Effects of α_1-Receptor Blockade on the Hemodynamic Responses to Exercise in Young Normotensives and Hypertensives

by

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(ABSTRACT)

The purpose of this study was to determine if α_1-adrenergic receptor blockade alters the hemodynamic response to exercise in young (<25 yr) male adult borderline hypertensives differently than in young normotensives. Five hypertensive (HTN, MAP>105 mmHg) and 7 normotensive (NTN, MAP<95 mmHg) college-age males underwent two 30 min bouts of cycle ergometry exercise at 50% $\dot{V}O_{2pk}$ in a warm (25°C, 50% rh) environment; one bout occurred followed α_1-receptor blockade with prazosin (HTN-α, NTN-α) and the other following placebo administration (HTN-p, NTN-p). At rest, HTN-p exhibited an elevated cardiac output ($\dot{Q}$, p=.024) and MAP (p=.007). Resting $\dot{Q}$ was similar for HTN-α and NTN-α. Resting heart rate (HR) was elevated more in HTN-α than NTN-α (p=.013) and not different for placebo. Resting and exercise forearm blood flows were similar between groups and altered similarly with prazosin. Exercise resulted in greater (p=.035) $\dot{Q}$ for HTN vs NTN (HTN-α > NTN-α; HTN-p = NTN-p). HR was higher (p=.043) with prazosin for both groups. Regardless of drug treatment, MAP was stable for

NTN while it declined after 10 min of exercise in HTN. Rectal temperatures rose above baseline after 10 min. Since $\dot{Q}$ was similar between groups with placebo but not with α_1-blockade, and FBF, MAP, and HR were similarly altered between drug trials, it was concluded that young male hypertensives have an elevated blood pressure due to an elevated $\dot{Q}$. In this group, α_1-blockade may reduce $\dot{Q}$ by reducing central venous return.

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Chapter I

INTRODUCTION

Hypertension is recognized as being a major risk factor for atherosclerosis. Hypertensive disorders alone account for over 3% of all deaths attributable to cardiovascular diseases, or diseases due to atherosclerotic lesions occurring in the vasculature. As one of the primary risk factors for these diseases, it accounts for an overall increased incidence of cardiovascular mortality and morbidity. For example, while only 1-2% of normotensive people experience significant cardiovascular diseases, 10-15% of the hypertensive population are at risk (Lew, 1973). This risk is largely preventable in that treatment of hypertension can be beneficial; reducing diastolic blood pressure only 5-6 mm Hg can reduce the incidence of CVD 20 to 25% and the incidence of stroke 40% (Poulter, 1991). Additionally, it is not a minor problem in that an estimated 37 to 60 million Americans have borderline hypertension (Kaplan, 1984; Kenney & Zambraski, 1984). Consequently, an impressive quantity of research has been conducted in which possible causative mechanisms of hypertension as well as effective modes of treatment have been investigated. Nevertheless, the cause(s) of over 90% of all hypertension remains unknown.

Views differ as to the mechanisms of hypertension.

Laragh & Resnick (1988) assert that all essential hypertension lies on a continuum between the two extremes of high and low plasma renin activity. Other researchers support the notion that essential hypertension (HTN) originates solely as a function of a hyperkinetic circulation (Julius, 1988). Folkow (1982) suggests that hypertension results from an interaction of an inherited predisposition to the disease, permissive environmental elements and secondary adjustments that occur as a function of these two.

Regardless of the initiating mechanism(s), an elevated total peripheral resistance (TPR) is a hallmark of chronic essential hypertension. It is generally accepted that early elevations in TPR are functional in nature, being due to neural or humoral factors. Over time, structural adaptations in the peripheral vasculature occur. Once present, these alterations result in the maintenance of an elevated TPR, even though arterial smooth muscle cell tone is minimal.

Evidence exists to support the notion of a functional rather than structural mechanism behind the elevated TPR seen in HTN. In his review, Webb (1984) cited a number of lines of evidence supporting the functional mechanism. This evidence suggested that isolated vascular preparations from hypertensive animals possessed an increased sensitivity to

vasoactive stimuli. Further support is given by the findng that most studies comparing norepinephrine (NEpi) levels between young (age $\leq$ 40 years) hyper- and normotensives have noted significantly greater levels in the hypertensives (Goldstein, 1983). Thus, mildly elevated levels of NEpi in subjects sensitive to this neurotransmitter may be a factor in the early elevation of TPR.

Research supports the idea of functional differences in the vascular smooth muscle of hypertensive subjects compared to normotensives. For example, the combination of arterial occlusion and intra-arterial infusion of the Ca^{++} channel blocker nifidepine resulted in similar forearm vascular resistances between 22 age-matched pairs of normotensive and hypertensive subjects (Schulte, Braun, Meyer-Sabellek, Wegscheider, Gotzen, & Distler, 1988). Moreover, forearm vascular resistance was similar between groups of normotensives and borderline hypertensives following pharmocologic blockade with nonselective ß-, α-, and acetylchoine-blockers (Ogilvie, Nadeau & Lutterodt, 1982). It remained higher in "established hypertensives" in this study. The latter group was at least 10 years older than the other two and, presumably, were hypertensive for an equally longer period of time. It is uncertain how big a factor ageing alone (Safar, 1989) played in elevating FVR in these older hypertensive subjects .

Other published research supports the notion of structural, rather than functional, alterations in the maintenance of chronic elevations of TPR. Using prolonged arterial occlusion to maximize vasodilatation, essential hypertensives were consistently found to have higher forearm vascular resistances than normotensives (Sannerstedt, Sivertsson & Lundgren, 1976; Takeshita and Mark, 1980; Takeshita, et al., 1982). Furthermore, vascular hypertrophy has been found in post-mortem examinations of hypertensive humans (Kamal and Campbell, 1979) and animal models (Owens, Schwartz & McCanna, 1988).

It is uncertain if an elevated blood pressure is the cause of this structural adaptation. Folkow (1982) attributed this increase to hypertrophy of the vascular wall secondary to an elevated blood pressure, as the wall:lumen ratio is increased almost exclusively in the precapillary resistance vessels of spontaneously hypertensive rats (Folkow, 1978). The finding that lowering blood pressure (BP), even in normotensive rats, attenuates age-related structural alterations in aortic intima (Haudenschild and Chobanian, 1984) supports this assertion.

Other researchers have found that blood pressure <u>per se</u> is not a critical component of the vascular changes seen with hypertension. In comparing rats with systemic hypertension to rats with local hypertension, it was found

that both groups exhibited systemic vascular wall thickening (Liu, Bishop & Everbeck, 1988). Spontaneously hypertensive rats (SHR) treated with hydralazine still manifested vascular alterations even though their blood pressures were lower than untreated normotensive rats (Jesperson, Nuborg, Pedersen, Mikkelsen & Mulvaney, 1985).

A number of reviews (Folkow, 1982; Tipton, 1984; Triggle, 1989) have reached the conclusion that SHR and possibly human essential hypertensives possess a genetic predisposition to vascular hypertrophy. The finding of elevated vascular resistance in adult normotensive children of hypertensive parents (Takeshita, et al., 1982) supports this idea. Thus, evidence exists for and against the role of an elevated BP as the instigating agent behind the chronic elevations in TPR seen with HTN.

It is uncertain as to the time-course of the functional-to-structural progression of the elevated TPR. Few studies have specifically focused on the temporal interaction between HTN and alterations in the peripheral vasculature. Sannerstedt et al. (1976) noted that young (age=19 to 22 yr) hypertensive men with a normal cardiac index had a significantly greater hand vascular resistance with maximal vasodilatation than did similar subjects with a high cardiac index. Takeshita and Mark (1980) found that similarly aged (age=25 yrs) hypertensive men exhibited

significantly greater forearm vascular resistance during maximal vasodilatation than did their normotensive counterparts. As previously mentioned, Takeshita et al. (1982) has noted that normotensive men of hypertensive parents had a similar response, suggesting the existence of a genetic component to the elevated vascular resistance.

In these three studies, the method used to promote maximal vasodilitation was a 10-min period of arterial occlusion with or without forearm exercise. Consequently, the vascular resistance measured was in response to reactive hyperemia. Recent studies have called into question the adequacy of arterial occlusion as a method to promote maximal vasodilatation. In the earlier mentioned Schulte study (Schulte, et al., 1988), neither arterial occlusion nor Ca^{++} channel blockade alone revealed a significantly different FVR. Others have noted that 13 min of arterial occlusion is more effective than 10 min in reducing reactive hyperemia (Pedrinelli, Taddei, Spessot, & Salvetti, 1987). Thus, the arterial occlusion used in previous studies, especially when it is the sole vasodilating source, may not be an adequate stimulus to promote maximal vasodilatation.

Statement of the Problem

It is generally accepted that subjects with hypertension of several years duration have an increased forearm vascular resistance which reflects a structural

change in the vascular smooth muscle. It is unclear if young hypertensives or subjects with hypertension of a few months duration have an elevated total peripheral resistance. The research in this area is inconclusive. Some investigators have found an elevated peripheral resistance of various etiologies, some have not. One significant problem with these various findings is the methods employed to evaluate peripheral resistance. Another is simply subject selection; unlike spontaneously hypertensive rats, human hypertensives are not homogeneous with respect to the mechanisms of their hypertension.

With the present study, efforts were taken to avoid some of these methodologic problems. The methods used for measuring vascular resistance have been shown elsewhere (Kenney, Tankersley, Newswanger, and Puhl, in press) to alter forearm vascular resistance in normotensives and the nature of this alteration is restricted to the cutaneous vasculature. In addition, efforts were made to select, as carefully as possible, a set of hypertensive and normotensive subjects that were relatively homogeneous on a number of hypertension-related variables. Additionally, the parameters of hypertension selected for investigation were those that have been measured in a large number of similar studies; therefore, comparisons of results with the published literature could be made.

Significance of the Study

This study was designed to compare forearm vascular conductance between young hypertensives and matched normotensives. Additionally, the nature of any forearm vascular conductance differences between groups was determined. It was thought that these findings would be a useful contribution to the body of knowledge currently present. With this study being the initial work, it is desired that the time-course of the alterations in the peripheral resistance which occur with essential hypertension would be determined eventually.

Research Hypothesis

H_o: $Alpha_1$-adrenergic receptor blockade does not alter forearm vascular resistance differently in young adult male essential hypertensives as compared to young normotensives.

Delimitations

The following delimitations are present in this study:

1. The exact etiology of the hypertension in the subjects was not determined, although efforts were made to ensure that the hypertension was essential.
2. Only subjects not engaged in a program of regular cardiovascular exercise were used.
3. The subjects were volunteers.

4. Only 5-7 subjects per group were studied.

5. The subjects were males less than 25 years of age.

Limitations

The following limitations are consequently present in this study:

1. The experimental group of subjects was not identical in either pathology or extent of their hypertension.
2. The findings are limited to subjects who are not highly trained.
3. The subjects were selected in a non-random fashion.
4. The findings are not generalizable to the population of essential hypertensives.

Basic Assumptions

The following assumptions were made:

1. two separate measurements of blood pressure, taken in a seated posture in a laboratory environment, were adequate to determine the presence of hypertension;
2. subjects did not have hypertension associated with kidney dysfunction;
3. subjects exerted a maximal effort during the determination of maximal oxygen consumption;
4. no heat acclimation occurred over the course of

the study; and

5. the maximal oxygen consumption of the subjects did not change over the course of the study.

Definitions and symbols

Cardiac output ($\dot{Q}$) - the amount of blood ejected by the heart in a minute; the product of heart rate and stroke volume.

Forearm blood flow (FBF) - a relative measure of blood flow within the forearm; expressed as ml of blood*100 ml^{-1} of tissue*min^{-1}.

Forearm vascular conductance (FVC) - a relative measure of the forearm vasculature's ability to convey blood, expressed as a value which is normalized for driving pressure; the quotient of FBF/mean arterial pressure.

Forearm vascular resistance (FVR) - a relative measure of forearm vascular impedance to blood flow which is normalized for driving pressure; the quotient of mean arterial pressure/FBF.

Hypertension (HTN) - chronically elevated blood pressure; defined here as a mean arterial pressure $\geq$ 105 mmHg on two separate days.

Maximal volume of oxygen consumption ($\dot{V}O_{2pk}$) - the criterion measure of aerobic exercise capacity; expressed as the volume of oxygen consumed by an individual at peak exercise and normalized for body weight (ml O_2*kg^{-1}

body weight*min^{-1}).

Mean arterial pressure (MAP) - a measure of the chronic pressure load experienced by the systemic vasculature; estimated as (diastolic blood pressure + 1/3 pulse pressure).

Chapter II

REVIEW OF LITERATURE

Mean arterial pressure is the product of cardiac output and total peripheral resistance; consequently, any factor influencing either of these can affect blood pressure. As illustrated in Figure 1, the number of potential factors is considerable. The majority of these effector mechanisms are under either direct or indirect neurogenic control. In individuals with borderline essential hypertension, it is thought that the neural "drive" to the cardiovascular system is elevated. As described by Conway (1984), this overactivity can be manifested by a potentiated pressor response to stressful stimuli, an increased variability in blood pressure and heart rate, increased plasma levels of catecholamines, elevated sympathetic nerve activity, and/or a "circulatory pattern consistent with autonomic stimulation." Typically, this elevation in blood pressure can be attributed to a sympathetically-mediated elevation in cardiac output (Julius, 1988) as autonomic blockade will normalize the blood pressure by lowering the cardiac output. They may also possess an elevated total peripheral resistance (TPR) due to the increased sympathetic nerve activity. This elevation will be addressed in a later section.

A different cardiovascular model is found in the

established hypertensive. These subjects typically have neither elevated plasma catecholamine levels nor elevated cardiac outputs (CO). Rather, the rise in blood pressure is attributable more to an alteration in total peripheral resistance than to an elevated cardiac output. For example, in a study evaluating TPR and CO, the hypertensive group with the largest CO possessed the lowest TPR while the group with the smallest CO possessed the greatest TPR (Messerli, De Carvalho, Christie & Frohlich, 1978). In response to a tilt test, those subjects with elevated CO experienced a greater increase in TPR. Nevertheless, the group with a low CO still had a 171% greater TPR than did the group with the high CO.

In subjects with chronic hypertension, the elevation in TPR is usually due to structural changes in the vasculature, especially the precapillary resistance vessels. A substantial body of literature also suggests that functional differences in the vasculature of hypertension-prone or borderline hypertensive individuals either initiate or potentiate the development of hypertension. These two mechanisms probably interact such that an increased TPR due to an enhanced sympathetic drive is maintained later by vascular hypertrophy (Egan, 1989).

The time course of this shift from functional to structural predominance is unknown. In the rat model,

Folkow (1982) noted that this shift occurs in a matter of weeks. Extrapolating this finding to man, Folkow suggested that this shift occurs within months of the onset of HTN. As man is more genetically complex than the inbred spontaneously hypertensive rat (SHR), this extrapolation seems tenuous. Some people have argued that the SHR is not a good model for human HTN (McGiff & Quilley, 1981).

This review will, therefore, focus primarily on the two distinct notions of structural and functional alterations which occur in the peripheral vasculature with HTN. A large number of studies have evaluated these responses in the SHR. Only a limited number have evaluated these factors with humans, particularly as regards changes in limb vascular resistance. As the human response is germane to the present study, it will be emphasized. The effects of the α_1-adrenergic blocker, prazosin, also will be discussed as its cardiovascular effects are important to data interpretation. For the sake of completeness, the vascular smooth muscle α receptors also will be reviewed.

Based on the equation of Poiseuille, a critical factor determining vascular resistance is the internal radius of the vessel. The equation relates that minor changes in the lumenal diameter of the vessel have an exponential effect on blood pressure. Thus the finding of even small intergroup differences may be physiologically important. However, the

methods used to promote and evaluate alterations in the lumenal diameter frequently differ between studies thereby complicating the interpretation of the results.

Functional alterations

Compared to the body of research supporting structural alterations, few studies exist that support the role of a functional abnormality in the peripheral vasculature of hypertensives. Even less have evaluated forearm blood flow (FBF) and forearm vascular conductance (FVC=FBF/mean arterial pressure). Furthermore, the results of these studies raise doubts about the effectiveness of the procedures typically used to produce maximal dilation. For example, it has been shown that 13 min of arterial occlusion was more effective in maximizing forearm vasodilitation than the 10 min commonly employed (Pedrinelli, Taddei, Spessot & Salvetti, 1987). The use of calcium-channel blockers with the arterial occlusion also seems superior to occlusion alone. Thus, when reading this section, remember the methodological differences between the studies cited in this section and the succeeding one.

Several lines of research suggest that essential hypertensives may have a defect in the Ca^{++} channels of their vascular smooth muscle membranes that contributes to an increased vascular tone (Nghiem & Rapp, 1983). Using women with a mean age of 40 yr, it was found that the

hypertensive subjects experienced a greater change in FBF for a given dose of verapamil than did the normotensive controls (Hulthén, Bolli, Amann, Kiowski & BÜhler, 1982). Calculations of FVR, which normalizes FBF for differences in mean arterial pressure, suggest that FVR follows a trend similar to FBF. In a group of men, these results were essentially the same (Robinson, Dobbs & Bayley, 1982).

