FITNESS-RELATED ALTERATIONS IN BLOOD PRESSURE CONTROL:
THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM

DISSERTATION

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BY

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Baroreflex function and cardiovascular responses to lower body negative pressure during selective autonomic blockade were evaluated in endurance exercise trained (ET) and untrained (UT) men. Baroreflex function was evaluated using a progressive intravenous infusion of phenylephrine HCL (PE) to a maximum of 0.12 mg/min. Heart rate, arterial blood pressure, cardiac output and forearm blood flow were measured at each infusion rate of PE. The reduction in forearm blood flow and concomitant rise in forearm vascular resistance was the same for each subject group. However, the heart rate decreases per unit increase of systolic or mean blood pressure were significantly (P<.05) less in the ET subjects (0.91 ± 0.30 versus 1.62 ± 0.28 for UT). During progressive lower body negative pressure with no drug intervention, the ET subjects had a significantly (P<.05) greater fall in systolic blood pressure (33.8 ± 4.8 torr versus 16.7 ± 3.9 torr). However, the change in forearm blood flow or resistance was not significantly different between groups. Blockade of parasympathetic receptors with atropine (0.04 mg/kg) eliminated the differences in response to lower body negative pressure. Blockade of cardiac sympathetic receptors with metoprolol (0.02 mg/kg) did not affect the
differences observed during the control test.

It was concluded that the ET subjects were less
effective in regulating blood pressure than the UT subjects,
because of 1) an attenuated baroreflex sensitivity, and 2)
parasympathetic-mediated depression of cardiac and vasocon-
strictive responses to the hypotensive stress.
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Abstracts


Publications


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CHAPTER I
INTRODUCTION

In 1969, Stegemann et al. (244) reported that endurance trained athletes had an altered blood pressure control system, when compared with a group of nonathletes, as evidenced by a greater incidence of syncope during head-up tilt after multi-hour water immersion. Since this report, several studies (154,155,208,245) have addressed the question of whether endurance exercise training affects orthostatic tolerance and what physiological mechanisms could explain a relative intolerance in this subject population. Many factors are involved in the regulation of blood pressure during an orthostatic stress, while endurance exercise training produces an array of physiological adaptations that may affect these dynamic regulatory processes. Therefore, the explanation for the relative orthostatic intolerance previously observed in endurance exercise trained men is not necessarily simple nor succinct.

Effects of an Orthostatic Stress

An orthostatic stress refers to the alteration of homeostasis induced by assuming an upright or erect posture. The primary hemodynamic effect is redistribution of the blood volume (primarily the venous volume), with the primary
shift being from the central blood volume in the thoracic region into the splanchnic regions and lower extremeties. Secondary changes include a reduction in the venous return, and ventricular filling, and consequent reductions in stroke volume and cardiac output. The magnitude of these changes thereby determine the type and magnitude of physiological responses that occur. Many non-pathological conditions, such as pregnancy (204) and prolonged bed rest (160,181) are associated with a tendency for orthostatic intolerance, where assuming an upright position or simply standing very still results in a hypotension-induced dizziness and possible syncope. There are also many pathological conditions for which orthostatic intolerance is a secondary complication (232). The acute responses to an orthostatic stress, induced by reductions in central blood volume, have been reviewed by Blomqvist and Stone (26) and involve initially a reflex vasoconstriction, relative tachycardia (increase in heart rate), increase in plasma catecholamines and possible venoconstriction. As the stress is prolonged, several humoral responses occur including increases in plasma aldosterone, renin, angiotensin and vasopressin. In addition, when one stands upright there is significant tension maintained in the lower limbs which produces a somatopressor reflex that augments the vasoconstrictor responses (68). All of these responses are produced to preserve central blood volume and arterial blood pressure.
If the responses are inadequate, the arterial pressure may fall to levels which do not maintain adequate cerebral blood flow and consciousness. The result is an undesirable syncopeal episode. The following sections will delve, in detail, into the normal mechanisms of blood pressure regulation during an orthostatic stress. In addition, the factors that may explain the occurrence of an endurance exercise training-induced tendency for orthostatic intolerance will be reviewed.

