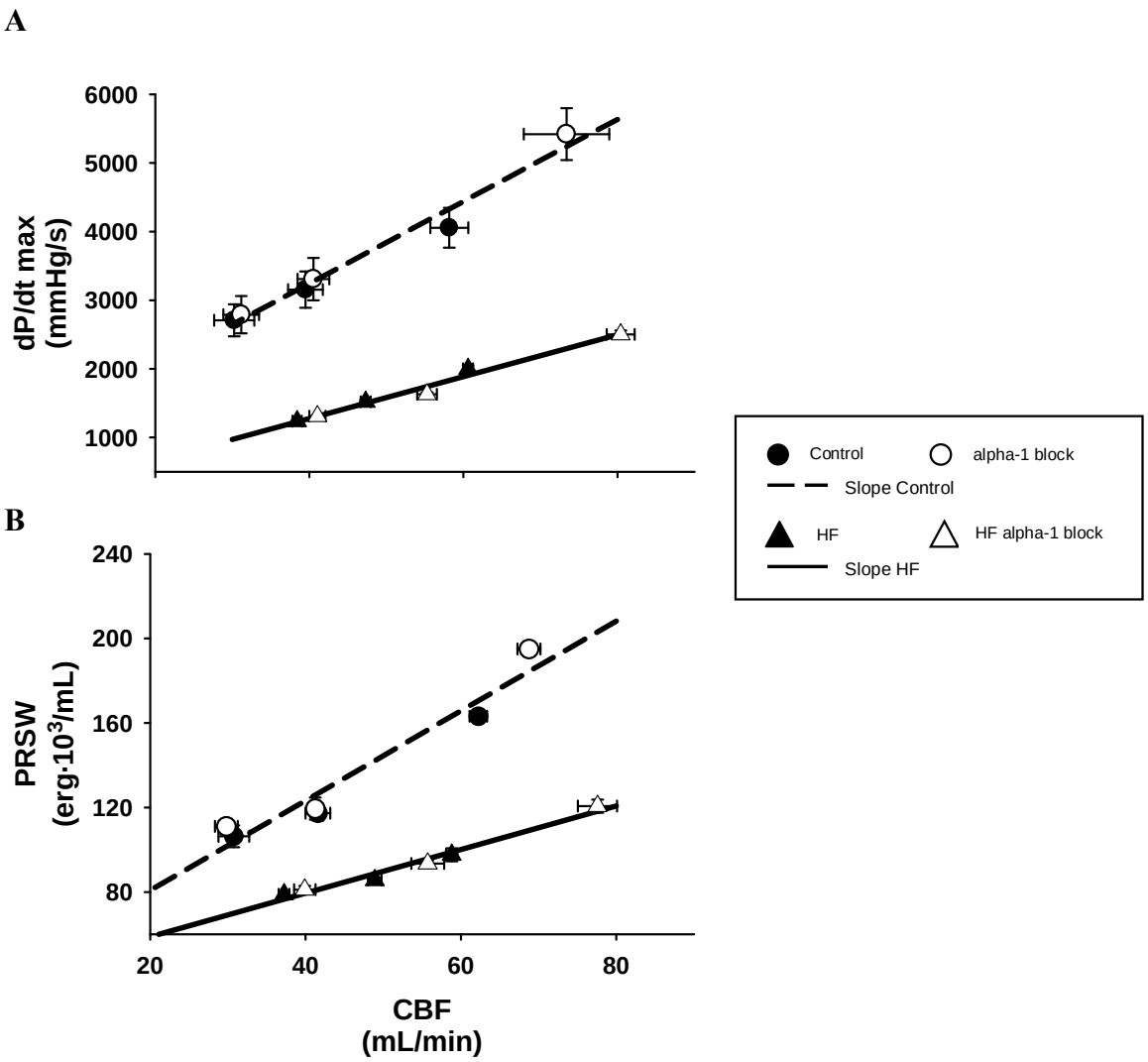


Figure 3.4: Contractility indicated by dP/dt_{max} (A) and preload recruitable stroke work (PRSW) (B) with respect to coronary blood flow (CBF). As no significant difference between control and α_1 blockade was found ($P > 0.05$), a single relationship is represented by a single line. The averaged values in heart failure are represented with black triangles (▲) while averaged values during α_1 blockade are shown as open triangles (Δ). In panels B and C, control and heart failure are combined with their corresponding α_1 blockade conditions. The averaged values in control are represented with black circles (●) and control with α_1 blockade with open circles (○), while averaged values during heart failure are shown with triangles as previously described.

Discussion

Our major finding is that the inability to raise ventricular contractility during metaboreflex activation in subjects with heart failure is, in part, due to coronary

vasoconstriction and the resultant limitation in the ability to raise coronary blood flow and O_2 delivery. Thus, ventricular dysfunction during exercise in heart failure stems both from the impaired contractile function as well as restrained ability to raise coronary blood flow due to α_1 mediated coronary vasoconstriction.