When combined, arterial occlusion with local i.a. infusions of nifidepine resulted in similar FVR for 22 normotensive and hypertensive subjects who were matched for age and weight (SchÜlte, Braun, Meyer-Sabellek, Gotzen & Distler, 1987; SchÜlte, Braun, Meyer-Sabellek, Wegscheider, Gotzen & Distler, 1988). When used separately, arterial occlusion, arterial occlusion with local heating, and nifdeipine administration alone resulted in a higher FVR in the hypertensive group. These studies suggest that the combination of local metabolite production, via arterial occlusion and local heating, and blockade of an influx of extracellular Ca^{++} in the vascular smooth muscle will relax the elevated vascular smooth muscle contractile state seen in hypertension. However, Folkow (1988) contends these findings support his idea of rapid development of structural alterations, suggesting that if a structural alteration did not occur, these interventions should have resulted in a greater reduction in FVR in the hypertensive group than in

the normotensive one (Folkow, 1988).

In the SHR, at least, the smooth muscle membrane seems to "leak" Ca^{++} inward at a rate faster than it can be removed (Noon, Rice & Baldessarini, 1978). Aortic strips from SHR, of an unspecified age, relaxed in a Ca^{++}-free bath but contracted to 60% of maximum when Ca^{++} was added. Strips from normal rats were unaffected by the manipulations. This derangement may be genetic in the SHR. For example, SHR were treated <u>in utero</u> and till death at 4-5 months of age with a nonselective ß-blocker. Aortic strips from these animals still manifested an increased sensitivity to extracellular Ca^{++} not found in similarly treated normotensive rats (Goldberg & Triggle, 1978). Human essential hypertension may be linked to a membrane-related ion-transport defect, but it is unclear as to the magnitude or uniformity of this defect. While it is uncertain if these findings in SHR can be extrapolated to humans, it does suggest a mechanism behind the effectiveness of Ca^{++}-channel blockers in normalizing FVR in borderline hypertensives.

The addition of Bay K 8644, a voltage-gated Ca^{++} channel agonist, to artery preparations resulted in dose-dependent contractions significantly greater in the SHR than in control rats (Aoki & Asano, 1986). Nifedipine, added to unstimulated arteries, also yielded dose-dependent relaxations in the SHR but not in the controls. Note that

nifidepine antagonizes α_1 and α_2 receptor-mediated activation of vascular smooth muscle (Alabaster & Solca, 1985).

Animal studies suggest the Ca^{++} channel defect is not linked to the voltage-gated channel but to the chemical-gated channel. This channel is most likely linked to the neurotransmitter norepinephrine (NEpi). Mulvany and Nyborg (1980) found that resistance vessels from SHR possessed a greater Ca^{++} sensitivity in the presence of NEpi than did control rats. Vessels from both strains responded similarly to either K^{+}- or NEpi-induced depolarization in a calcium-free bath. The rats used were 4 weeks (pre-hypertensive) and 4 months (hypertensive) of age. Potassium-mediated depolarization results in a Ca^{++} influx while NEpi induces intracellular Ca^{++} release along with the Ca^{++} influx.

It has been demonstrated that human hypertensives possess neither an increased receptor sensitivity to NEpi (Horwitz, Clineschmidt, Van Buren & Ommaya, 1974; Strecker, Hubbard & Michelakis, 1975) nor impaired catecholamine clearance (Goldstein, Horwitz, Keiser, Polinsky & Kopin, 1983). Most research suggests that human hypertensives may possess a greater level of circulating catecholamines than normotensives. Goldstein (1983) noted, however, that this elevation was highly variable. Any small "resting" difference between groups seems greatly potentiated with

either mental (Bolli, Amann, Hulthén, Kiowski & BÜhler, 1981) or physical exertion (Chodakowska, Wocial, Skorka, Nazar & Chwalkinska-Moneta, 1980; Goldstein, 1981). There is also some evidence that an unspecified factor in the plasma of hypertensives may potentiate the vascular smooth muscle responsiveness to NEpi (Pillai & Sutter, 1989). As a result, mildly elevated levels of NEpi, interacting with an altered Ca^{++}-channel activity, may increase vascular smooth muscle contraction in hypertensives more than normotensives. Thus, the elevations in NEpi that elevate CO in borderline hypertensives may also contribute to the elevation in TPR by direct and indirect actions of peripheral vascular smooth muscle.

Over time, hypertensives may undergo a down-regulation of ß-receptors in the vasculature (Abboud, 1984; Egan,1989) that would leave α-receptor mediated vasoconstriction unopposed. Moreover, α-receptors do not seem to down-regulate (Senard et al., 1989) as would be expected. McAllister (1979) noted evidence supporting this hypothesis--hypertensives treated with proponalol experienced an augmented pressor response to isometric handgrip exercise that was not present in normotensive subjects. However, combined infusion of phentolamine, an α-receptor blocker, and propanolol, a ß-receptor blocker, completely abolished this response. Using a mixed-age group of subjects, BÜhler

et al. (1980) found that hypertensives had a reduced sensitivity to isoproterenol, a ß-agonist, and this reduction became greater with advancing age. Additionally, local phentolamine infusions decreased FVR to a greater extent in a group of hypertensives than in controls (Kiowski, BÜhler, van Brummelen & Amann, 1981). These subjects were studied under resting conditions and ranged in age from 18 to 70 yrs. In age-matched subjects, prazosin but not sodium nitroprusside resulted in significantly lower FVR in a group of hypertensives than controls (Amann, Bolli, Kiowski & BÜhler, 1981). Prazosin is an α_1-receptor blocker while sodium nitroprusside is a nonspecific vasodilator. Consequently, this group of studies suggest that the elevation in TPR seen with hypertension is due to an α-adrenergic mediated vasoconstriction that is unopposed, or opposed to a lesser extent by ß-adrenergic mediated vasodilation.

Frequently, arterial occlusion is a commonly used mechanism for promoting maximal vasodilation. Studies employing this technique in evaluating differences between HTN and normotensive (NTN) subjects usually suggest that structural alterations have occured in the group with HTN. The use of arterial occlusion may have been a limiting factor in that the increase in blood flow was relatively restricted to the muscle mass. Considerable elevations in

muscle blood flow can occur with only minor changes in muscle volume (Rowell, 1986). Kenney and colleagues (1984) used cycle ergometry in a heated environment and found essential hypertensives had a blunted forearm blood flow (FBF) response compared to normotensives. Over the course of 60 min of exercise in the heat, FBF increased only about 2 ml*100 ml^{-1}*min^{-1} in the HTN group while the normotensives experienced an elevation approximately 3.5 times this. While resting FBF were similar, FVR was initially about 1.5-fold greater in the HTN group, increasing to about 2-fold greater by the completion of exercise. In this environment and with these stimuli, alterations in FBF are confined to the skin. As non-acral skin has an active vasodilator system that appears to be mediated by both cardiopulmonary baroreceptors and thermoregulatory control systems (Kellogg, Johnson & Osiba, 1990), this study suggests that hypertensive subjects may have an impaired active vasodilatory system.

Together, these studies suggest that hypertensive subjects may possess a vascular smooth muscle defect that singly, or in conjunction with mildly elevated catecholamine levels, results in an elevated peripheral vascular resistance. Possible down-regulation of adrenergic vasodilatory mechanisms may increase this resistance. Additionally, other vasoconstrictor agents, such as

angiotensin II (Griendling, Tsuda, Berk & Alexander, 1989) or a reduced responsiveness to endothelium-dependent vasodilator agents (Lograne, Daniele & Galli, 1989) may play a role. If so, the importance of these other agents in elevating peripheral resistance is uncertain.

Structural Adaptations

A number of researchers suggest that structural changes in the vascular beds of hypertensive subjects are the natural response of the body to sustained elevations in blood pressure (Folkow, 1987; Sivertsson, 1988; Safar, 1989). They base their arguments primarily on the law of Laplace, where wall tension=blood pressure*diameter of arterial lumen/arterial wall thickness. In the presence of an increased blood pressure, the body attempts to normalize vascular wall tension by increasing the wall thickness and decreasing the lumen diameter. These changes are effective and appropriate in the short term, but become pathologic with continuing evolution. These alterations increase the impedance of the Windkessel vessels, such as the aorta and large arteries, and increase flow resistance in the precapillary arteries and arterioles (Mulvany, 1984). Left ventricular hypertrophy is also a common consequence. Both adaptations lead to increases in the pressure/flow relation, the metabolic demand for circulatory function and the potential for end-organ necrosis.

Many investigators have found a decreased dilator capacity in the forearm vasculature of essential hypertensives. Studies by Pickering (1936) and Prinzmetal and Wilson (1936) first noted that hypertensive subjects had similar or reduced forearm and/or hand blood flows compared to normotensives. Methods used to evaluate blood flow were reactive hyperemia, local and whole body heating as well as neural ganglionic blockade. These researchers concluded that vascular "hypertonus" was not sympathetically driven. While not calculated by the authors, it appears that vascular resistance was greater in the hypertensive groups.

Folkow's group (Folkow, Grimby & Thulesius, 1958) was probably the first to control adequately for age and gender differences between the studied groups. Using patients aged 39 to 66 years old, they found a significantly higher whole-forearm FVR (3.48 vs 1.81 units) in the hypertensive group at maximal dilation. Elsewhere, evaluation of FBF and skin blood flow in moderate-to-severe hypertensives revealed a doubled FBF but similar FVR compared to normotensive controls (Brod, Fencl, Hejl & Zirka, 1959). The elevation in the inter-group difference in mean arterial pressure accounts for the similar FVR. However, skin blood flow did not differ between groups; therfore, skin vascular resistance was almost twice as high in the hypertensive group as in the control group. These variables were

assessed under "resting" conditions. While the magnitude of HTN did not seem to be critical in this study (Brod et al., 1959), Conway (1963) noted that the vasodilatory response to local ischemia and exercise was directly related to the BP level. He did not find the duration of HTN to be important. Collectively, these studies suggested that subjects with relatively severe hypertension retain a normal FVR, due to a significantly elevated local blood flow, at rest but are unable to vasodilate to the degree seen in normotensive subjects. This limitation may be due to the structural alterations occurring in the peripheral vasculature which limit the increase in lumen diameter.

Later, Sivertsson (1970) found a 1.7-fold greater minimal resistance in the hand vascular bed (R_{min}) of untreated HTN compared to NTN controls. Moreover, the HTN group experienced a steeper dose-response curve to i.a. norepinephrine. Sivertsson concluded this group had a greater vascular smooth muscle mass which could therefore contract to a relatively greater degree. Evaluating 18 to 22 year old men and using a similar method to promote maximal vasodilation, it was found that HTN subjects had an approximately 10% greater R_{min} than the controls (Sannerstedt, Sivertsson & Lundgren; 1976). Of this group with HTN, subjects with a normal cardiac index (CI) had a 17% greater R_{min} while those with an elevated index had a

R_{min} similar to controls. The decreased central venous return, due to the elevated R_{min}, probably normalized CI while the elevated CI in the latter group was likely the main factor behind their HTN.

A five-year follow-up to this study noted essentially unchanged blood pressures for both groups but supported this explanation (Sivertsson, 1984). R_{min} increased, while the CI had decreased significantly in the HTN group. These changes were most dramatic in the group with an originally elevated CI. This finding supports the previously cited theory that young hypertensives have a hyperkinetic circulation and a normal TPR that, over time, becomes normokinetic but with an elevated TPR (Julius, 1988). However, it refutes Folkow's estimate (Folkow, 1982; Folkow, 1987) of the time-course of HTN progression as R_{min} in the HTN group was, at most, only 10% greater after 5 years.

Takeshita and Mark (1980) noted a 40% higher (FVR) in HTN just after the release of 10 min of arterial occlusion. The NTN and HTN subjects had similar resting FVR and were young (25±1 yr). Elsewhere, this study was extended using 6 min of arterial occlusion in conjunction with autonomic blockade (proponalol 0.2 mg/kg, atropine 0.04 mg/kg, phentolamine 15 mg i.v.) (Ogilvie, Nadeau & Lutterodt; 1982). Subjects with either established or borderline HTN had significantly higher FVR than normotensive controls

(4.2±0.3, 3.8±0.4, 2.3±0.1 units, respectively). When expressed as a percent change, FVR was similar between groups with these interventions although the percent increase in forearm blood flow was considerably higher in the control group. These data suggest that the increased peripheral vascular smooth muscle mass, seen in established hypertension, responds in a manner similar to that of normotensives.

Takeshita and coworkers (1982) suggested that subjects predisposed to HTN may have a structural abnormality that precedes rather than coincides with the development of HTN. Here, they compared the FVR of 23 normotensive men (age=24 yrs) with hypertensive relatives to 17 normotensive men (age=24 yrs) with no family history of HTN. Minimum FVR was 25% higher in the former group (2.0±0.02 vs 1.5±0.01 units, respectively). To my knowledge, they did not perform follow-up re-evaluations on these subjects so it is unknown if this group eventually developed HTN.

In a unique study, Clement and Duprez (1984) evaluated calf and finger blood flow in hypertensive subjects using ECG-triggered strain gauge plethysmography. Venous occlusion was applied for three ECG complexes and removed for two with this cycle being repeated for 20 min. At rest, finger vascular resistance was lower in the HTN group. However, following arterial occlusion from 1to 5 min, both

calf and finger vascular resistances remained higher in this group compared to normotensives. Finger blood flow was accepted as being representative of skin blood flow while calf blood flow represented both skin and muscle. These subjects were known to be moderately hypertensive for at least two years. Here, it appears that hypertension of a relatively short duration affects both skin and muscle vascular resistances.

In evaluating vessel distensibility of the forearm and hand, it was noted that, at the same transmural pressure, constricted vessels of normotensive subjects had a greater resistance and distensibility than when dilated (Patel et al., 1988). However, the hypertensive subjects exhibited a greater vascular resistance and reduced distensibility compared to the controls at an equal transmural pressure. The vessels of the hypertensive group were stiffer as it required a greater transmural pressure to elicit an equal level of conductance. Unfortunately, neither age nor blood pressure were given for either group.

There is evidence that muscle blood flow may be altered with hypertension. In the tibialis anterior muscle, hypertensive subjects were noted to have greater blood flows and vascular resistances following recumbent rest and exhaustive ischemic exercise (Amery, Bossaert & Verstraete, 1969). Folkow's group have evaluated isolated hindquarter

preparations of the SHR. They noted an elevated R_{min} that paralleled the BP elevation (Folkow, Hallbëck, Lundgren & Weiss, 1970a), a steeper dose-response curve to norepinephrine (Folkow et al., 1970b) suggestive of an increased vascular smooth muscle mass and a 20% reduction in venous compliance that approximates a 10% decline in wall distensibility (Nilsson, Haralksson & Folkow, 1981).

In the spinotrapezius muscle, SHR were noted to have an increased number of transverse arterioles and a reduced inter-arteriole distance (Schmid-Schöenbein, Skalek & Firestone, 1987). However, these arterioles were of a smaller bore than those found in control rats. Transverse arterioles are thought to be a major contributor to vascular resistance and, therefore, these alterations may partially account for the elevated BP. An increased vascular resistance is seen in 5 to 6 wk old SHR, but it is isolated to smaller arterioles (<30 μm); by 12 to 13 wks of age, larger arterioles have become involved (Zweifach, Kovalcheck, DeLano & Chen, 1981). Rather than a reduced dilator capacity, le Noble and coworkers (1990) noted a reduced capillary density and arteriolar reserve in the cremaster muscle of 5 to 6 wk old SHR. Capillary rarefaction, or a reduction in capillary density, is also seen in human hypertensives (Henrich, Romen, Heimgärten, Hartung & Bäumer, 1988). It is unclear if these vascular

alterations precede, coincide with or follow the increase in blood pressure.

Studies using the SHR model usually suggest that the vascular hypertrophy is pressure-dependent with an increased involvement occurring with an increased duration or magnitude of hypertension (see Lee, 1989). However, a number of investigators have found that the hypertensive rat will develop structual alterations that are pressure-independent. Owens (1987) noted that, while captopril and proponalol were equally effective in lowering blood pressure in the SHR, proponalol did not affect medial hypertrophy. SHR, treated with hydralazine from the age of 4 wks, experienced medial thickening and an enhanced contractile response even though their blood pressures were well below that of control rats (Jespersen, Nyborg, Pedersen, Mikkelsen & Mulvany, 1985). Hydralazine is a peripheral smooth muscle vasodilator that is thought to interfere with intracellular Ca^{++} movement. As intracellular Ca^{++} is crucial for smooth muscle vasoconstriction, this study suggests that SHR will develop an abnormal peripheral vasculature even when the primary mechanism of vasoconstriction is obstructed. Sprague-Dawley rats subjected to coarctation of the abdominal aorta developed vascular wall thickening in their normotensive hindquarters (Liu, Bishop & Overbeck, 1988). Thus when evaluating hypertension-mediated alterations in

the vascular smooth muscle, it is important to note that these alterations may not be due solely to an increased blood pressure. Rather, other factors, such as elevated catecholamines or Angiotensin II, may play a significant role in these alterations.

Alpha$_1$-adrenergic Receptors and Their Role in Forearm Blood Flow

Alpha$_1$-receptors differ from ß and α_2-receptors in that occupation of the former does not lead to activation of guanine nucleotide regulatory proteins (Raymond, Hnatowich, Lefkowitz & Caron, 1990). Rather, receptor occupation leads to degradation of phospatidylinositol 4,5-bisphosphate by a specific phospholipase C. Diacylglycerol (DG) and insitol 1,4,5-trisphosphate (IP_3) result. IP_3 in turn releases stored Ca^{++} from the endoplasmic reticulum. DG activates a protein kinase C (PK-C) and binds to phosphatidylserine and Ca^{++}. This DG-phosphatidylserine-Ca^{++} subunit serves as a membrane attachment site for PK-C. It is thought that PK-C exerts feedback control on the signal transduction process. This information was summarized from Agranoff (1989).