Normal Blood Pressure Regulation

Arterial blood pressure is a function of cardiac output (Q) and peripheral vascular resistance (PVR), and thus is determined and regulated by factors affecting both Q and PVR. These two variables are interdependent in a complex manner such that alteration of one variable is usually associated with a concomitant or consequential alteration of the other. A classic example of this phenomenon was illustrated by the work of Coleman and Guyton (42) in which hypertonic volume loading produced hypertension and a rise in Q. However, within days the resulting high regional blood flows caused local vasoconstriction and an increase in PVR which, in turn, resulted in a fall in Q back to control levels. The resulting chronic hypertension was associated with the elevated PVR, yet was initially caused by the elevated Q. The mechanisms by which PVR and Q are manipulated involve subtle adjustments in cardiac function, blood
volume, and degree of venous and arteriolar constriction. These adjustments are achieved by changes in sympathetic and parasympathetic nervous activity, hormone secretion rates, and local tissue metabolic demands. Guyton (112) has proposed that there is a temporal hierarchy of control mechanisms for the regulation of blood pressure, whereby the neural reflexes provide a virtually instantaneous modulation of arterial pressure. The neural reflexes serve to buffer against wide variations in the beat-to-beat pressure (53). The humoral responses (namely renin-angiotensin, aldosterone and vasopressin), capillary fluid shifts between the vascular and interstitial spaces, and vascular compliance changes (stress-relaxation phenomenon) occur within hours of a pressure aberration (32,113,118). These immediate and short term control mechanisms provide a buffer for pressure perturbations but do not provide absolute homeostatic control of blood pressure over the long term. Extensive work by Guyton and colleagues (114-117) has shown that the long term control (from days to years) of arterial pressure is provided by the renal mechanisms involved in the regulation of body fluid volumes. Their findings suggest that this system has an infinite feedback "gain" for regulation of blood pressure in a healthy individual.

It is apparent that control of blood pressure during an acute orthostatic stress primarily involves the neural mechanisms, with some involvement of the other short term
regulatory mechanisms, if the stress is prolonged. The renal-mediated long term mechanism is probably not employed during acute gravitational (G) stress, but does become an important blood pressure and volume regulator during chronic simulated zero G stress, as has been shown in bed rest studies (82,98). As blood pressure regulation during acute orthostatic hypotension primarily involves neural mechanisms, the following discussion will focus on reflex and short term control mechanisms.

**Arterial Baroreflexes**

There are three major groups of mechanoreceptors (pressure or volume receptors) located in the cardiovascular system including: a) the arterial baroreceptors located in the adventitia of the carotid sinuses and aortic arch; b) the low-pressure or cardiopulmonary receptors located in the walls of the vena cavae, pulmonary artery and right atrium of the heart; and c) the cardiac receptors that are located in the walls of the ventricles. The arterial baroreceptors have been identified in the aortic arch, at the origin of the brachiocephalic and left subclavian arteries, and in the carotid sinuses at the bifurcation of the common carotid artery (5,30,174,189). Both regions contain sensory nerve endings composed of single, thick myelinated fibers that branch into a rich arborization of small fibrils that terminate in neurofibrillar end plates (4,265). Another receptor type has been observed in the carotid sinus consisting
of thin myelinated fibers that form a diffuse arborization before terminating in a loose plexus (265). The nerve fibers from the sinus nerve join the glossopharyngeal nerves, while the aortic afferents unite before joining with the vagus trunk (150). The afferent neurons that originate from these receptor territories appear to be primarily of the A-type myelinated fiber with diameters ranging from 2 μm to 12 μm as measured in cats, dogs and man (7, 64, 91, 102). If normal range conduction velocity-diameter ratios are used, these diameters comply with the conduction velocity range (10-55 m/sec) found for these nerve fibers by Aars (1) and Paintal (196). Unmyelinated C-type fibers have also been found in the sinus nerve (93, 94) and exhibit a relatively low threshold for mechanical compression. However, Jones and Thoren (135) clearly demonstrated in the rabbit that the myelinated fibers have a significantly lower threshold and reach their maximal activity at a considerably lower mean arterial blood pressure than the unmyelinated fibers. Therefore, they concluded that the myelinated fibers mediate most of the normal reflex responses, and that the unmyelinated fibers are necessary only when the pressure becomes abnormally high.