Previously we have shown in normal subjects that the muscle metabreflex-restrained coronary vasodilation functionally limited left ventricular contractility (20). Even during moderate to heavy exercise in normal subjects there is a constant push/pull situation between the vasodilatory stimuli of metabolic as well as possible β_2-mediated feed forward vasodilation (34), vs. the vasoconstricting effects of coronary vascular α_1 adrenergic receptor stimulation (37; 38; 72; 82). In heart failure, sympathetic activity is chronically elevated (25; 56) as are circulating catecholamine levels (25; 40). During muscle metaboreflex activation in heart failure, sympathetic activity is markedly increased (39). This increased sympathetic drive coupled with a limited ability to increase metabolic rate likely shifts the push/pull balance towards vasoconstriction, thereby limiting the increase in coronary blood flow and therefore oxygen supply to the heart. (3; 20). This reduced ability to increase O_2 delivery contributes significantly to the inability to raise ventricular contractility. The suppressed increases in left ventricular contractility likely limits the ability to increase cardiac output and therefore impedes the main function of the reflex which is to restore blood flow to ischemic working skeletal muscle.

Effect of heart failure

Several structural and functional impairments occur during heart failure including ventricular remodeling as well as extensive cellular damage. The reduced cardiac function results from a myriad of complications including abnormal myosin cross-bridge activity (102; 103), prolonged calcium transients due to dysfunctional calcium channels on the sarcoplasmic

reticulum (35), reduced myocyte β_1 adrenergic receptor density as well as a greatly reduced adenylate cyclase activity, indicating that myocardial β_1 receptor function is also attenuated (13). This reduced number and function of myocardial β_1 receptors helps explain the reduced calcium handling capacity as sympathetic activity is increased during heart failure (25; 56). The ventricular structural remodeling further attenuates cardiac function (46; 102; 103).

In the present study we hypothesized that limited oxygen delivery to the myocardium may be another important factor contributing to the reduced cardiac performance during metaboreflex activation in heart failure. We showed that muscle metaboreflex activation during heart failure elicited coronary vasoconstriction, which in turn suppressed increases in blood flow to the myocardium which would have occurred with the pressor response. With the coronary vasodilation and larger increases in coronary blood flow after a receptor blockade, increases in contractility and cardiac power were seen with metaboreflex activation in heart failure. Canetti et al showed that the maximal capacity for coronary arteries to dilate is impaired during heart failure (14), indicating a possible restraint of coronary blood flow during high oxygen demand situations such as exercise and metaboreflex activation.

Coronary Hemodynamics and Ventricular performance

We showed that the CVC-Cardiac Power relationship is normally markedly suppressed with heart failure compared to normal subjects (Figure 4). In a recent study from this laboratory (20) we used an analysis based on that done by Huang and Feigl (43). This relates the vascular response as a function of the O_2 consumption. The vascular response may be blood flow if pressure is constant, but since pressure changes we used vascular conductance since changes in pressure will change flow directly independent of any change in the vasculature. We used cardiac power (stroke work times heart rate) as an index of the steady-state O_2 demands of the heart (28; 49; 67). We showed that in the normal heart there is a linear relationship between

CVC and Cardiac Power and that the slope of this releationship is shifted upwards after α_1 receptor blockade. This indicates that after blockade of the coronary vasoconstrictor effects of the rise in cardiac sympathetic activity during metaboreflex activation, a given increase in myocardial workload would give rise to a greater vasodilation. However this linear model is lost in heart failure. Metaboreflex activation caused trivial increases in cardiac power and frank coronary vasoconstriction occurred. Therefore, to analyze this relationship, the ratio of ΔCVC to ΔCP was calculated separately for the transitions from rest to exercise, and from exercise to metaboreflex activation. With metaboreflex activation in normal subjects, this ratio is reduced from that with the transition from rest to mild exercise; however during metaboreflex activation after α_1 receptor blockade a higher ratio was observed. This indicates that a larger vasodilation will occur for a given increase in cardiac power after removal of the vasoconstricting effects of the rise in cardiac sympathetic activity. In contrast, after induction of heart failure, with metaboreflex activation this ratio actually becomes quite negative meaning that coronary vasoconstriction occurred with the increase in ventricular work. This ratio was reversed to a positive value with α_1 blockade. This marked change in the vasodilation/function relationship with α_1 blockade underscores the severe consequences of coronary vasoconstriction in heart failure.

In both normal subjects and after induction of heart failure, there was a single linear relationship whether with or without α_1 blockade conditions, heart failure substantially lowered the slope of this relationship. Blockade of coronary vasoconstriction extended this relationship to higher levels of flow and contractility. The lower slope seen in heart failure shows that whereas ventricular function is dependent on flow, this dependency is less than in the normal heart. However, in heart failure ventricular function is already so depressed that relatively small increases in contractile strength may make significant differences in overall cardiovascular

function.