The sympathetic neurotransmitter, norepinephrine (NEpi), is the predominant agonist for α-adrenergic receptors. Adrenergic fibers innervate, at most, only portions of the vascular smooth muscle immediately adjacent to the tunica adventitia. As with the myocardium, arterial

smooth muscle behaves as syncytia (Hirst & Edwards, 1989) and contract due to cell-to-cell conduction. Norepinephrine triggers the aforementioned but also causes a membrane potential change. If sustained and/or of sufficient magnitude, this depolarization will open voltage-gated Ca^{++} channels, and Ca^{++} influx will occur. Both intracellular and extracellular Ca^{++} can cause vascular smooth muscle contraction; these contractions are dependent on extracellular Ca^{++} if they are to be sustained.

Rowell (1986) has made three generalizations regarding sympathetic vasoconstrictor innervation that are pertinent. First, only the α-adrenergic fibers are distributed ubiquitously throughout the cardiovascular system. Second, only these fibers contribute to resting vascular tone. Third, only these fibers are thought to be on the efferent arm of major homeostatic reflexes. Consequently, blockade of these receptors may have profound effects on nervous control of the cardiovascular system.

Only α_1-receptors are thought to be present on the arterial side of the cutaneous vasculature (Rowell, 1986), while cutaneous veins probably possess both α_1- and α_2-postjunctional receptors (Johnson, Brengelmann, Hales, Vanhoutte & Wenger, 1986). Nonacral skin, as in the forearm, differs from acral skin in that it possesses an active vasodilator system that seems to be inhibited by

stimulation of low-pressure cardiopulmonary baroreceptors (Kellogg, Johnson & Osiba, 1990).

Forearm blood flow may be considered as divisible into two components, cutaneous blood flow and muscle blood flow (MBF). Skeletal muscles are predominately innervated by ß-adrenergic receptors with α-receptors comprising only 5 to 15% the total (Williams, Caron & Daniel, 1984). Research suggests that muscle blood flow may be more readily altered than skin blood flow. With mild-to-moderate workloads, leg ergometry has resulted in a decline in forearm MBF, while skin blood flow increased (Johnson & Rowell, 1975). Additionally, sympathetic output due to uncomfortable stimuli (a cold pressor test) has resulted in consistent increases in muscle nerve sympathetic nerve activity while skin nerve activity was quite variable (Fagius, Karhuvaara & Sundlöf, 1989). Furthermore, blockade of resting muscle tone results in a much smaller increase in MBF than that which would occur with metabolic vasodilitation as the former does not relax the arterial smooth muscle via local metabolic mediation (Rowell, 1986). Finally, evidence exists suggesting that precapillary arterioles in skeletal muscle are regulated predominately by α_2-receptors (Faber, 1988). Thus, the effect prazosin may have on muscle blood flow would appear to be minor compared to its effect on cutaneous blood flow. If prazosin did alter MBF, this

effect would have only a minor influence on the FBF determination, as muscle blood volume increases very little even if MBF is increased considerably (Rowell, 1986).

About 80% of the NEpi released locally is inactivated by presynaptic uptake (Hirst & Edwards, 1989). This NEpi occupies the presynaptic α_2-receptors. Activation of these receptors then inhibits further release of NEpi. Therefore, it constitutes a negative feedback control system. Postsynaptic α_2-receptors are probably not involved in mediating cutaneous vasoconstriction. Local α_2-blockade has been shown to either decrease or not alter FBF (Cubeddu, 1988). Cubeddu (1988) noted that α_2-blockade increases FBF only when administered in pharmacologic doses and then probably by acting on sites not immediately adjacent to the synaptic cleft (Langer, Shepperson & Massingham, 1981). When FBF was increased with the α_2-blocker, yohimbine, FVR did not appear to change (Farrow, Mers, Banta, Steigerwalt & Lockette, 1990). Moreover, heart rate, systolic blood pressure and FBF responses to graded lower body negative pressure with and without yohimbine were parallel. Local forearm infusions of an α_2-agonist, in the presence of either an α_1- or α_2-antagonist, resulted in the conclusion that postsynaptic α_2-receptors do not mediate smooth muscle contraction (Thom, Calvete, Hayes, Martin & Sever, 1985). Collectively, these data suggest that α_1-, but not α_2-,

receptors are involved in control of FBF.

Actions of Prazosin, an α_1-Adrenergic Receptor Blocker

Clinically, selective α-receptor blockers have been a distinct improvement over nonselective α-blockers. Nonselective blockers were limited in their utility due to side-effects such as a marked sinus tachycardia and a rapid loss of blood pressure control (Grimm, 1989). Prazosin has an affinity for α_2-receptors at least 200 times weaker than that for α_1-receptors (Humphreys & Waite, 1989). Therefore by blocking only α_1-receptors, prazosin preserves the α_2-receptor-mediated negative feedback system of norepinephrine. As a result, it has a lower incidence of these side-effects. Unlike other adrenergic receptor blockers, this drug seems to possess no negative, and possibly some positive, effects on blood lipids (Humphreys & Waite, 1989). It affects neither renal blood flow nor glomerular filtration rate (Staneszek, Kellerman, Brogden & Romankiewicz, 1983), although the renin angiotensin system may be activated (McAreavy et al., 1981). The functional significance of the latter is unclear; Angiotensin II is an extremely potent vasoconstrictor, but many of its intracellular actions at the vascular smooth muscle cell are similar to those seen with α_1-receptor activation (Griendling, Tsuda, Berk & Alexander, 1989).

Prazosin acts by directly occupying the α_1-receptor and

its effects are due solely to this occupancy. It does not act centrally and does not antagonize central α-agonists (Andréjak et al., 1981). Prazosin is not a direct smooth muscle relaxant (Graham, Oates, Stoker & Stokes, 1977) but does produce both arteriolar and venous vasodilatation (Staneszek et al., 1983). Thus it acts to reduce total peripheral resistance with little or no direct effects on cardiac output or baroreceptor function (Mancia et al., 1980; Mulvihill-Wilson et al., 1983). Sasso and O'Connor (1982) have argued that prazosin depresses baroreceptor arc sensitivity as a fall in blood pressure, seen with their subjects, was unaccompanied by an alteration in heart rate. In animal hearts, prazosin seems to have a negative chronotropic effect (Staneszek et al., 1983); therefore, Sasso and O'Connor may have been misinterpreting their findings.

Subjects on prazosin need to be aware of the "first dose phenomenon." Some patients experience significant dizziness and sinus tachycardia when initially given the drug (Graham et al., 1976). This response is caused by postural hypotension with an impaired central venous return. These effects are usually transient and can be obviated by initial low-dose therapy with subsequent titration of the drug. Furthermore, the occurrence of these side-effects is at a rate similar to other types of antihypertensive drugs

(Grimm, 1989) and is similar worldwide (Török, Bìrò & Podmaniczky, 1989). Newer forms of α_1-receptor blockers seem to have fewer of these side-effects as they have a slower onset and their effects are more long-lived (Humphreys & Waite, 1989). For use in the present study, these alternative agents to prazosin are limited in that they have significantly weaker affinities for the α_1-adrenergic receptor.

Chapter III

Journal Manuscript
to
Journal of Hypertension

Effects of α_1-Receptor Blockade on The Hemodynamic Responses to Exercise in Young Hypertensives

Running Head: α_1-Blockade and Hemodynamic Responses

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ABSTRACT

The purpose of this study was to determine if α_1-adrenergic receptor blockade alters the hemodynamic response to exercise in young (<25 yr) male adult borderline hypertensives differently than in young normotensives. Five hypertensive (HTN, MAP>105 mmHg) and 7 normotensive (NTN, MAP<95 mmHg) college-age males underwent two 30 min bouts of cycle ergometry exercise at 50% $\dot{V}O_{2pk}$ in a warm (25°C, 50% rh) environment; one bout occurred followed α_1-receptor blockade with prazosin (HTN-α, NTN-α) and the other following placebo administration (HTN-p, NTN-p). At rest, HTN-p exhibited an elevated cardiac output ($\dot{Q}$, p=.024) and MAP (p=.007). Resting $\dot{Q}$ was similar for HTN-α and NTN-α. Resting heart rate (HR) was elevated more in HTN-α than NTN-α (p=.013) and not different for placebo. Resting and exercise forearm blood flows were similar between groups and altered similarly with prazosin. Exercise resulted in greater (p=.035) $\dot{Q}$ for HTN vs NTN (HTN-α > NTN-α; HTN-p = NTN-p). HR was higher (p=.043) with prazosin for both groups. Regardless of drug treatment, MAP was stable for NTN while it declined after 10 min of exercise in HTN. Rectal temperatures rose above baseline after 10 min. Since $\dot{Q}$ was similar between groups with placebo but not with α_1-blockade, and FBF, MAP, and HR were similarly altered between drug trials, it was concluded that young male

hypertensives have an elevated blood pressure due to an elevated $\dot{Q}$. In this group, α_1-blockade may reduce $\dot{Q}$ by reducing central venous return.

Keywords: essential hypertension, vascular resistance, exercise, plethysmography, cardiac output, mean arterial pressure

Introduction

Most investigators agree that the mechanism of elevation in blood pressure in young borderline hypertensives is primarily an elevated cardiac output with or without an elevated peripheral resistance [1,2,3]. If present, the elevated peripheral resistance is neurogenically mediated, as is the cardiac output [1]. With time, it is thought that the mean arterial pressure (MAP) becomes elevated due to an increased total peripheral resistance (TPR) that is, in turn, related to a structurally-altered peripheral vasculature [2,4,5,6]. The elevated cardiac output ($\dot{Q}$) seems to be normalized due to the elevation in TPR associated with a reduced venous return [5]. Thus, it appears that the neurogenically-mediated elevation in TPR and MAP seen in young or borderline hypertensives evolve to a structurally-based elevation as the duration or magnitude of hypertension continues.

Folkow [2] suggests that this shift occurs rapidly, in a matter of weeks. Others suggest that hypertensive subjects may have a structural abnormality that precedes the development of hypertension [7]. Still others suggest that the elevation in TPR remains, predominately due to neurogenically-mediated mechanisms [8,9,10]. If present, it is not clear where in the vasculature this neural mechanism is acting or what vasoreceptor types are being acted upon.

Therefore, this study was conducted to determine if α_1-adrenergically-mediated mechanisms contribute to the elevation in blood pressure in young borderline hypertensives and if this elevation is due to α_1-adrenergically-mediated alterations in the peripheral vasculature.

The α_1-blocker selected, prazosin, was chosen for a number of reasons. It is highly specific in that its affinity for α_1-receptors is at least 200 times that of α_2-receptors [11]. It is not a direct smooth muscle relaxant [12], does not alter presynaptic release of catecholamines [13] but it does produce both arteriolar and venous vasodilatation [14]. Additionally, prazosin can lower total peripheral resistance without directly affecting either cariac output [15] or baroreceptor function [16].

Finally, dynamic upright leg exercise was used in the present study as it does not alter muscle blood flow in the forearm [17]. Therefore, potential group differences in muscle blood flow [18] do not contaminate the findings of the investigation. Any alterations in forearm blood flow seen in the present study can therefore be isolated to the skin. As the cutaneous tissues lack ß-receptors [19], group-related or treatment differences in skin blood flow give inference to either the effects of exercise or α_1-receptor blockade.

Methods

Subjects

Twelve subjects were included, with seven considered normal volunteers (NTN) and five defined as essential hypertensives (HTN). The hypertensive subjects were selected on the basis of demonstrating a MAP consistently between 105 and 115 mm Hg, with the normotensive subjects having consistently less than 95 mm Hg. Baseline blood pressure determinations were made on two separate days following 15 min seated rest in a quiet environment. Arterial blood pressure was measured on the left arm using the auscultatory method. One technician measured all the subjects; if a subject had a borderline blood pressure, then a second technician performed a subsequent measurement. Additionally, if the subjects had no prior personal history of elevated blood pressure, then further blood pressure measurements were made. MAP was equal to diastolic blood pressure + 1/3 pulse pressure. As depicted in Table 1, the subjects were physically similar. All the subjects were under 25 years of age (range=19-24) with none possessing either a family history of hypertension or engaged in a program of regular aerobic exercise.

INSERT TABLE 1 ABOUT HERE.

Informed consent was obtained from each subject and the research protocol was approved by the Institutional Review Board of Virginia Polytechnic Institute and State University.

Study design

Functional capacity was initially determined with a maximal graded exercise test using a cycle ergometer (Bodyguard 990, Oglænd, Norway). Each exercise test began at a load of 60 W; and this was increased by 60 W at 2 min intervals until the subject was unable to maintain the appropriate pedalling cadence or requested to stop. Inspired-side minute ventilation was determined using a Parkinson-Cowan meter (Instrumentation Assoc., Inc., New York) and expired respiratory gas fractions were assessed using Applied Electrochemistry CD-3A and S-3A analyzers (Ametek, Pittsburgh, PA). The highest value recorded for exercise $\dot{V}O_2$ was accepted as the peak oxygen consumption ($\dot{V}O_{2pk}$). Each of two experimental trials consisted of the subject resting for 15 min in a seated posture on the stationary cycle and then exercising at a power output equivalent to 50% $\dot{V}O_{2pk}$ for 30 min in an environmental chamber controlled at 25°C/50% relative humidity. This mild stressor was utilized to augment the peripheral vasodilation of exercise. During each trial, the subject was under the influence of either prazosin, an α_1-adrenergic receptor

blocker (HTN-α, NTN-α), or a placebo (HTN-p, NTN-p). The drugs were given using a counter-balanced single-blinded procedure whereby half the subjects of each group received prazosin during the first trial and the other half received placebo. While the technician did not know specifically what drug had been ingested, subject signs and symptoms often alerted the technician to the particular pharmacologic agent used in a given trial.

To avoid the "first dose phenomenon" occasionally seen with prazosin [20] each subject reported to the laboratory the day before each test. Following measurements of heart rate (HR) and blood pressure (BP) during these visits, the subject ingested two capsules, each containing either 1 mg prazosin or placebo. The HR and BP were then assessed every 15 min for 1 hour to ensure the subject was tolerating the drug. On the day of the trial, the subject ingested two more capsules (2 mg) 3 hours before the test and one additional capsule (1 mg) immediately before the 15 minute pre-exercise baseline period.

Throughout each experimental trial, HR, BP, FBF, and $\dot{Q}$, were measured following the schedule shown in Figure 1. Heart rate was determined electrocardiographically using a CM_5 lead configuration. Using a thermistor inserted 10 cm past the anal sphincter, rectal temperature (T_{re}) was measured concurrent with BP. Blood pressure was measured as

previously described. Blood flow of the right forearm was assessed using venous occlusion plethysmography with a mercury-in-Silastic strain gage system [21]. The hand was excluded from the measurement by placing a pediatric BP cuff around the wrist and inflating this to >250 mm Hg 1 min before FBF measurements were taken. Reproducibility of the calibration curves used to determine the FBF values was $r > 0.99$. This was assessed by comparing calibration curves measured before and after each trial.

INSERT FIGURE 1 ABOUT HERE.

Cardiac output was assessed minute-by-minute using impedance cardiography (model 304A, Surcom, Inc., Minneapolis, MN). This instrument had a constant current oscillator frequency of 100 KHz at 4 ma rms, a voltage electrode input impedance which was linear from 10 to 80 Ω, and an automatic balance range for detecting impedance changes of +0.10 to +0.30 Ω. The methodological guidelines for using impedance cardiography were those suggested by the Society for Psychophysiological Research [22]. The cardiograph was interfaced with a personal computer (IBM PC/AT) such that 55 seconds of HR and impedance waveform data were collected and stored each minute.

A commercially available software package (Bio-

Impedance Technology, Inc., Chapel Hill, NC) was employed to perform ensemble averaging of the waveforms following beat-by-beat manual editing of the collected data. Here, individual complexes were excluded if the time interval between the R-wave of the ECG and the dZ/dt_{max} from the impedance cardiograph exceeded 200 ms. This procedure was necessary to remove artifactual stroke volume readings. The derived stroke volume value was then used to estimate $\dot{Q}$. Impedance cardiography is as reliable as more conventional methods of determining exercise $\dot{Q}$ [23]. It also offers the advantages of not altering the subject's response to exercise and allows for repeated measurements of $\dot{Q}$. While subject to criticism [22], the absolute $\dot{Q}$ measures obtained were used here.

The presence of α_1-adrenergic receptor blockade was confirmed prior to the start of the experimental trial using a cold pressor test. In this procedure, ice was applied to the subject's forehead for 1 min prior to and during three FBF measurements. The FBF values were then compared to those obtained during the 15 minute rest period. If present, the α_1-blockade would prevent the decline in FBF normally induced by cold pressor effects as a result of sympathetically-mediated vasoconstriction.

The data for key variables measured serially in the exercise trials were analyzed using repeated measures

analysis of variance. If present, significant between-group differences were located using either the Tukey or Fisher's LSD procedure. The drug effect and exercise time were considered within-group effects. An α level of .05 was chosen a priori.