Many electrophysiological and histological studies have demonstrated that the majority of secondary neurons, for both the carotid sinus and aortic arch baroreceptors, are located in the nucleus tractus solitarius (38, 52, 101, 227,
242). Although further definition of the intricate neuronal pathways within the brainstem is evident in the current literature, the fundamental circuit for the arterial baroreflexes reflects an intraneuronal union of the afferent and efferent neurons at the nucleus tractus solitarius.

**Afferent and efferent pathways:** Both the afferent and efferent pathways mediating baroreflex effects were first ascribed to the vagus nerve (91). Subsequently, Adrian et al. (6) described that pulse-synchronous rhythmical bursts of sympathetic nerve signals also were associated with the asynchronous arterial pulse. This has since been attributed to pulsatile arterial baroreceptor afferent activity as evidenced by elimination of the rhythmical sympathetic activity upon cutting of the baroreceptor afferent nerves (157,230). Wallin and Eckberg (259) recently found that deactivation of the carotid baroreceptors with neck pressure (simulating hypotension) was associated with an increase in sympathetic nerve traffic of the peroneal nerve in man. Conversely, when neck suction (simulating hypertension) was used to stimulate the receptors, the sympathetic nerve traffic in muscle decreased markedly or even disappeared. Moreover, several studies (27,108,260) have found that different sympathetic neurons supplying different target organs respond differently to changes in arterial pressure or baroreceptor activity. Hence, the once accepted tenet that all efferent sympathetic nerve activity is uniform and produces a uni-
fied, chorus of actions has been clearly discounted. Consequently, description and discussion of sympathetic actions must be succinct and specific to the measurements made.

**Baroreflex effects on the heart:** The arterial baroreflex efferent pathways primarily affect two general target tissues; the heart and the vascular tree. Cyon and Ludwig (54) first described the cardiac slowing that occurs when the depressor nerve (vagus) is stimulated, and subsequently provided the first documented hypothesis of reflex neural control of the heart. Increases in arterial pressure are associated with a reflex bradycardia which has been shown to be primarily mediated by the vagus nerve (43,150,206,261).

In a review of the literature, Kirchheim (150) argued for vagal mediation alone of arterial baroreflex alterations in heart rate during both hypotensive and hypertensive stresses. However, Coleman (43) clearly demonstrated that the bradycardiac response to a prolonged (5 minutes) elevation in arterial pressure was mediated exclusively by the vagus nerve only during the first ten seconds. Within fifteen seconds, sympathetic modulation (withdrawal) began to play a role in the heart rate response and rapidly became the dominant effector mechanism. These findings were in close agreement with the earlier findings of Wang and Borison (261) who described the early phase of the heart rate response to be vagally-mediated with the sympathetic component developing more slowly. Using neck suction to stretch
(stimulate) the carotid baroreceptors in humans, Eckberg (76,78) and Raczkowska et al. (206) have shown that the initial heart rate response was mediated predominantly by parasympathetic pathways, where cholinergic receptor blockade with atropine eliminated the response. A similar temporal relationship of autonomic responses appears to occur during deactivation (hypotension) of the arterial baroreceptors. Several studies have shown an initial parasympathetic-mediated (vagal withdrawal) heart rate increase (76,149,152). Others have demonstrated a combined (233,258) sympathetic and parasympathetic or exclusively sympathetic (106) heart rate response to prolonged (>20 seconds) hypotension induced by either a bilateral carotid artery occlusion or a nitroglycerin infusion. Therefore, the efferent pathways mediating arterial baroreflex effects on heart rate appear to involve exclusively the parasympathetic pathway initially, and a combination of parasympathetic and sympathetic pathways when the pressure aberration is prolonged.