In the present study prazosin was used as an α_1 – adrenergic blocker. The clinical efficacy of systemic α_1 – adrenergic blockade to improve performance of the failing heart has been tested clinically. Short-term results showed that prazosin therapy provides favorable hemodynamic responses (5; 9; 16; 18; 26; 31; 64; 68; 92), such as: reduced pulmonary venous congestion, improved end diastolic and systolic volumes, increased coronary flow, cardiac output, and improved NYHA functional class. However, studies found that such responses were attenuated in the long-term (18; 26) and that there was no improvement in mortality (16). Another concern with the long-term clinical use of prazosin is the possible attenuation of ventricular preload below that of optimal filling pressure (9). The lack of efficacy of prazosin as a treatment for heart failure may indicate there are still other factors involved in heart failure and also be a compensatory affect of the body. The systemic effects of prazosin may also complicate its clinical usefulness. If alpha receptor blockade could be targeted to the coronary vasculature, a different outcome of treatment may be possible.

Limitations

In our previous study (20) a concern was discussed regarding the possibility of a larger increase in cardiac output induced by a baroreflex response to the reduced arterial pressure during α_1 blockade. In this study however α_1 blockade did not have a significant influence on arterial pressure making any baroreflex effect similar with or without α_1 blockade.

We observed systemic vasodilation (with exception of the hindlimbs) with muscle metaboreflex after α_1 blockade. A large portion of this change likely occurs in skeletal muscle (51). In previous experiments from this laboratory, after infusion of propranolol this systemic vasodilation no longer occurred (82), indicating a likely β_2 mediated adrenergic vasodilation. It is possible that some of the coronary vasodilation observed is also β_2 mediated vasodilation.

However any β_2 vasodilation would likely be modest (33).

Due to difficulties in attaining PRSW during heart failure, we were limited to a small sample size (N=3). However a clear trend is visible to supplement the results observed with dP/dt_{max}. Although, dP/dt_{max} is considered sensitive to changes in loading conditions (48; 60), it is still considered a widely used index of contractility.

In summary, muscle metaboreflex activation during heart failure further increases sympathetic tone to α_1 adrenergic receptors and functionally restricts coronary vasodilation. This limits increases in blood flow to the myocardium which thereby limits the increase in left ventricular performance. This is likely one factor limiting the ability of the reflex to raise cardiac output during heart failure. Thus, the inability to effectively raise cardiac output during metaboreflex activation in heart failure is not only due to the ventricular dysfunction, but also is in part a result of coronary vasoconstriction.

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ABSTRACT

MUSCLE METABOREFLEX CONTROL OF CORONARY BLOOD FLOW AND VENTRICULAR CONTRACTILITY DURING DYNAMIC EXERCISE IN NORMAL AND HEART FAILURE CONDITIONS

by

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Muscle metaboreflex activation during dynamic exercise induces a substantial increase in cardiac work and oxygen demand via a significant increase in heart rate, ventricular contractility and afterload. This increase in cardiac work should cause coronary metabolic vasodilation. However, little if any coronary vasodilation is observed due to concomitant sympathetically induced coronary vasoconstriction. In heart failure, cardiac output does not increase with MMA presumably due to impaired left ventricular contractility, and large decreases in coronary vascular conductance are observed. The purpose of this dissertation is to determine whether the muscle metaboreflex-induced restraint of coronary vasodilation functionally limits coronary blood flow and suppresses increases in left ventricular (LV) contractility in normal dogs and whether this coronary vasoconstriction could explain in part, the reduced ability to increase cardiac performance during heart failure conditions. We used chronically instrumented dogs (n=9, control and n=7, heart failure) and measured arterial pressure (MAP), cardiac output (CO), circumflex blood flow (CBF), and calculated coronary vascular conductance (CVC), maximal derivative of ventricular pressure (dp/dt), and preload recruitable stroke work (PRSW) at rest and during mild exercise (2mph) before and during

activation of the muscle metaboreflex. Experiments were repeated after systemic alpha-1 adrenergic blockade (prazosin 50-100μg/kg). In control studies during α_1 blockade we observed significantly greater increases in CVC, CBF and PRSW, as well as CO and dP/dt_{max}, with metaboreflex activation vs. those seen without α_1 blockade. In heart failure experiments during MMA, the increases in CBF, CVC, CO, and $+dP/dt_{max}$ were significantly greater after α_1 adrenergic blockade. We conclude that the coronary vasoconstriction elicited by MMA limits the ability of muscle metaboreflex to increase left ventricular contractility in normal and heart failure conditions.

AUTOBIOGRAPHICAL STATEMENT

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Publications

1. **Coutsos M**, Sala-Mercado JA, Ichinose M, Li Z, Dawe EJ, O'Leary DS. Muscle Metaboreflex-Induced Coronary Vasoconstriction Functionally Limits Increases in Ventricular Contractility. J Appl Physiol. 2010 Aug;109(2): 271-8.
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