Results

The results in Figure 2 show that resting FBF was lowest ($p>.05$) for HTN-p. With α_1-blockade, both groups responded with similar increases in FBF ($p=.055$). Compared to NTN, HTN exhibited significantly ($p=.007$) greater resting blood pressures with and without prazosin administration (Fig. 3). Both groups experienced a decline in resting MAP with α_1-blockade ($p=.042$). Prazosin resulted in significantly ($p=.008$) greater resting HR for both groups (Fig. 4). A significant drug-by group interaction ($p=.013$) indicated that HTN-α had higher HR than NTN-α with the α_1-blocker. Both groups had similar resting HR during the placebo condition. The resting $\dot{Q}$ of HTN-p was significantly ($p=.083$) greater than NTN-p. Following prazosin administration, this difference was removed (Fig. 5). Core temperature, estimated by rectal temperature (T_{re}), was elevated ($p<.001$) during the placebo trial for both groups (Fig. 6). After 10 min of exercise, this elevation became nonsignificant.

With exercise, FBF increased significantly for each

group (Fig. 2). Due to considerable variability in the blood flow responses, no intergroup differences were seen. The MAP increase found with exercise was blunted by prazosin ($p=.006$) with a significant ($p=.009$) time-by-group interaction effect observed which was attributable to a response decline in both HTN trials (Fig. 3). Here, NTN-α exhibited a stable but lowered MAP while the MAP of HTN-α declined continuously after 5 min of exercise. By min 20 of exercise, MAP for HTN-α and NTN-α were similar. With exercise, HR was elevated ($p=.043$) during the prazosin trial for both groups. While $\dot{Q}$ were significantly ($p=.035$) greater during exercise for HTN, prazosin affected the two groups differently ($p=.006$). Here, prazosin blunted the $\dot{Q}$ response in HTN but potentiated it in NTN (Fig. 5).

INSERT FIGURES 2 TO 6 ABOUT HERE.

Discussion

The results of this study suggest that α_1-receptor activation is involved in the central cardiovascular component of the borderline hypertension seen in college-age males. Cardiac output was significantly greater in HTN during the placebo condition and this difference was removed following prazosin administration. As evidenced by the

greater HR and the blunted MAP in HTN-α, the decline in $\dot{Q}$ was most likely due to a reduction in central venous return. While $\dot{Q}$ was higher in HTN regardless of drug treatment, the significant drug-by-group interaction indicated that α_1-blockade blunted the rise in HTN significantly more so than in NTN.

It does not appear that α_1-adrenergic mediated mechanisms are involved in the peripheral manifestions of borderline hypertension. While the resting MAP of HTN remained greater than NTN, prazosin lowered MAP similarly for both groups. Resting FBF was elevated for both HTN and NTN. The lack of a significant drug or group effect on FBF during exercise may have been due to the activation of a cutaneous vasodilator system [24] driven by elevations in core temperature [17]. This notion is supported by the similar elevations in T_{re} seen in both groups.

Only two other studies have evaluated the hemodynamic response of hypertensives to dynamic exercise when under the influence of prazosin [15,16]. In both, the exercise was mild (<75 W) and of brief duration (<10 min total). In these studies and in ours, exercise increased MAP and $\dot{Q}$ to a similar degree regardless of drug administration. However, resting MAP was reduced via different mechanisms with α_1-blockade. In our subjects, it was due to a fall in $\dot{Q}$ probably due to an attenuated stroke volume. The other

researchers noted essentially unaltered resting and exercise HR and $\dot{Q}$ after prazosin. Rather, MAP was decreased by reductions in total peripheral resistance of approximately 25 [15] and 50% [16]. In both studies [15,16], the subjects were considerably older than those in the present study. Additionally, it appears that the relative workloads were considerably lower [15] or higher [16] than our subjects. Consequently, it is possible that both the age difference [25] and the relative exercise intensity could have resulted in response patterns differing greatly from those we observed over the 30 min of exercise.

There is only a limited investigative literature on the effects of α-adrenergic blockade upon FBF in hypertensives. That which has been done has not involved dynamic exercise. Intra-arterial infusions of prazosin found to increase FBF forearm vascular conductance (FVC=FBF/MAP) to a greater extent in hypertensives than in the normotensive controls [26]. Calculated FVC for HTN was 112% that of NTN at rest, becoming 54% greater following drug infusion. In related work from the same laboratory, the resting FBF and FVC of age-matched normo- and hypertensives were compared following intra-arterial administration of phentolamine, a nonspecific α-blocker [8]. FVC of HTN was 80% that of NTN at rest and was unchanged after α-blockade. FBF declined similarly between groups. While the former study suggests that

sympathetic activation of α-adrenergic receptors is involved in the elevation of MAP and FBF in hypertensives, the latter does not. In the present research, the resting FBF was similar between HTN and NTN regardless of drug intervention. Thus, our findings disagree with a study involving prazosin but agree with that using a nonselective α-blocker.

Using subjects ranging in age from 25 to 63 years, the effects of graded increases in lower body negative pressure (LBNP) on the hemodynamic responses of hypertensive subjects with and without prazosin were studied [15]. Among other variables, FBF and forearm vascular resistance (FVR=MAP/FBF) were measured. Compared to the placebo trials, FBF was increased with prazosin and remained increased up to -40 mm Hg LBNP while FVR was lowered with prazosin and remained lowered during LBNP. However, only the intercept and not the slope of these responses was affected by prazosin. These findings support our results in demonstrating that, while resting FBF was increased with prazosin, the FBF response pattern to sympathetic nervous activation is unchanged.

This study evaluated both systemic and local vascular responses to α_1-adrenergic receptor blockade in the exercising hypertensive human. It was unique in that the subjects were age-matched, relatively young, borderline hypertensive, and undergoing an exercise bout typical of

that suggested for fitness development. As prazosin resulted in a greater blunting of both resting and exercise $\dot{Q}$ in HTN compared to NTN, it supports the interpretation that young borderline hypertensive subjects possess an elevation in MAP due, at least in part, to α_1-adrenergic mechanisms.

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Table 1. Clinical characteristics of groups studied.

	Normotensives	Hypertensives
Age (years)	22.1 ± 0.8	21.8 ± 0.5
MAP (mmHg)	108.8 ± 0.5	90.9 ± 1.7 *
SBP (mmHg)	140.5 ± 1.5	114.4 ± 1.2 *
DBP (mmHg)	92.9 ± 1.2	79.1 ± 1.4 *
Weight (kg)	70.9 ± 3.1	85.7 ± 6.0 +
Height (cm)	171.0 ± 15	177.0 ± 43
BMI (kg/m^2)	24.2 ± 1.3	27.2 ± 1.2
Body fat (%)	12.7 ± 1.6	11.8 ± 2.0
$\dot{V}O_{2pk}$ ($ml*kg^{-1}*min^{-1}$)	46.8 ± 2.9	44.7 ± 2.0
n	7	5

Data are expressed as means ± SEM. * $p<.0001$, + $p=.038$.

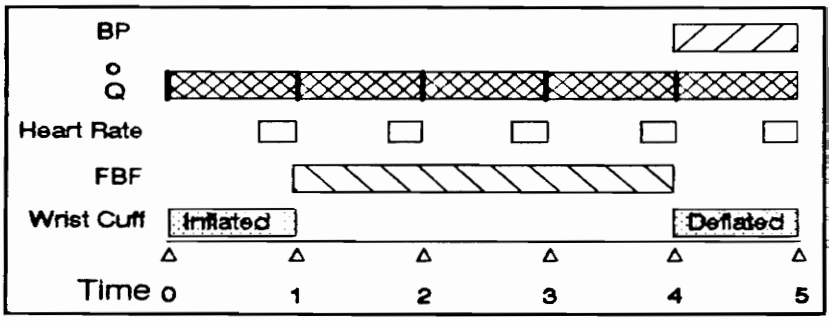
BP
Q
Heart Rate
FBF
Wrist Cuff
Inflated
Deflated
Time
0
1
2
3
4
5

Figure 1.

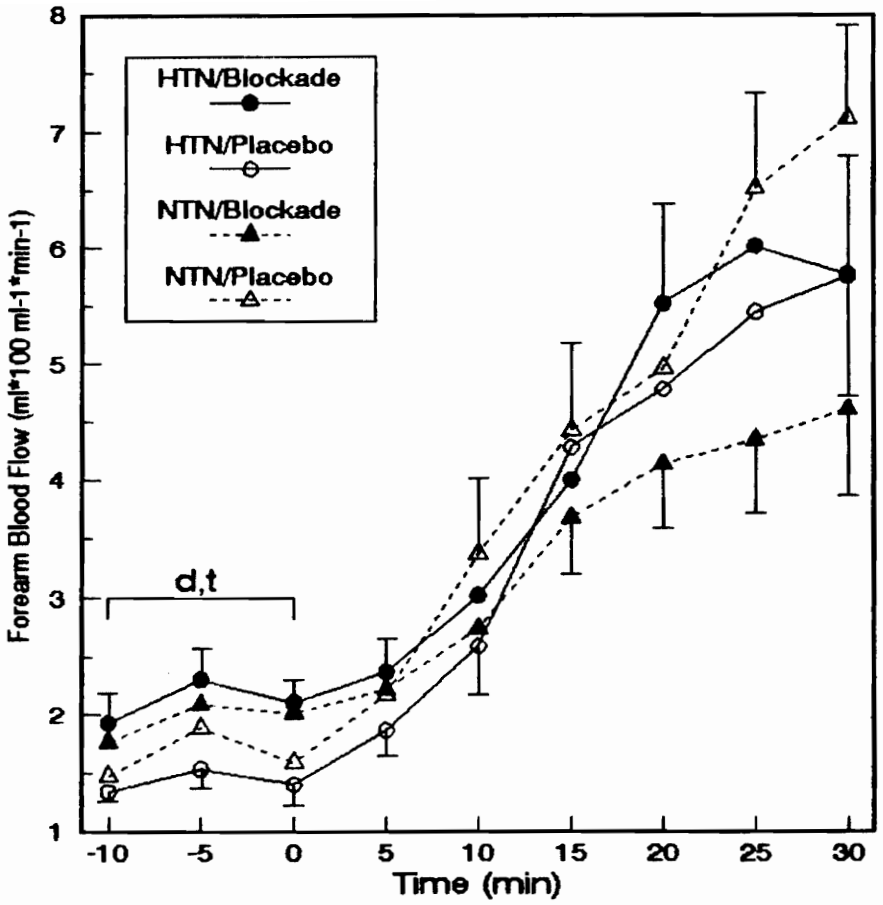
HTN/Blockade
HTN/Placebo
NTN/Blockade
NTN/Placebo
d,t
Forearm Blood Flow (ml*100 ml-1*min-1)
Time (min)
8
7
6
5
4
3
2
1
-10
-5
0
5
10
15
20
25
30

Figure 2.

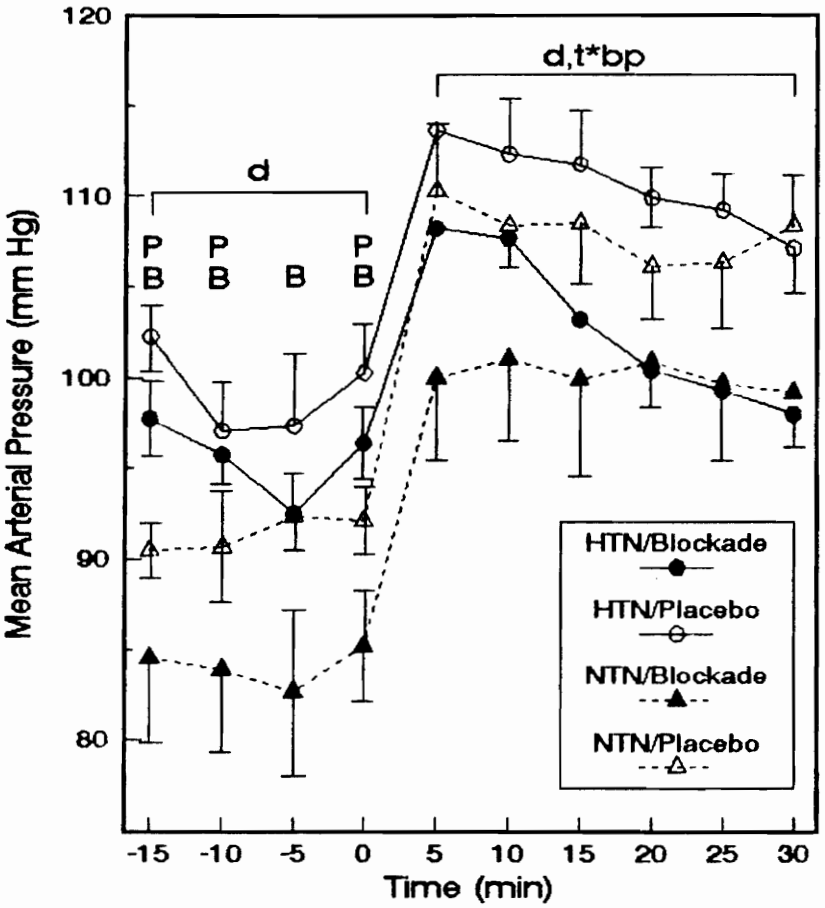
120
110
100
90
80
Mean Arterial Pressure (mm Hg)
d
d,t*bp
P
B
P
B
B
P
B
HTN/Blockade
HTN/Placebo
NTN/Blockade
NTN/Placebo
-15
-10
-5
0
5
10
15
20
25
30
Time (min)

Figure 3.

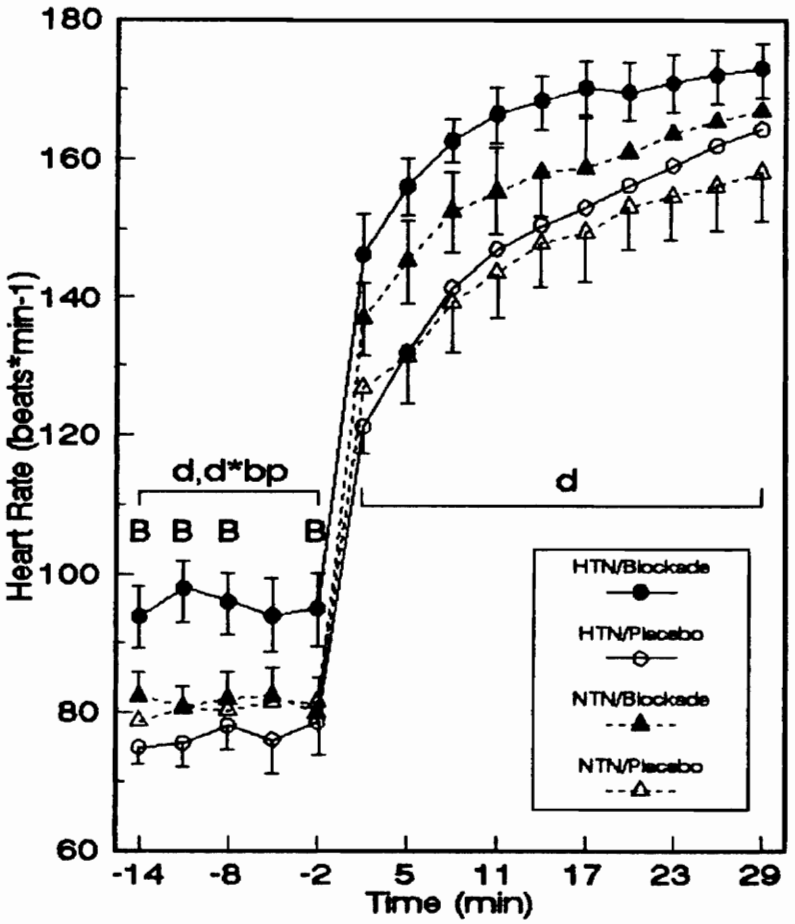
180
160
140
120
100
80
60
Heart Rate (beats*min-1)
d,d*bp
d
B B B B
-14 -8 -2 5 11 17 23 29
Time (min)
HTN/Blockade
HTN/Placebo
NTN/Blockade
NTN/Placebo

Figure 4.

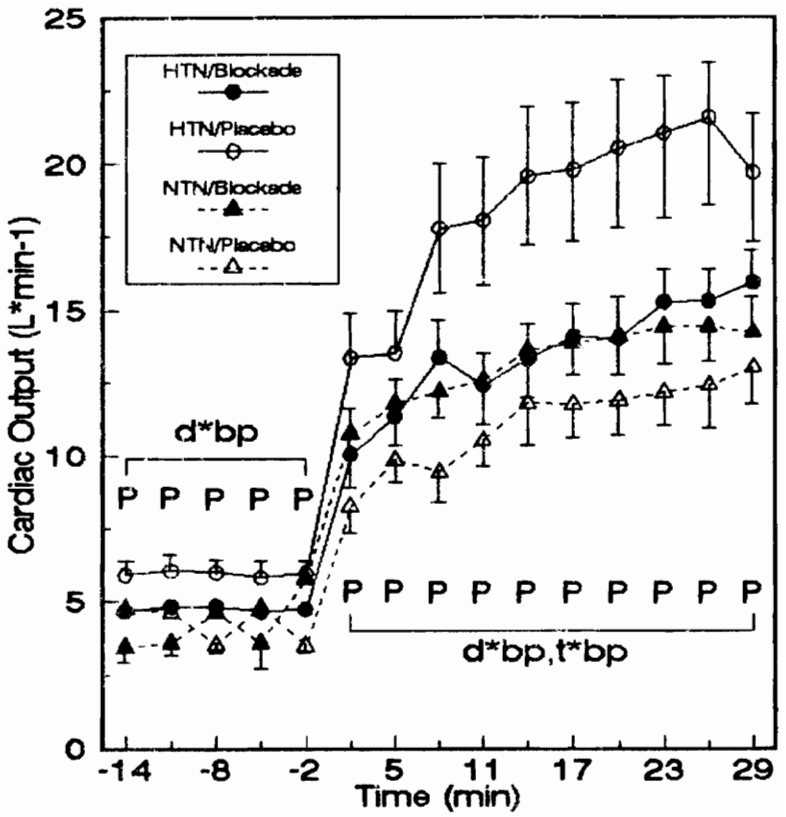
HTN/Blockade
HTN/Placebo
NTN/Blockade
NTN/Placebo
Cardiac Output (L*min-1)
25
20
15
10
5
0
d*bp
P P P P P
P P P P P P P P P P
d*bp,t*bp
-14
-8
-2
5
11
17
23
29
Time (min)

Figure 5.