Sarnof et al. (229) were the first to suggest that arterial baroreflexes affect cardiac contractility. They observed a rapid rise in cardiac output and arterial pressure with an accompanying decrease in left atrial pressure after carotid artery perfusion pressure was reduced. This hypothesis was refuted by Salisbury et al. (223) on the contention that the changes in cardiac output and arterial
pressure were secondary results of a reflex change in peripheral vasomotor tone. Kirchheim et al. (151) and Vatner et al. (257) more recently proposed that there was minimal baroreflex effect on contractility as evidenced by minimal changes in both peak aortic flow velocity and left ventricular \( (dP/dt)_{\text{max}} \) in dogs. DeGeest et al. (59) designed an experimental canine preparation in which the heart was hydraulically isolated from the remaining circulation, but neurally intact. Preload, afterload, and heart rate were controlled during changes in the carotid sinus perfusion pressure. Increases in carotid sinus perfusion pressure were accompanied by decreases in peak isovolumic left ventricular pressure and was interpreted as a fall in contractility. Similarly, Downing and Gardner (72) found in a cat model that cardiac function curves, plotting stroke volume or work against left ventricular end diastolic volume, were shifted to the left with an increase in slope during carotid sinus hypotension. With filling pressure, afterload pressure, and heart rate constant these findings provide further substantiation of the hypothesis presented by Sarnof et al. (229). Although the evidence has mounted in support of this hypothesis, there remains a considerable debate over this issue. In separate review articles, Kirchheim (150) and Downing (71) agree that further elucidation is needed regarding the baroreflex effect on cardiac performance.
Baroreflex effects on arterial circulation: In conscious animals, marked decreases in carotid sinus perfusion pressure produce rapid but transient changes in cardiac output. As a steady state condition is regained only one-third of the reflex rise in arterial pressure is attributable to a rise in cardiac output (151). It then follows, as the data of Kirchheim and Gross (151) illustrated, that the predominant effector of this change in arterial pressure is the rise in total peripheral resistance. As noted earlier, reflex sympathetic responses do not represent a necessarily homogeneous effect. This is further demonstrated when considering regional vasoconstrictor responses. Most of the data collected suggest that renal blood flow is autoregulated during acute changes in arterial or carotid sinus pressure. Several studies of renal hemodynamics, in pentobarbital-anesthetized or unanesthetized dogs, have shown that during common carotid occlusion no change from control in renal blood flow occurs during the new steady state condition (29,127,149). Similarly, in unanesthetized dogs, minimal or no steady state changes in renal blood flows were observed during bilateral carotid sinus nerve stimulation (255,256). Several of these studies (127,255, 256) also found no change in steady state mesenteric blood flow during either a common carotid occlusion or carotid sinus nerve stimulation. Other investigations have found significant changes in mesenteric blood flow when both the
cardiopulmonary receptors and the arterial baroreceptors were stimulated (173,190,197,220). Therefore, mesenteric blood flow appears to be autoregulated in a similar manner as the renal circulation when arterial baroreceptors are manipulated; however, the mesenteric beds do appear to be responsive to reflex neural control from the cardiopulmonary receptors. The action of the cardiopulmonary baroreflex will be discussed in more detail in subsequent paragraphs.

In contrast to the minimal carotid baroreflex-induced changes in renal and mesenteric blood flow, skeletal muscle blood flow is remarkably affected. In anesthetized dogs and cats, carotid artery occlusion produced significant decreases in iliac and hindlimb blood flows (95,119). When the carotid sinus nerve was stimulated, the iliac blood flow of unanesthetized dogs rose between 90 and 110 percent above the control flow. This response translated into an average decrease in iliac vascular resistance of 62-66 percent (255,256). Epstein et al. (87) found similar changes in forearm blood flow and resistance in conscious men upon stimulation of the carotid sinus nerve. Likewise, Ebert (75) found that carotid baroreceptor activation (with neck suction) caused a significant decrease in forearm vascular resistance while carotid baroreceptor deactivation (with neck pressure) resulted in an increase in resistance. Lastly, considerable data have accrued over the past 25 years suggesting that skin blood flow is not affected by the
arterial baroreflex (29,61,166,167,213). Hence, the regulation of skin and skeletal muscle blood vessels is provided by independent mechanisms. Although these mechanisms are probably interactive, these observations further demonstrate the heterogeneous nature of blood pressure control. In addition, these previous findings emphasize the importance that control of muscle blood flow or vascular resistance has in the acute regulation of blood pressure.