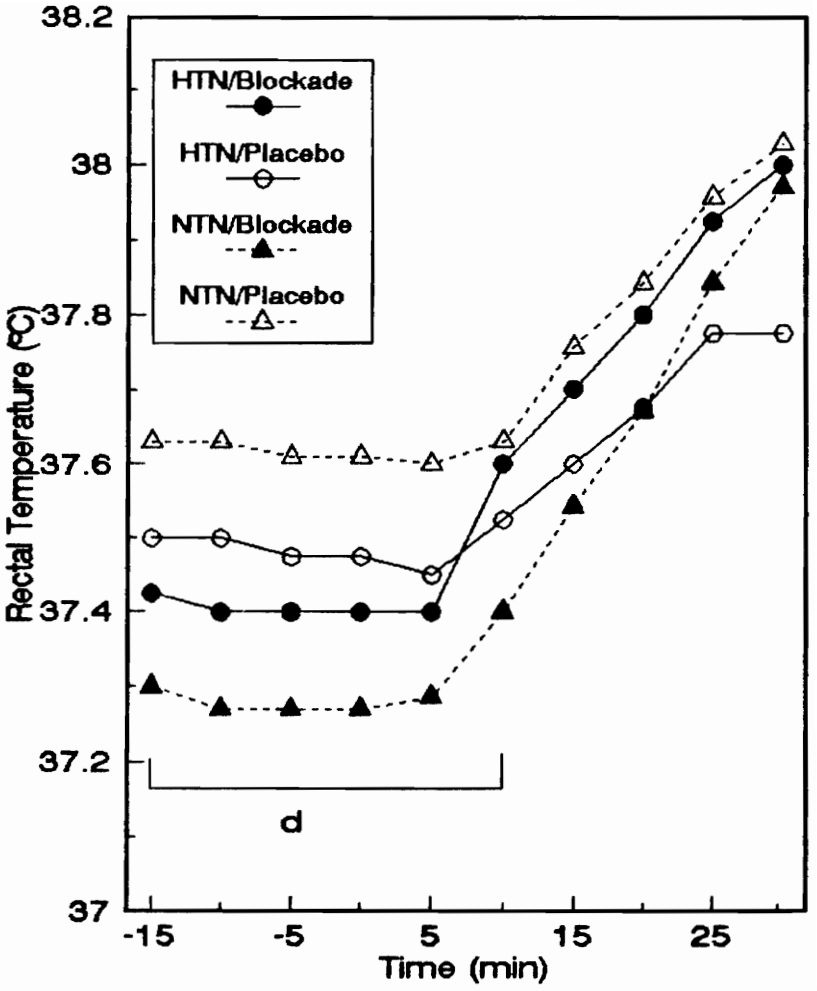
38.2
38
37.8
37.6
37.4
37.2
37
Rectal Temperature (°C)
HTN/Blockade
HTN/Placebo
NTN/Blockade
NTN/Placebo
d
-15
-5
5
15
25
Time (min)

Figure 6.

Figure Captions

Figure 1. Diagram of data collection schedule. Only one five minute interval is represented; this schedule was repeated throughout the trial.

Figure 2. Forearm blood flow (FBF) responses to α_1-adrenoceptor blockade and exercise in young male adults considered either hypertensive or normotensive. For the time-point where letters are presented, lower-case letters denote significant ($p<.05$) within-group differences (d=drug effect, t=exercise time effect). Values are means ± SEM.

Figure 3. Mean arterial pressure (MAP) responses to α_1-adrenoceptor blockade and exercise. Capitalized letters denote time-points where the groups differed significantly ($p<.05$; B=blockade trial, P=placebo trial). Legend for other symbols are presented in Figure 2.

Figure 4. Heart rate (HR) responses to α_1-adrenoceptor blockade and exercise. Letters are as in Figures 2 and 3.

Figure 5. Cardiac output ($\dot{Q}$) responses to α_1-adrenoceptor blockade and exercise. Legend for symbols are presented in Figures 2 and 3.

Figure 6. Rectal temperature (T_{re}) responses to α_1-adrenoceptor blockade and exercise. Letters are as in Figure 2 and 3.

Chapter IV

SUMMARY AND CONCLUSIONS

This study was designed to serve as a step in the investigation of the vascular pathophysiology associated with the elevation in blood pressure seen in hypertensives. Folkow (1982, 1987) is a frequently cited proponent of the notion that this elevation is "fixed" or relatively permanent. He proposes, and a considerable number of animal studies support, the theory that structural alterations in the peripheral resistance vessels result in, or are caused by, the blood pressure rise. Moreover, he suggests that these alterations occur rapidly, possibly within months in humans. Experimental support in humans is usually found using a group of hypertensives with a wide variety of ages. As the duration of hypertension is not usually known (or given in published work), one must assume that both the differences in this factor and the aging process alone account for some of this support.

When young (<30 years) hypertensives age-matched to a control group are used, this support is not nearly as strong. Furthermore, these subjects frequently fall into two distinct groups--those with an elevated total peripheral resistance (TPR) and a normal cardiac output (CO) versus those with a normal TPR and an elevated CO. The work of Sivertsson (Sannerstedt, Sivertsson & Lundgren, 1976;

Sivertsson, 1984) is a classic example. Using college-age men, he noted that subjects meeting the former criteria typically had a greater minimal peripheral resistance than the latter group. His 1984 follow-up study supported his earlier suggestion that the former group was further advanced in the progression of their hypertensive state and that the latter group would eventually become like them. Lund-Johansen (1989) followed a much larger group of subjects for 20 years and reported similar results.

In the 1976 study, Sivertsson noted that the parents of the "normokinetic" hypertensives also possessed a greater minimal resistance. Work by Takeshita's group (Takeshita, et al., 1982) and others (Borghi, Costa, Boschi & Ambrosioni, 1988) supports Sivertsson but suggests that the structural abnormality precedes the hypertension rather than arises because of it. Both studies imply that this abnormality is genetically determined. It is interesting to note that the spontaneously hypertensive rat, a widely used animal model for essential hypertension, can also manifest structural changes in the peripheral vasculature regardless of the blood pressure. Nevertheless, young human hypertensives may quite possibly fall into the two distinct groups suggested by Sivertsson with this distinction being only modestly related to the presence of hypertension.

This study attempted to avoid some of these potential

interpretative complications. All the subjects were relatively young, of similar body composition and fitness levels and none acknowledged the presence of a family history of hypertension. Based upon the resting cardiac output and heart rate data, the hypertensive subjects appeared to fit into Julius' "hyperkinetic" classification (1988) of hypertension. Consequently, these were ideal subjects to use to evaluate whether or not borderline hypertensives possess an α_1-receptor mediated mechanism behind their hypertension.

The present study evaluated the hemodynamic response of young borderline hypertensives to exercise when under the influence of prazosin, an α_1-adrenergic receptor blocker. The study design allowed for the relative isolation of a component of the forearm vasculature which has α_1-receptors as the predominant sympathetic efferent receptor--the skin. As far as the sympathetic nervous system is concerned, α-receptors are the primary receptor sites for vasoconstrictor activity. Thus, alterations in FVC during the study could be inferred to be in the cutaneous vasculature and, if not due to the prazosin administration, due to the presence of a chronically elevated perfusion pressure. Use of a normotensive control group allowed for direct hemodynamic comparisons to be made, both in terms of the elevated blood pressure and drug intervention.

The differences in FBF between the hypertensive group and the normotensive controls were neither statistically significant nor functionally critical. Post hoc statistical analyses indicated a low power (.30) suggesting the nonsignificance may have been due to a small sample size. Nevertheless, the results suggest that the differences were physiologically unimportant. In the resting state, the responses to prazosin were very similar between groups. This also held true for the exercise bouts. However, in the last half of the exercise bout, the FBF responses began to vary more between groups and between treatments. While these differences were not significant, the increased variability may have been due to the interaction between the α_1-blockade and the vasodilatory system (Kellogg, Johnson & Park, 1990) associated with a hyperthermic state. This suggestion is supported by the observation that all the subjects elevated their core temperature above baseline by 10 min of exercise.

The results of this study suggest that the notion of a peripheral vasculature involvement in the pathology of borderline hypertensives is erroneous. Had the FBF or FVC of the hypertensives been significantly lower than the normotensives following α_1-blockade, then this hypothesis would have been supported. This was not the case. Using primarily Ca^{++} channel blockers, other researchers (Hulthén,

Bolli, Amann, Kiowski & BÜhler, 1982; Robinson, Dobbs & Bayley, 1982; Schulte, Brown, Meyer-Sabellek, Gotzen & Distler, 1987; Schulte, Brown, Meyer-Sabellek, Wegscheider, Gotzen & Distler, 1988) performing related work have noted findings similar to this study. In those studies, the researchers evaluated the forearm vascular resistance (FVR) response to various vasodilator stimuli and noted that the hypertensive and normotensive subjects exhibited similar FVR.

Folkow (1988) refuted the works performed by Schulte's group (1987, 1988), mainly by suggesting that the pharmacologically-induced alterations in FVC or FVR would have resulted in greater increases in FBF in the hypertensive group were the elevation in TPR functional in origin. The hypertensive group possessed greater forearm blood flows than the control group when both were under the influence of prazosin. These were not, however, statistically significant. Consequently, Folkow's assertions (1988) are supported here.

A number of related hemodynamic variables were monitored (heart rate, cardiac output, blood pressure) in addition to the FBF measures. The responses seen with the prazosin administration strongly implicate α_1-adrenoceptors as being involved in the blood pressure elevation in young hypertensives. Cardiac output was significantly elevated in

the hypertensive group throughout their placebo trial. During the prazosin trial, the response of this variable was nearly identical that of the normotensive group. At rest, the hypertensives possessed significantly greater heart rates with prazosin than with placebo. This was not the case with the control group. Thus, it appears that stroke volume was reduced with the prazosin in the hypertensive group but not the normotensives.

The significant drug and time-by-group interaction effects seen with MAP during exercise also suggest that the hypertensive groups were affected to a greater degree by the α_1-blocker. At rest, the prazosin affected each group to a similar degree. However, the differences in exercise MAP became nonsignificant while the drug effect remained. The timing of the interaction coincided closely with the rise in T_{re}. With T_{re}, the significant drug effect disappeared once T_{re} began to rise. The vasodilator system (Kellogg, Johnson, & Osiba, 1990) probably became the predominant mechanism for vasodilation at this time. This vascular modulation would effectively negate any differences in peripheral blood flow seen between prazosin and placebo. While speculative, it seems plausible that borderline hypertensives differ from normotensives in the nature or magnitude of the response of this vasodilator system. One possiblity would be that the sensitivity of the

cardiopulmonary baroreceptors in young borderline hypertensives may be reduced. As it appears that the vasodilator system is linked to these receptors and their unloading seems to reduce the effects of this system (Kellogg, Johnson, & Osiba; 1990), the reduced sensitivity combined with the α_1-blockade may have resulted in an unimpaired activation of the vasodilator system.

Recommendations for future research

The following are general observations based upon the present study and the associated review of literature. The suggested studies are felt to be plausible, worthwhile studies that a competent graduate student could perform.

1. It appears that more work should be done in human essential hypertensives. The phenomenon of spontaneous hypertension seen in the rat has been extensively studied. Unfortunately, humans are not rats, being considerably more diverse in their lifestyles and genetic make-up. Rather than being a weakness of a study, more thorough accounting of these variables may lead to findings unique to humans. An example is the aforementioned classfication of young borderline hypertensives into groups based on their TPR, cardiac output, and family history.
2. Repeat the present experiment but attempt to control for both intracellular release and extracellular influx

of Ca^{++}. This could be done with local iontophoretic applications of bretylium, an inhibitor of pre-synaptic norepinephrine release, combined with oral ingestion of Ca^{++}-channel blockers.

3. Repeat the study but salt-load the subjects to inhibit the renin-angiotensin system maximally.

4. Repeat the study but include:

   a. a group of older borderline hypertensives and controls to evaluate better the effects of the duration of hypertension, or

   b. a group of young hypertensives with established, e.g. pronounced hypertension, to evaluate better the effects of the magnitude of hypertension, or

   c. a group of more fit subjects to determine if fitness development alters the FVC response to prazosin, or

   d. as an additional treatment, graded lower body negative pressure to unload the cardiopulmonary baroreceptors and/or neck suction to alter carotid baroreceptor activity.

5. Perform investigation 4d, above, but in both neutral and hyperthermic environments to investigate further the active vasodilator system in essential hypertensives.

6. Explore further the parental influence on the peripheral vasculature.

7. Determine the mechanism(s) behind the "normokinetic" and the "hyperkinetic" forms of essential hypertension. Are these linked somehow to the parental/genetic influence?
8. Attempt to evaluate the receptor density of α-receptors in the subjects studied. This possibly could be done using tritiated yohimbine and prazosin to bind to platelet α-receptors in blood samples.
9. Evaluate differences between FVC and calf vascular conductance in the supine and upright postures. Are both altered to the same extent in hypertensives? As the calf is exposed to a greater resting pressure in normal subjects, is the effect potentiated in hypertensives?

Conclusions

This study suggests that young borderline hypertensives possess an elevation in their blood pressure as a result of an elevation in their cardiac output. Their cardiac outputs were considerably higher than matched normotensives and this difference was abolished with α_1-receptor blockade. FBF did not differ between groups either in the presence or absence of prazosin. Consequently, it appears that any differences in the peripheral vasculature of borderline hypertensives do not play a role. The response of the hypertensive subjects to 30 minutes of moderate intensity exercise in a mildly

warm environment differs from control subjects in that they experienced a relatively declining MAP compared to a stable response in the normotensives. This response may be linked to the active system modulated by thermoregulatory reflexes.

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APPENDIX A

The Informed Consent and Divisional Approval

The Informed Consent

Title of Study:

Effects of α_1-Receptor Blockade on Forearm Blood Flow Responses to Exercise in Young Normotensives and Hypertensives

The purposes of this experiment include:

1) Determining if the cardiovascular response (assessed by the measurement of heart rate, blood pressure, cardiac output, and forearm blood flow) to dynamic exercise, i.e. cycling, differs between normotensives and hypertensives when under the influence of α_1-adrenergic receptor blockade.

2) Determining if the nature of the changes in the peripheral vasculature, due to this blocker, differs between young normotensives and hypertensives.

I voluntarily agree to participate in this testing program. It is my understanding that my participation will include:

1) The initial determination of a number of physiological measures:

a. average blood pressure (I'll have my blood pressure measured daily for two days.)

b. maximal oxygen consumption [($\dot{V}O_{2peak}$) This is a measure of my aerobic fitness and entails my exercising maximally on a cycle ergometer. This will be done only once, at the beginning of the study.)

c. height and weight

d. per cent body fat (This will be done using a skinfold technique.)

2) During the data collection part of this study, I will be asked to come to the lab for two exercise sessions. These sessions will be identical but that I will exercise under the influence of a different drug each time. One drug I will take will be a placebo, a "sugar pill," while the other is prazosin, an α_1-adrenergic receptor blocker.

For each bout of exercise, heart rate (HR) will be measured electrocardiographically using 3 electrodes applied to my torso. Blood pressure (BP) will be measured by the auscultatory method, the method used in most doctors' offices. Forearm blood flow (FBF) will be determined using the noninvasive mercury-in-silastic strain gauge plethysmography method. In this method, a silastic band will be lightly wrapped around my forearm. Blood flow to this arm will be blocked briefly with a blood pressure cuff inflated to 250 mm Hg and then released. Cardiac output (CO) will be determined using the CO_2 rebreathing method. For this method, I will breathe a mixture of air that is predominately oxygen but with a small quantity of carbon dioxide (≈10%). I will breathe this mixture only about 10 breaths.

The exercise will consist of biking on a cycle

ergometer for 30 minutes at 50% of my $\dot{V}O_{2pk}$ as assessed by the test determining my maximal oxygen consumption. FBF will be assessed for 3 of every 5 minutes of the exercise session. Blood pressure will be assessed every 5 minutes. CO will be assessed after 15 and 30 minutes of cycling. Core, skin and environmental temperature will be measured every 5 minutes. Core temperature will be assessed via a rectal thermistor. I will insert this thermistor, a lubricated thin plastic-coated flexible wire, approximately 10 cm past my rectal sphincter. Skin temperature will be assessed by dime-sized electrodes applied to 4 skin sites (chest, upper arm, thigh and lower leg).

I will perform these exercise bouts in an environmental chamber. This chamber will be heated to 25°C (77°F) and 50% relative humidity.

3) The day before, three hours prior to and immediately before these exercise sessions, I will ingest 2 capsules orally. One of these capsules contains a placebo (it does nothing to you) while the other is a drug: an α_1-adrenergic receptor blocker (prazosin). This drug "covers" receptors that are part of the sympathetic nervous system. Blocking these receptors is one way to lower blood pressure. The side-effects of this drug are mild but vary from person-to-person. Most frequently, people become slightly light-headed due to the drop in blood pressure. Rarely, people

experience an increased heart rate. The reported occurrence of people having an increase in HR over 100 beats per minute is less than 5%, while that of people fainting due to the drop in BP is less than 1%. These effects are transient and occur when the drug is first given; I will be monitored for 60 minutes after administration to make sure I am feeling well. I know that I am not to exercise during the time between ingesting the first capsule and reporting to the laboratory the next day.

I understand that participation in this experiment may produce certain discomforts and risks including:

1) temporary muscle soreness may be a consequence of these exercise sessions,

2) some degree of heat intolerance due to exercising in the heat, and

3) some degree of hypotension, e.g., light-headedness, due to the effects of the drug and/or the exercise in the heat.

Certain personal benefits may be expected from participation in this experiment. These include:

1) quantification of my aerobic level of fitness, and

2) determination of possible mediating factors that may be involved in my high blood pressure.

I understand that any data of a personal nature will be held confidential and will be used for research purposes

only. I also understand that these data may only be used when not identifiable with me.

I understand that I may abstain from participation in any part of the experiment or withdraw from the experiment should I feel that activities might be injurious to my health. The experimenter may also terminate my participation should he feel that the activities might be injurious to my health.

I understand that it is my personal responsibility to advise the researchers of any pre-existing medical problem that may affect my participation or of any medical problems that might arise in the course of this experiment and that no medical treatment or compensation is available if injury is suffered as a result of this research. A telephone is available which would be used to call the local hospital for emergency service.

I have read the above statements and have had the opportunity to ask questions. I understand that the researchers will, at any time, answer my inquiries concerning the procedures used in this experiment.

Date _____ Time _____

a.m./p.m.

Participant signature

_____

Witness _____

Project Director Warren D. Franke Telephone 231-5006/961-0141

Human Subjects Chairman Dr. Charles Baffi Telephone 231-8284

Dr. Ernie Stout, 301 Burruss Hall, 231-5281

To receive the results of this investigation, please indicate this choice by marking in the appropriate space provided below. A copy will then be distributed to you as soon as the results are made available by the investigator. Thank you for making this important contribution.

_____ I request a copy of the results of this study.

Participant name _____

Local address _____

_____

Local phone number _____

CERTIFICATE OF APPROVAL FOR RESEARCH
PROPOSAL IN THE DIVISION
OF HPE

Submitted to

Charles Baffi
Chairman, Division Human Subjects Committee and/or
Chairman, Institutional Review Board

by

Warren Franke
Principal Investigator

Title:

Effects of α_1-Blockade on Forearm Blood Flow Responses to Exercise in Young Normotensives and Hypertensives

Background/Scientific Justification:

It is well recognized that hypertensive subjects have an elevated total peripheral resistance. The etiology of this elevation is uncertain but is probably due to either structural and/or functional alterations in the peripheral vasculature. Currently, it is thought that young hypertensives have functional alterations but older hypertensives have structural alterations. The time-course of this shift is unknown. Studies with hypertensives have yielded mixed results; FBF increased in some studies but not in others. Frequently, the age of these subjects was quite variable and, therfore, age alone may have played a role in the results. With the present investigation, only young (<30 years of age) subjects will be used to obviate this methodological problem. Cutaneous vascular smooth

muscle tone is dependent upon α_1-adrenergic mediated mechanisms. Blocking this tone pharmacologically enhances FBF in normotensives. Therefore, by using this form of blocker, the presence of an elevated peripheral resistance due to α_1-mediated mechanisms can be determined in young essential hypertensives.

Purpose:

The purpose of this study is to determine the effects of alpha$_1$-adrenergic receptor blockade on the forearm blood flow responses to exercise in young normotensives and hypertensives.

Experimental Methods and Procedures:

For this study, hypertension is defined as a mean arterial pressure $\geq$ 105 mm Hg from measurements made on two separate day. This hypertension can not be secondardy, i.e. renovascular, in nature.

Initially, subjects will undergo a graded maximal exercise test on a bicycle ergometer designed to elicit $\dot{V}O_{2pk}$. This test will consist of sequential 2-min stages of exercise with increases in workload of 30 W with each stage. Heart rate (ECG), BP (auscultatory), $\dot{V}O_2$ and cardiac output (CO_2 rebreathing method) will be monitored during each stage.

No earlier than one week later, the subject will return to the lab for receipt of one of the two experimental

treatments. Both treatments will be identical but for the randomized, double-blind administration of either prazosin or a placebo. The second treatment will be administered one following the first and at the same time of day. On the day before, the subject will report to te lab and ingest, under medical supervision, a capsule containing 1 mg prazosin. Prazosin can cause a "first dose phenomenon" wherein the subject exhibits symptomatic hypotension and reflex sinus tachycardia. This effect occurs in less than 5% of subjects with syncope occurring less than 1% of the time (Grimm, HTN 13:I-131, 1989).

On the day of testing, the subject will self-administer another capsule 3 h before reporting to the lab. After coming to the lab, he will ingest another capsule. The subject will be outfitted with a rectal thermistor, four skin thermistors, ECG electrodes and the strain gauge. He will then undergo 15 min of seated rest in the environmental chamber heated to 25°C, 50% rh. Thereafter,the subject will exercise for 30 min at 50% $\mathring{V}O_{2pk}$. FBF will be measured for 3 of every 5 min. BP will be measured immediately after the FBF measurement. CO will be assessed at the 15th and 30th min of exercise. Core, skin and environmental temperature will be measured every 5 min while the subject is in the chamber.

Statement describing level of risk to subjects:

Risks associated with this study include:

1) temporary muscle soreness may be a consequence of these exercise sessions,

2) some degree of heat intolerance due to exercising in the heat and

3) some degree of hypotension, e.g. light-headedness, due to the effects of the drug and/or exercising in the heat.

Procedures to minimize subject risk:

Avoidance of the first dose phenomenon during the exercise sessions will be done by administering the drug during a period of inactivity. Dr. Michael Payne has reviewed this study and approved the methods. All other procedures are commonly performed and pose no inherent risk to the subject other than those present in performing exercise.

A similar study, involving the same quantity of prazosin but using more fit subjects exercising at a higher relative intensity in a hot environment, has been performed by the principle investigator. No negative side-effects occurred to any of the subjects. As the present study involves a relatively low intensity of exercise and the heat stress is minimal, negative side-effects are not anticipated. Note that the earlier study had been approved by the IRB.

Risk/benefit ratio:

The subject will have his $\dot{V}O_{2pk}$ determined as well as the determination of the presence of an elevated peripheral resistance. Moreover, if present, the nature of this elevation will be determined. The risks of this study are minimal. As noted, the incidence of adverse side-effects with this drug are low (<5%) and can be treated symptomatically. Otherwise, the other procedures (FBF, BP, CO measures) pose no special risk to the subject.

APPENDIX B

Health History Questionnaire

Health History Questionnaire

Name: _____ ID#: _____

Sex: _____ Age: _____ Phone: _____

Please circle year in school: 1 = Freshman 2 = Sophomore

3 = Junior 4 = Senior 5 = Grad School

Medical History

Have you ever had:	Yes	No
Heart disease or heart problems	_____	_____
Lung disease or difficulty breathing	_____	_____
Difficulty with cold hands or feet	_____	_____
Stroke	_____	_____
Kidney disease	_____	_____
High cholesterol	_____	_____
Diabetes	_____	_____
Any operations (type/date)	_____	_____

_____

_____

Have you ever had a blood pressure reading above normal (≥140/90)?	_____	_____
Have you ever been diagnosed as having hypertension?	_____	_____
Are you being treated for hypertension?	_____	_____

If "yes," please describe.

_____

_____

Have you ever had problems with exercising in the heat? _____ _____

If "yes," please describe.

_____

_____

Please list any medications you are currently taking.

_____

_____

Are you allergic to any medications, drugs or foods? If yes, please list.

_____

_____

Has anyone in your family ever been diagnosed as having any of the following?

		Yes	No
Relationship	Age		
	High blood pressure/hypertension	_____	_____
_____	Heart attack/heart disease	_____	_____
_____	Stroke	_____	_____
_____	Diabetes	_____	_____
_____	Kidney disease	_____	_____

Health Habits

How often do you:

drink caffeinated tea, coffee or soda _____ times per day

drink alcohol _____ times per day

add salt to a meal before testing _____ times per day

smoke cigarettes _____ times per day

How much stress do you experience on a daily basis?

1 2 3 4 5

A lot Average None

Exercise Habits

During the past three (3) months, have you engaged in a program of regular physical exercise? _____ Yes _____ No

If "yes," please list below any activities (competitive, recreational or leisure) which you participated in during an average week in the past month.

Activity	Frequency (x/week)	Duration
_____	_____	
_____		
_____	_____	
_____		
_____	_____	
_____		

Do you have any orthopedic problems which may restrict your ability to participate in exercise consisting of stationary cycling?

If "yes," please explain. _____ Yes _____ No

_____

_____

Miscellaneous

What times are good for you in terms of being able to exercise? Allot 2 hours for each test.

APPENDIX C

Detailed Methodology

DETAILED METHODOLOGY

This appendix describes the methods used in the selection of subjects, determination of their functional capacity, and the procecedures used in the experiment. It is intended that this section allows for the replication of this study by another investigator.

Subject Selection

Normotensive subjects were recruited from the student population of Virginia Polytechnic Institute and State Univeristy. By use of a health history questionnaire (Appendix B), a family history of hypertension and coronary heart disease was determined. If the former were present, the subject was excluded from the study. Subjects with a high degree of physical activity, i.e., aerobic exercise greater than three times weekly totalling more than 90 min duration, were also excluded. Subjects with a high $\mathring{V}O_{2pk}$, but not active to this extent, were not excluded. Blood pressure determinations for these subjects were performed at the time of the initial $\mathring{V}O_{2pk}$ measurement and on another occasion. Body composition and frame size were assessed immediately following the determination of functional capacity. Subjects were excluded if their mean arterial pressure (MAP) was greater than 95 mm Hg.

Hypertensive subjects underwent the same procedures. They were not excluded from the study if they had a family

history of hypertension. They were, however, similarly limited in their degree of physical activity. Subjects were accepted into this group only if their MAP was between 105 and 115 mm Hg. It was determined in the same manner as with the normotensive group.

At the time of the maximal exercise test, each subject was fully apprised of the nature of the study, the requirements of their participation and given a brief tour of the data collection site. Subjects were also given a written explanation of the study and completed an informed consent (Appendix A) and medical history before participating.

Determination of Functional Capacity

Subjects were asked to refrain from any vigorous activity in the preceding 24 hrs and to refrain from eating 3 hrs prior to the test. Upon arrival, each subject was weighed and his height determined. He was then fitted with three electrodes in a CM_5 lead configuration. A blood pressure cuff was applied to the right arm.

Using a cycle ergometer (Bodyguard 990, Oglænd, Norway), the exercise test itself consisted of graded 60 W increases in workload. Each stage was two min in duration with the subject being given considerable verbal encouragement throughout. Test termination occurred when the subject stopped volitionally or was unable to maintain

the 60 rpm cadence. Visual and auditory cues were used to ensure the subject pedalled at 60 rpm.

Inspired-side minute ventilations were determined using a Parkinson-Cowan meter (Instrumentation Associates, Inc., New York, NY). The meter was connected to a non-rebreathing two-way valve (#2700, Hans Rudolph, Kansas City, MO) via a three-foot length of 1 3/8" I.D. corrugated tubing. The subject inhaled through this port and exhaled through a second. This latter valve was connected to a mixing chamber via a four-foot length of the tubing. Gas samples were continuously extracted from the chamber at a total rate of 1 $L*min^{-1}$. Gas analysis was performed continuously using Applied Electrochemistry CD-3A and S-3A/1 analyzers (Ametek, Pittsburgh, PA) for CO_2 and O_2, respectively.

During the test, the subject's electrocardiogram (ECG) was monitored continuously. Heart rate (HR) was determined using the six-second method from hard copies of the ECG obtained during the last 15 s of each minute. Blood pressure (BP) was determined at the beginning of the second min of each stage using the auscultatory method. A general rating of perceived exertion was obtained during the last 20 s of each stage. Fe_{CO2} and Fe_{O2} were read from the analyzers during the last 15 sec of each min and V_I was assessed immediately after each min; both were manually recorded. Using an in-house computer program (courtesy of

.H. Williams), these values were corrected for STPD and $\dot{V}O_{2pk}$ was determined following termination of the exercise test.

Accuracy of the Parkinson-Cowan meter was determined prior to the test by drawing 90 L of ambient air through the meter using a calibrated 3 L syringe (Hans Rudolph). The gas analyzers were calibrated before the test using known gases and re-checked following the test. If needed, the dessicant was replaced before each test. This dessicant was in-line between the mixing chamber and the vacuum pumps pulling air into the gas analyzers. Calibration of the resistance of the cycle ergometer was done before each test using exact weights.

Experimental Procedures

Preliminary procedures.

The day before an experimental trial occurred, the subject reported to the laboratory. Following a few min seated rest, seated and standing BP and HR were determined. The subject was then given two capsules to ingest. If the latter, each capsule contained 1 mg of the drug. Seated and standing BP and HR were determined at 15 min intervals over the succeeding hour. If the subject was not experiencing adverse side-effects, he was allowed to leave. Otherwise, he was monitored for an additional period of time. The subject was cautioned not to exercise or engage in vigorous

activity for the next 24 hr. Note that neither the subject nor the principle investigator knew whether these capsules contained either the placebo or prazosin; however, subject signs and symptoms often gave the researcher insight into the pharmacologic agent administered.

The following day, the subject ingested two more capsules three h before reporting to the laboratory. During this three hr period, he was allowed to ingest noncaloric beverages only. Upon arrival to the laboratory, the subject disrobed and was weighed nude. He then self-inserted the lubricated rectal thermistor to a depth of 10 cm past the anal sphincter. He then entered the environmental chamber where he was outfitted with three spot electrodes (for monitoring HR) and four band electrodes (for cardiac output determination via impedance cardiography). The three limb thermistors were applied to the skin using wide elastic bands with attached wire loops. Each thermistor was held under a loop, thereby permitting unhindered sweat evaporation. The chest thermistor was attached using an ECG electrode. The subject then sat upon the cycle ergometer.

The BP cuff was applied to the left upper arm. The right arm was elevated above heart level and suspended at the wrist and elbow using wide inelastic straps. The mercury-in-silastic strain gage was wrapped around the forearm at a site usually 1/3 the forearm length distal to

the elbow. A pediatric BP cuff was attached to this wrist and an adult cuff was applied to the upper arm. At this time, the subject ingested the fifth capsule.

Data collection.

The wrist cuff was inflated to > 250 mm Hg for 1 min and ice was applied to the subject's forehead for 2 min. At the end of these 2 min, three measures of FBF were obtained using mercury-in-silastic strain gage plethysmography (Whitney, 1953). This technique is described in more detail later in this appendix. The FBF determinations were done to ascertain if the capsules were producing the desired effect, i.e. FBF would not be altered if prazosin had been administered but would decline if the placebo was.

Thereafter, resting data were collected for 15 min. Within each 5 min block of time, the data were collected as shown in Table 1.

Within each 5 min period, FBF was measured 6-8 times. HR was measured throughout each min via a software package determining cardiac output (BIT, Inc., Chapel Hill, NC) from the impedance cardiograph measures and at the end of each minute using the same approach as in the assessment of functional capacity. With the former, HR was determined on a beat-to-beat basis using the R-R interval. Finally, the temperature and relative humidity were measured during the fifth min.

At the end of the 15 min rest period, the subject began cycling at a workload corresponding to 50% $\mathring{V}O_{2pk}$. The subject exercised for 30 min at this workload with the variables assessed during the resting period being measured in the same manner. The subject was allowed room temperature water to drink ad libitum. At the completion of the exercise bout, the workload was reduced to approximately 60 W and the subject was encouraged to cycle for several minutes before exiting the environmental chamber. The subject was then weighed again to assess fluid loss with the mass of water ingested being considered in this assessment. He was monitored for 15-30 min thereafter; if no side-effects were manifested, he was then allowed to leave.

These procedures were repeated 4-7 days later using the other drug. Thus, every subjects exercised in this manner under the influence of both prazosin and placebo. Drug administration for the hypertensive group was determined using a binary random number generator with 1/2 the subjects receiving prazosin first and 1/2 receiving placebo. At this time, it was thought that 10 subjects would be in each group. The normotensive group was given the drugs in the reverse order such that subject 10 in the normotensive group followed the same order of drug administration as subject 1 in the hypertensive group.

Impedance cardiography.

As a method to determine cardiac output, this procedure is relatively uncommon in the field of exercise science. Therefore, a brief explanation of the method will be given here. For more detailed explanations see Sherwood and co-workers (1990) and Miles and Gotshall (1989). Note that values obtained with this technique are as representative of cardiac output as are more common techniques, such as the CO_2 rebreathing method (Miles & Gotshall, 1989). This method has the distinct advantage of allowing for serial measures that do not interfere with other physiologic parameter.

With impedance cardiography, four band electrodes are applied to the patient. Two are applied to the neck, one more proximal to the head (#1) and one more distal (#2). Two are attached to the torso, one at the level of the xiphisternal joint (#3) and one several centimeters below (#4). A constant, sinusoidal alternating current flows through electrodes 1 and 4.

The impedance signal can be expressed as an analogue of Ohm's law:

$$Z = V/I$$

where Z is impedance, V is voltage and I is current. Electrodes 2 and 3 are used to detect changes in the voltage of the current flowing between electrodes 1 and 4. As a result, electrodes 1 and 4 need to be at least 3 cm apart

from electrodes 2 and 3 to avoid nonlinearities in this electrical field (Miles & Gotshall, 1989).

For this study, the important causative factor altering the voltage is that due to alterations in the local quantity of blood, i.e., the stroke volume. Three components are important in determining SV. The largest is the basal thoracic impedance (Z_o) which represents the total conductance of the thoracic medium. Other factors affecting Z are respiratory activity and the blood volume ejected during systole. The latter alters Z < 1% while the former can account for 3% of the change in Z (expressed here as dZ). Outputs from the impedance cardiograph are Z_o, dZ and dZ/dt, which is the first derivative of dZ with respect to time. Using the formula of Kubicek and colleagues (1966), these values and that of the distance between electrodes 2 and 3 are used to determine SV.

The method of SV determination used in the present study is ensemble averaging of the impedance signals. This method is as valid as beat-to-beat averaging (Kelsey & Guethlein, 1990) but offers the advantage of attenuating and/or filtering artifact resulting from respiration and movement. Ensemble averaging is simply the computerized averaging of the dZ/dt and ECG signals over a number of heart beats. The R wave of this averaged ECG signal is then used as a reference point in determining the onset of the

averaged dZ and dZ/dt. In the present study, the data from 55 seconds of cardiac activity were used to determine CO for each minute. Beat-by-beat post-test editing resulted in individual cardiac cycles being excluded from this analysis. Criteria for exclusion were the presence of outlying data points for dZ/dt, and/or the distance from the R wave of the ECG and the B point of the dZ/dt complex exceeding 200 ms. The B point represents the onset of left ventricular ejection. For each minute, at least 20 cardiac cycles were acceptable.

Mercury-in-silastic strain gage plethysmography.

While this technique is the most commonly employed for the non-invasive measurement of limb blood flow, it is relatively new to this laboratory. Therefore, a brief description of the technique employed here will be given. Typically, the strain gage is electrically connected to the plethysmograph; the plethysmograph outputs to both a voltmeter and a strip-chart recorder. The plethysmograph sends a small current flow through the strain gage and monitors the alteration in resistance to this flow which occurs due to changes in the length of the gage. This alteration is displayed on the voltmeter and a hard copy is obtained with the strip-chart recorder.

In this laboratory, the plethysmograph (Parks Medical Electronics, Inc., Aloha, OR) was allowed to warm-up for 15

min prior to being used. Initially, the strain gage was weighted with a 10.08 gm weight. Concurrently, the voltage was noted on the voltmeter. This tension was the resting tension used when applying the gage to a subject. The stylus on the recorder was subsequently adjusted to obtain a reasonable baseline. The gage was then stretched 1% with this deflection being recorded. A deflection of about 35 mm was commonly used in the present study. This 1% calibration was performed at least three times to ensure stability of the measure.

The cuff was placed on the subject's forearm about 1/3 to 2/3 the forearm length from the elbow. Gage tension was then adjusted to achieve a voltage the same as when the gage was stretched with the 10.08 gm weight. The BP cuff was then manually inflated to 40-50 mm Hg for 15 sec and released for 10 sec, with this procedure being repeated for each FBF measure. Throughout this period, a strip chart recorder (Harvard Apparatus, South Natick, MA) recorded the change in length of the mercury-in-silastic gage caused by the increasing forearm blood volume. Between measures, the gage tension was adjusted to maintain the previously described resting value. After the test, the gage was recalibrated using the original resting voltage. This was done to check for "drift" occurring over the course of the experimental trial. For the present experiment, this drift

never exceeded 1% of the initial deflection.

Following test completion, the deflections noted on the strip chart paper were extrapolated to 60 sec and compared to the calibration deflection. This ratio is a measure of the percent change in forearm volume due to the venous occlusion. To convert this number to a measure of blood flow, it is doubled (see Whitney, 1953) and expressed as "ml of blood flow*100 ml of tissue^{-1}*min^{-1}."

Statistical Analyses

This study is a split plot design with the between-subjects factor being group (hypertensive vs. normotensive) and the within-subjects factors being drug (prazosin vs. placebo) and time-point of exercise. As such, the data were analyzed using repeated measures analysis of variance for each variable under consideration. If significant between-groups differences were found, they were then located using the Tukey post hoc test. An α level of .05 was chosen a priori. All data have been expressed as mean ± s.e.m.

Forearm vascular conductance was determined using the formula FVC=FBF/MAP. Here, the mean of the 3 min of forearm blood flow measurements collected immediately prior to the blood pressure determination were used in the numerator. Total peripheral resistance was calculated as TPR=MAP/CO. MAP was estimated as the sum of systolic blood pressure and 1/3 pulse pressure. CO was taken as the mean of the three

min of CO data bracketing the minute during which MAP was determined. Both CO and MAP were expressed as a multiple of the mean of the 15 min of resting data. CO was determined on a per-minute basis with SV being the value obtained from the impedance cardiograph and HR being that measured in the last 15 s of each min.

APPENDIX D

Raw Data

DRUG=PRAZOSIN

ID	BP COND	FBF -10	FBF -5	FBF -0	FBF +5	FBF +10	FBF +15	FBF +20	FBF +25	FBF +30
1	HTN	2.18	2.69	2.43	2.15	2.94	3.94	7.58	8.83	8.83
2	HTN	1.63	1.94	1.87	1.65	2.42	3.20	4.74	5.30	5.99
3	HTN	1.17	1.49	1.49	3.37	2.94	3.89	3.24	3.84	3.81
4	HTN	1.94	2.35	2.22	2.41	3.82	5.35	7.49	7.82	6.44
5	HTN	2.72	3.05	2.53	2.26	3.01	3.66	4.58	4.31	3.81
11	NTN	1.75	1.55	1.54	1.35	1.62	3.40	2.98	3.24	4.06
12	NTN	2.14	2.73	4.05	2.29	2.45	2.06	3.15	2.51	2.51
13	NTN	2.88	2.34	2.09	2.51	2.58	3.05	4.32	6.58	7.88
14	NTN	1.24	1.89	1.80	1.88	4.98	6.01	6.35	5.56	6.17
16	NTN	1.35	2.77	1.41	1.76	2.28	4.31	5.25	5.91	4.79
17	NTN	1.87	2.28	1.81	3.37	3.16	3.03	2.36	2.46	2.65
18	NTN	1.09	1.05	1.42	2.36	2.12	3.93	4.57	4.22	4.22

DRUG=PLACEBO

ID	BP COND	FBF -10	FBF -5	FBF -0	FBF +5	FBF +10	FBF +15	FBF +20	FBF +25	FBF +30
1	HTN	1.16	1.23	1.00	2.00	1.53	2.99	3.55	4.22	5.48
2	HTN	1.39	1.92	1.99	1.69	3.71	5.90	7.07	8.49	8.47
3	HTN	1.55	1.86	1.68	1.54	3.17	4.18	4.10	4.09	4.42
4	HTN	1.24	1.10	1.25	1.42	1.75	4.38	4.58	5.76	5.48
5	HTN	1.34	1.56	1.08	2.68	2.81	4.01	4.67	4.72	4.97
11	NTN	1.00	1.00	1.11	2.13	4.75	7.13	7.59	10.56	11.31
12	NTN	1.71	1.89	1.32	2.12	4.45	5.44	6.15	7.74	7.25
13	NTN	1.21	1.39	1.30	1.24	1.25	1.72	1.97	2.88	2.68
14	NTN	1.22	2.72	1.43	3.28	5.77	6.01	8.08	9.39	12.90
16	NTN	2.14	2.22	1.97	2.55	2.39	3.73	3.49	5.17	4.36
17	NTN	1.21	2.26	1.51	1.83	1.70	2.25	2.31	4.08	3.12
18	NTN	1.83	1.75	2.51	2.03	3.30	4.75	5.21	6.75	8.23

DRUG=PRAZOSIN

ID	BPCOND	MAP -15	MAP -10	MAP -5	MAP -0	MAP +5	MAP +10	MAP +15	MAP +20	MAP +25	MAP +30
1	HTN	99.33	99.33	93.33	92.67	114.00	104.67	102.00	98.00	92.67	92.67
2	HTN	103.33	96.67	95.33	103.33	112.00	112.67	95.33	100.00	100.67	96.00
3	HTN	94.00	91.33	86.67	94.00	106.00	108.00	106.67	102.00	104.00	104.67
4	HTN	101.33	100.00	100.00	102.00	108.00	109.33	111.33	107.33	101.33	100.00
5	HTN	90.67	91.33	87.33	90.00	100.67	103.33	100.67	94.67	98.00	96.67
11	NTN	96.00	95.33	93.33	93.33	114.00	114.67	116.00	111.33	113.33	115.33
12	NTN	64.00	60.67	58.67	73.33	78.00	78.67	79.33	80.00	80.00	82.28
13	NTN	84.67	84.00	86.00	82.67	101.33	98.00	100.00	102.67	100.67	98.00
14	NTN	96.67	90.67	90.00	94.67	102.67	112.67	112.67	114.00	110.67	109.33
16	NTN	90.00	84.67	82.67	79.33	96.67	98.67	93.33	97.33	97.33	95.33
17	NTN	80.67	86.67	84.00	89.33	99.33	95.33	91.33	98.67	97.33	97.33
18	NTN	80.00	85.33	84.00	84.00	108.00	109.33	106.67	102.00	98.67	96.67

DRUG=PLACEBO

ID	BPCOND	MAP -15	MAP -10	MAP -5	MAP -0	MAP +5	MAP +10	MAP +15	MAP +20	MAP +25	MAP +30
1	NTN	92.67	90.00	92.00	99.33	115.33	109.33	109.33	110.67	109.33	104.67
2	HTN	102.67	88.00	83.33	88.67	113.33	112.00	112.67	115.33	108.67	110.67
3	HTN	100.67	100.00	103.33	100.67	108.67	106.67	109.33	108.00	108.67	101.33
4	HTN	104.00	103.33	110.00	104.67	120.00	120.00	115.33	104.00	108.00	116.00
5	HTN	103.00	104.00	98.00	108.00	110.67	113.33	112.00	111.33	111.33	102.67
11	NTN	96.67	96.67	98.00	96.67	120.67	120.67	121.33	122.67	124.00	124.00
12	NTN	92.00	92.00	95.33	96.00	116.67	111.33	107.33	100.00	102.67	100.00
13	NTN	86.00	86.00	90.67	85.33	96.67	95.33	100.00	96.67	100.00	103.33
14	NTN	90.00	94.00	94.00	95.33	120.67	117.33	116.67	114.00	112.67	114.00
16	NTN	88.00	88.00	90.67	91.33	101.33	98.00	98.67	94.67	99.33	99.33
17	NTN	87.33	84.00	94.00	93.33	109.33	108.67	108.00	108.67	106.67	114.67
18	NTN	93.33	94.00	84.00	86.67	106.00	106.67	107.33	106.00	98.67	102.67

DRUG=PLACEBO

ID	BPCOND	CO -15	CO -14	CO -13	CO -12	CO -11	CO -10	CO -9	CO -8	CO -7	CO -6	CO -5	CO -4
1	HTN	5786.5	6328.0	7401.6	7482.5	7175.0	6867.5	6539.4	6601.0	7437.0	6789.6	5976.0	6408.6
2	HTN	5445.0	5548.5	5320.6	5944.0	6117.2	6450.4	6507.0	5859.8	6651.0	6158.8	6012.0	5896.0
3	HTN	5070.0	5074.3	4676.0	4443.6	4992.0	3927.0	4580.6	5087.9	4249.0	3710.7	4514.4	4721.2
4	HTN	6768.0	7318.5	7568.4	7711.2	6772.8	6615.1	6457.4	6109.0	7120.8	7898.8	7514.0	6724.0
5	HTN	5327.0	5387.4	5542.4	5494.0	5586.0	5351.6	5313.6	5940.0	5544.0	5530.0	4197.6	5390.0
11	NTN	2016.0	2648.8	2418.0	2476.8	3326.4	2553.0	2368.8	2352.9	2622.0	2983.5	2259.2	2456.8
12	NTN	3143.4	3266.0	4272.0	3564.0	3106.1	2974.4	3448.6	3195.5	2820.0	3496.0	3374.6	3365.2
13	NTN	2744.0	3952.4	3837.6	3870.4	4429.0	4291.1	3743.3	3377.4	4121.6	3584.0	3894.7	3790.4
14	NTN	2464.0	2464.0	2648.8	2625.7	3052.7	2402.4	2558.4	2709.7	2670.2	2622.8	2321.7	3051.5
16	NTN	4815.0	4766.3	4760.0	4004.0	4402.2	4985.6	4803.3	4612.5	4422.6	4835.7	5287.0	4147.5

ID	CO -3	CO -2	CO -1	CO 0	CO 1	CO 2	CO 3	CO 4	CO 5	CO 6	CO 7	CO 8
1	6804.0	7203.0	5999.5	7830.0	11736.0	14538.6	19151.1	16262.4	17780.0	17780.0	18340.0	18480.0
2	5877.0	5997.2	6067.2	6828.8	10992.0	11193.0	12373.2	13273.6	12987.6	14382.0	14471.0	14339.7
3	4691.6	4401.9	4544.8	4267.5	8493.0	10579.1	11136.0	10080.4	10511.0	11080.2	12083.2	11350.0
4	6399.0	6488.0	6923.0	10706.5	16728.0	19035.0	19628.0	20874.9	20934.5	22466.7	25579.8	24055.0
5	6026.4	5628.3	6416.0	5896.0	9094.8	13156.0	12893.4	14237.4	14681.6	14191.1	18320.2	20760.4
11	2655.0	2533.3	3026.1	3334.8	5888.2	5627.7	7503.2	5649.9	6660.0	6844.5	7410.0	7047.8
12	3355.8	3520.0	3542.2	3572.8	4519.4	6062.5	6807.2	7670.0	8190.0	7134.0	7470.0	8295.0
13	4131.0	3897.6	3921.6	3897.6	5498.4	10873.2	11412.0	11507.3	12458.7	12350.0	11916.8	11737.6
14	2412.4	2992.0	2618.0	3060.0	8124.3	7191.0	6165.9	6221.6	6992.0	7379.0	5501.4	5884.3
16	4792.0	4520.0	4033.0	4998.0	9258.3	12446.0	12518.4	12196.1	12538.8	12272.0	13081.2	13635.6

ID	CO 9	CO 11	CO 12	CO 13	CO 14	CO 15	CO 16	CO 17	CO 18	CO 19	CO 20
1	21909.0	19807.5	20975.1	18480.0	18214.0	26771.4	21128.0	24366.7	22866.5	20853.2	16980.0
2	15254.0	14722.5	16096.6	17567.6	17610.3	18384.7	19072.0	19392.0	20526.0	20782.5	20896.0
3	10077.2	10812.0	10137.5	10587.5	11439.0	10738.4	10285.0	11437.5	10512.5	11033.1	10785.6
4	22644.0	22715.0	23425.6	24576.7	24714.0	24755.7	25213.3	25254.0	25346.4	27476.5	29588.7
5	19123.2	20949.4	21903.2	23150.4	23973.9	22791.6	21901.5	19445.7	20576.0	20447.4	22925.8
11	6085.2	7917.0	6902.7	6264.0	9147.6	6981.0	6756.4	8540.0	8662.0	8181.0	8608.6
12	7062.6	7139.1	7184.0	7416.5	7214.4	7462.0	7965.9	8082.8	7982.6	7744.8	7682.0
13	11817.0	12549.8	12847.8	14592.6	14576.8	15053.7	15456.8	15279.2	14413.0	14460.0	13996.8
14	5416.5	9388.5	12919.5	13467.6	16815.5	14722.0	14097.6	14237.9	14484.0	14030.3	13073.0
16	13978.8	14182.0	13110.4	16235.2	15262.2	13100.0	14361.6	15241.8	13712.3	16918.8	14280.0

ID	CO 21	CO 22	CO 23	CO 24	CO 25	CO 26	CO 27	CO 28	CO 29	CO 30
1	23749.2	28715.4	24452.4	27361.1	21184.0	23743.5	30583.0	31416.0	29701.8	25177.0
2	20992.0	20237.7	20208.0	20684.7	20416.0	20625.0	20490.9	19866.0	20378.4	19926.0
3	11025.0	11712.5	11637.5	11607.8	11423.2	12216.3	11284.0	11564.2	10829.0	12610.0
4	27630.0	25647.7	23076.3	23367.1	24357.3	25520.8	25912.8	26790.4	27750.8	28050.0
5	23538.8	22314.6	21934.8	22771.1	25093.8	26112.6	24767.2	22478.2	18727.5	18625.2
11	9000.0	7919.2	7761.6	7142.6	6885.0	7392.0	7712.7	6735.3	7632.0	7833.8
12	7865.7	7638.8	7565.0	7915.8	7482.0	9082.5	8279.0	8425.1	8439.0	8404.2
13	14765.9	14933.2	16170.0	14250.0	15120.0	17003.5	16601.2	16838.1	16233.9	16672.0
14	15864.1	16473.6	16460.4	16617.0	16808.4	16902.1	17353.6	17928.0	14562.0	13098.0
16	14664.0	16073.2	15143.4	14628.9	14938.4	13579.2	15312.0	16013.6	15008.8	14400.0

DRUG=PLACEBO
(continued)

ID	BPCOND	CO -15	CO -14	CO -13	CO -12	CO -11	CO -10	CO -9	CO -8	CO -7	CO -6	CO -5	CO -4
17	NTN	3465.0	3509.1	3785.5	3795.0	3447.6	3510.8	3636.6	3864.0	4458.3	4249.6	3670.8	3524.4
18	NTN	4011.2	3791.4	3819.2	4290.0	4473.0	3887.4	4389.0	4623.3	3675.0	4016.0	4136.0	4484.4

ID	CO -3	CO -2	CO -1	CO 0	CO 1	CO 2	CO 3	CO 4	CO 5	CO 6	CO 7	CO 8
17	3461.2	3228.0	3696.0	4936.0	8000.6	11043.2	9530.4	9755.5	8853.6	11150.7	10920.0	9482.0
18	3595.5	3726.0	3978.0	3951.0	7391.7	8432.2	8715.3	8994.7	10251.2	9645.0	10124.4	10640.0

ID	CO 9	CO 11	CO 12	CO 13	CO 14	CO 15	CO 16	CO 17	CO 18	CO 19	CO 20
17	9579.5	11143.5	11545.6	12824.9	12259.0	11246.8	13603.8	12006.4	11025.0	10894.2	11056.5
18	11248.0	12312.0	12693.6	10617.6	11719.6	11004.4	10200.8	10889.6	10302.0	11764.0	11961.6

ID	CO 21	CO 22	CO 23	CO 24	CO 25	CO 26	CO 27	CO 28	CO 29	CO 30
17	11677.4	10624.5	11711.6	11562.8	11998.0	10715.8	10812.9	11401.0	10439.4	11229.2
18	11439.5	10988.0	12051.6	12416.8	12342.0	13263.4	11541.2	11730.0	12893.4	12934.4

DRUG=PRAZOSIN

ID	BPCOND	CO -15	CO -14	CO -13	CO -12	CO -11	CO -10	CO -9	CO -8	CO -7	CO -6	CO -5	CO -4
1	HTN	3476.8	3681.8	3575.7	3429.0	3459.2	3672.2	3458.4	3762.0	3595.2	3423.2	3401.0	3217.8
2	HTN	6040.0	6090.0	6965.4	6770.0	6158.8	6177.6	6773.5	6880.8	6498.9	6660.0	6375.0	6840.0
3	HTN	4305.6	3960.0	4059.0	4158.0	4004.0	4293.0	4428.0	3776.5	4718.8	4046.0	3412.5	3420.7
4	HTN	4490.0	4610.0	4756.5	5133.9	5555.0	4708.0	4836.0	4726.8	4491.9	4212.9	5678.9	5050.5
5	HTN	5324.0	4326.4	4665.6	4883.2	5302.0	4924.8	4807.0	4579.6	5340.0	5171.4	4686.0	4532.0
11	NTN	5121.1	4533.3	5772.8	5392.8	5086.8	4568.0	4954.4	5426.4	5016.0	5098.8	4672.2	4472.0
12	NTN	6406.4	6283.4	6107.4	6018.0	5826.6	5718.6	5514.6	5310.0	4441.5	4914.0	8002.8	7992.6
13	NTN	4539.0	4248.0	4302.0	4259.2	4107.6	4250.4	4580.0	4410.0	4493.5	4343.0	3852.0	4531.5
14	NTN	3189.8	2894.6	3071.1	2385.6	2606.1	2827.5	2933.7	3474.0	2484.0	3185.6	2631.1	2198.7
16	NTN	6642.0	5636.4	6003.0	5924.7	5913.6	5723.6	6015.1	5233.2	5319.6	5793.4	6066.0	5938.8

ID	CO -3	CO -2	CO -1	CO 0	CO 1	CO 2	CO 3	CO 4	CO 5	CO 6	CO 7	CO 8
1	3329.4	3549.6	3485.3	4350.0	8022.3	10683.3	9636.8	10398.6	13459.6	12157.6	13423.2	13464.0
2	6795.0	5736.0	6678.0	6679.4	12651.4	14770.0	14086.4	14014.0	15108.6	14855.3	15879.0	16213.0
3	3643.7	3904.4	3956.4	4482.0	6801.9	7254.0	7196.0	8059.2	8717.1	8891.4	8893.9	8648.8
4	3903.7	5538.6	6087.3	9776.7	9720.0	10011.6	9454.0	11430.8	10773.0	10238.4	10659.0	10890.0
5	4631.0	4730.0	5280.0	5163.5	9501.8	10780.0	10330.6	10416.0	10738.7	11172.0	10164.0	9852.7
11	4573.2	4555.2	4837.5	4860.0	11950.8	10894.2	11081.8	10535.3	10398.3	10598.0	10794.0	11786.0
12	7702.5	6981.4	7399.0	6734.0	10678.5	11728.4	11435.6	11793.6	12036.0	12387.6	11119.2	11620.5
13	4011.2	4232.8	4105.5	4114.0	7444.8	12375.0	12530.7	13922.2	13015.3	12861.2	13345.0	13451.4
14	2728.0	2602.6	2290.8	2635.3	5969.0	7261.0	8657.8	8465.6	8958.6	7836.8	7072.0	8816.4
16	5711.2	6021.0	5040.0	6810.0	14351.8	14420.5	15468.2	15100.8	15642.0	14872.0	15898.4	15181.0

ID	CO 9	CO 11	CO 12	CO 13	CO 14	CO 15	CO 16	CO 17	CO 18	CO 19	CO 20
1	13464.0	14026.4	14596.0	14596.0	14691.0	15288.0	15215.0	15394.0	15921.0	16287.0	15866.1
2	16447.8	16599.0	16736.0	17315.1	18112.0	16756.4	16560.8	18190.8	18582.0	18958.4	17904.0
3	8870.5	8990.0	9616.0	9872.0	10112.4	10480.0	12026.7	10604.5	10570.2	11091.6	9653.8
4	10986.2	12004.2	11670.8	12118.0	12722.4	12478.0	13860.0	13115.7	12538.8	13080.6	13141.0
5	9626.4	12127.3	10213.8	9205.0	13137.0	13201.2	12917.2	14981.8	10666.2	12611.7	9653.4
11	10948.2	11788.0	11203.8	12377.4	12585.0	12540.0	12513.6	13300.6	12700.8	12404.0	12919.5
12	12051.0	12540.0	12589.1	12645.6	12415.0	12566.4	12526.8	12392.6	12408.0	12606.0	12707.0
13	13105.2	12880.0	11344.4	13546.8	14008.0	15198.0	14566.6	15226.9	16047.5	16321.2	15625.2
14	9176.9	8836.8	8967.9	10370.7	8139.6	11373.6	9826.0	9656.0	9819.6	9262.8	8853.6
16	16689.6	16425.6	17983.2	18936.0	17748.0	18480.1	18252.0	17765.0	19172.8	19288.8	19266.0

ID	CO 21	CO 22	CO 23	CO 24	CO 25	CO 26	CO 27	CO 28	CO 29	CO 30
1	16213.8	17817.8	18373.2	17981.6	18096.9	17900.0	17820.00	17900.0	17820.0	17900.0
2	18353.8	17872.0	18080.3	18309.8	16736.0	19164.6	18414.00	19478.5	19107.0	19336.8
3	11040.0	10544.0	12546.0	12672.0	13009.3	12240.0	12824.80	13087.2	13431.2	13443.5
4	13124.0	12619.8	13725.6	14843.4	13424.8	12335.4	13460.36	14578.2	14418.0	14400.0
5	13446.4	13720.0	15224.0	14685.0	13798.4	16642.5	13621.90	16660.8	16217.4	11358.0
11	13828.1	13079.0	12155.0	11885.4	12483.9	12083.9	12890.50	12994.0	12735.0	13176.0
12	13302.7	13733.4	13162.5	13455.0	13636.0	13552.5	13636.00	13552.5	13636.0	13552.5
13	17631.5	18450.0	17748.0	17046.0	16578.0	17513.1	16597.70	16854.3	17019.0	17443.2
14	9080.1	10016.7	10557.0	9413.4	8483.2	9587.4	10801.60	8659.2	8950.0	8960.8
16	19195.5	19104.0	19176.4	18643.2	18971.9	17062.5	19129.50	17751.0	18643.4	18547.3

DRUG=PRAZOSIN
(continued)

ID	BPCOND	CO -15	CO -14	CO -13	CO -12	CO -11	CO -10	CO -9	CO -8	CO -7	CO -6	CO -5	CO -4
17	NTN	3876.0	4123.6	4224.0	4730.4	4481.4	4352.0	4595.4	4048.4	4542.4	4122.0	4494.8	4146.0
18	NTN	3730.3	4940.1	4374.0	4659.3	4292.5	3939.0	5120.0	4662.0	4644.0	4953.6	4656.0	5137.6

ID	CO -3	CO -2	CO -1	CO 0	CO 1	CO 2	CO 3	CO 4	CO 5	CO 6	CO 7	CO 8
17	4593.6	4231.5	3986.6	6443.8	10634.4	11315.2	11138.1	11264.0	10629.9	10877.8	11476.8	10777.8
18	4618.4	4969.8	4928.8	5222.1	6973.3	8496.0	11455.2	11191.0	12653.1	12679.0	13120.0	14124.0

ID	CO 9	CO 11	CO 12	CO 13	CO 14	CO 15	CO 16	CO 17	CO 18	CO 19	CO 20
17	12510.0	12833.1	12083.7	11950.8	12698.0	12759.6	12537.8	11480.0	13104.0	12724.6	13081.6
18	13792.8	13761.0	12163.2	16587.0	15036.0	14261.8	18177.0	14076.0	16064.8	15451.2	15589.0

ID	CO 21	CO 22	CO 23	CO 24	CO 25	CO 26	CO 27	CO 28	CO 29	CO 30
17	12218.1	13253.0	12768.0	13230.0	12686.4	12629.5	12597.90	13641.6	12585.6	12107.5
18	14331.0	17017.2	15085.8	13983.6	16524.0	17740.8	18061.10	17219.8	15000.2	15555.1

APPENDIX E

Data Analyses

ANOVA Table for Forearm Blood Flow--Pre-exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	0.022	1	0.022	0.05	.8246
Error	4.199	10	0.420		

Within Subjects Effects

Source	SS	df	MS	F	p
Drug	4.308	1	4.308	4.70	.0554
Drug*BPCond	0.657	1	0.657	0.72	.4169
Error	9.169	10	0.917		
Time	1.266	2	0.633	4.17	.0307
Time*BPCond	0.023	2	0.011	0.08	.9275
Error	3.304	20	0.152		
Drug*Time	0.049	2	0.024	0.17	.8440
Drug*Time* BPCond	0.075	2	0.038	0.27	.7698
Error	2.845	20	0.142		

ANOVA Table for Forearm Blood Flow--Exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	0.254	1	0.254	0.02	.8881
Error	121.199	10	12.169		

Within Subjects Effects

Source	SS	df	MS	F	p
Drug	6.109	1	6.109	0.44	.5236
Drug*BPCond	19.380	1	19.380	1.39	.2664
Error	139.836	10	13.984		
Time	253.198	5	50.640	35.61	.0001
Time*BPCond	2.690	5	0.538	0.38	.8613
Error	71.113	50	1.422		
Drug*Time	9.448	5	1.890	1.71	.1487
Drug*Time* BPCond	7.674	5	1.535	1.39	.2433
Error	55.133	50	1.103		

ANOVA Table for Mean Arterial Pressure--Pre-exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	2087.176	1	2087.176	11.67	.0066
Error	1787.998	10	178.800		

Within Subjects Effects

Source	SS	df	MS	F	p
Drug	646.428	1	646.428	3.45	.0931
Drug*BPCond	97.625	1	97.625	0.52	.4872
Error	1875.623	10	187.563		
Time	87.797	3	29.266	2.18	.1107
Time*BPCond	53.318	3	17.773	1.33	.2844
Error	402.192	30	13.406		
Drug*Time	36.352	3	12.117	0.91	.4487
Drug*Time* BPCond	6.996	3	2.332	0.17	.9126
Error	400.210	30	13.340		

ANOVA Table for Mean Arterial Pressure--Exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	250.032	1	250.032	0.43	.5280
Error	5849.830	10	584.983		

Within Subjects Effects

Source	SS	df	MS	F	p
Drug	2146.686	1	2146.686	11.95	.0062
Drug*BPCond	0.005	1	0.005	0.00	.2363
Error	1796.781	10	179.678		
Time	464.347	5	92.869	7.93	.0001
Time*BPCond	202.349	5	40.470	3.45	.0093
Error	585.758	50	11.715		
Drug*Time	35.023	5	7.005	0.50	.7715
Drug*Time* BPCond	84.064	5	16.813	1.21	.3179
Error	694.425	50	13.888		

ANOVA Table for Heart Rate--Pre-exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	744.524	1	744.524	1.28	.2840
Error	5809.952	10	580.995		

Within Subjects Effects

Source	SS	df	MS	F	p
Drug	2823.533	1	2823.533	10.92	.0080
Drug*BPCond	2328.126	1	2328.126	0.00	.0133
Error	2586.388	10	258.639		
Time	76.190	4	19.047	0.56	.6903
Time*BPCond	98.746	4	24.686	0.73	.5764
Error	1351.384	40	33.785		
Drug*Time	50.839	4	12.710	0.74	.5699
Drug*Time* BPCond	40.228	4	10.057	0.59	.6745
Error	686.374	40	17.159		

ANOVA Table for Heart Rate--Exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	2073.418	1	2073.418	0.68	.4277
Error	30,335.952	10	3033.595		

Within Subjects Effects

Source	SS	df	MS	F	p
Drug	10845.317	1	10845.317	5.37	.0429
Drug*BPCond	639.658	1	639.658	0.32	.5858
Error	20,181.103	10	2018.110		
Time	46,152.392	9	5128.004	119.51	.0001
Time*BPCond	246.371	9	27.375	0.64	.6263
Error	3861.740	90	42.908		
Drug*Time	703.496	9	78.166	2.47	.0830
Drug*Time* BPCond	250.693	9	27.855	0.88	.4594
Error	1637.676	70	23.395		

ANOVA Table for Cardiac Output--Pre-exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	43,824,958.231	1	43,824,958.231	0.61	.0243
Error	62,413,196.482	10	6,241,319.648		

Within Subjects Effects

Source	SS	df	MS	F	p
Drug	5.801	1	5.801	2.27	.1632
Drug*BPCond	41,021,994.029	1	41,021,994.029	10.77	.0083
Error	38,093,827.780	10	3,809,382.778		
Time	152,975.376	4	38,243.844	0.17	.9305
Time*BPCond	705,547.786	4	176,386.947	0.79	.5184
Error	8,883,414.142	40	222,085.354		
Drug*Time	81,666.873	4	20,416.718	0.25	.8928
Drug*Time* BPCond	96,722.625	4	24,180.656	0.30	.8618
Error	3,230,763.109	40	80,769.078		

ANOVA Table for Cardiac Output--Exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	830,548,886.345	1	830,548,886.345	6.070	.0335
Error	1,368,278,336.500	10	136,827,833.650		

Within Subjects Effects

Source	SS	df	MS	F	p
Drug	136,499,998.847	1	136,499,998.847	2.15	.1737
Drug*BPCond	763,859,377.031	1	763,859,377.031	12.01	.0061
Error	636,208,116.216	10	63,620,811.622		
Time	1,445,535,827.706	9	160,615,091.967	38.13	.0001
Time*BPCond	120,717,549.288	9	13,413,061.032	3.18	.0231
Error	379,086,662.283	90	4,212,074.025		
Drug*Time	28,187,286.593	9	3,131,920.733	1.72	.1632
Drug*Time* BPCond	35,286,976.215	9	3,920,775.134	2.16	.0906
Error	163,726,416.314	90	1,819,182.404		

ANOVA Table for Rectal Temperature

Pre-exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	0.064	1	0.064	0.39	.5470
Error	1.465	9	0.163		
Within Ss	1.60	7	0.194	4.00	.0011
Interaction	0.349	7	0.049	1.02	.4229
Error	3.063	63	0.049		

Exercise Data

Between Subjects Effects

Source	SS	df	MS	F	p
BPCond	0.046	1	0.046	0.09	.7660
Error	4.369	9	0.485		
Within Ss	4.894	11	0.445	7.92	.0000
Interaction	0.707	11	0.064	1.14	.3365
Error	5.563	99	0.056		

VITA

Warren David Franke was born in Johnson City, Tennessee on May 4, 1961. He is the son of Robert H. and Annie E. (May) Franke. After his father retired from the military in 1968, his family moved into his mother's childhood home in Winterville, North Carolina. He spent a typical childhood going to school, playing in the yard and working in the tobacco fields in the summer. While in high school, he enjoyed serving as an athletic trainer. Consequently, while at East Carolina University, he majored in Physical Education/Sports Medicine, graduating in 1983 with a B.S. degree and recognition as a Certified Athletic Trainer from the National Athletic Trainers Association. Thereafter, he matriculated in Wake Forest University, leaving that school in 1985 with a M.A. in Physical Education with an emphasis in Cardiac Rehabilitation.

He then spent two years working in southern Florida in areas related to his educational training. He left Florida after realizing the prevalent lifestyle was not for him. The author came to Virginia Tech in 1987, completing his doctoral work in July, 1991. After marrying Libby A. Gallagher in early August, 1991, he will begin work as an Assistant Professor in the Department of Physical Education and Leisure Studies at Iowa State University.