Baroreflex effects on venous circulation: The possibility that the venous circulation participates in cardiovascular regulation has been studied and debated since the turn of the century. Early findings from the laboratories of Bancroft (14), Donegan (69), Heymans (126) and Hooker (131) gave birth to the hypothesis that venous smooth muscle is dynamically involved in the regulation of systemic hemodynamics. However, this hypothesis has met with considerable opposition (31,67,132). Evidence for sympathetic innervation of the veins has been accumulating since the early observations of Hooker (69,99,100,109,110,131, 236). The importance of this neural supply has been questioned since the degree of innervation of veins is substantially less than that of the arterial and arteriolar vessels (99). Furthermore, Bevan et al. (20) found that the veins that drain the subcutaneous and muscular capillary beds are less densely innervated than the veins of the viscera. In one investigation it was proposed that the veins are more sensi-
tive to sympathetic nerve stimulation than the arterial vessels (121). This apparent functional venoconstriction also has been demonstrated to be a component of the arterial baroreflex response. Decreases in carotid sinus pressure were associated with a significant reduction in venous compliance (9), while carotid sinus nerve stimulation resulted in a significant venodilation and concomitant decrease in venous return (207). More recently, pressure-response curves for the venomotor effects of the carotid baroreflex have been described where the change in central venous blood volume was determined at different degrees of change in carotid sinus pressure (185,238). These baroreflex effects on the venous system appear to be mediated predominantly by the splanchnic, hepatic and large conduit veins (12,40,103, 121,141,142), and do not significantly involve the skeletal muscle veins (3,119). In summary, previous investigations in animals into arterial baroreflex effects on the venous system suggest that there is some reflex control of venomotor tone and venous compliance, particularly in the splanchnic veins. However, these effects appear to be of minor importance in the regulation of arterial blood pressure (218). Although the literature is sparse, this observation also appears to be true in humans. Bevegard and Shepherd (23) found no effect of brief stimulation of the carotid baroreceptors with neck suction on venomotor tone in a hand vein. Likewise, Epstein et al. (88) found little or
no response of cutaneous veins during several different maneuvers that affect the arterial baroreceptors. Due to a lack of appropriate techniques, the effects of the arterial baroreflex on splanchnic veins of humans has not been investigated. Thus it is not known whether the significant baroreflex effects on splanchnic veins observed in animal models holds true in man.

**Baroreflex resetting:** The arterial baroreflexes are, as noted earlier in this introduction, rapid responding and transient in nature. This transient nature of the arterial baroreflexes has become more apparent in recent years as several investigations have demonstrated that the baroreflex stimulus-response curve was shifted after arterial or carotid sinus pressure was held at a level different from the homeostatic set point (70,158,159). This phenomenon has been described as "resetting". In addition, there can be resetting of the threshold pressure, which is the lowest pressure at which reflex responses are obtained (186,222). The resetting process has been shown to partially involve the viscoelastic properties of the connective tissue surrounding the mechanoreceptors (45,125,159). Whereas, other studies (203,235) have suggested that resetting-type adaptations occur within the neuronal circuits of the brainstem, and may specifically involve the secondary neurons of the nucleus tractus solitarius. These resetting phenomena occur in both the carotid and aortic baroreceptor tissues and
appear to display similar temporal characteristics. The resetting process has been shown to occur within five minutes of a shift in the set point pressure (158,159,186). This phenomenon allows the arterial baroreflexes to provide short term modulation of arterial pressure over a wide range of pressures. However, because of the phenomenon of resetting, it is also apparent that these reflexes cannot play an important role in the long term regulation of arterial pressure.

**Cardiopulmonary Baroreflexes**

It was proposed over a century ago that neural reflexes originated in the heart and lungs (24). Subsequently, the work of Jarisch and Zotterman (134) substantiated the existence of an inhibitory reflex originating in cardiac sensory receptors, and this reflex became known as the Bezold-Jarisch reflex. In reality there are several different receptor populations in the cardiopulmonary regions, which are carried by several different afferent pathways. The cardiac mechanoreceptors responsible for the Bezold-Jarisch reflex are probably located in the ventricles and use vagal afferent nerve tracks to produce reflex bradycardia and hypotension (55,56,79,199). This reflex has been found to be functional in man during arteriography procedures (79) and in some acute myocardial pathologic conditions (175); however, the importance of this reflex in day-to-day living is uncertain. Other mechanoreceptors located in the ventri-
cular walls initiate reflexes that are mediated by sympathetic afferent nerve fibers and result in increases in sympathetic efferent nerve traffic to the heart (171, 172, 243). In addition, similar reflex responses, mediated by sympathetic afferent nerves, have been observed to originate in coronary arteries (33, 34). Again, the importance of these sympathetic-mediated reflexes for daily regulation of cardiovascular function is uncertain as these effects have only been demonstrated with electrical stimulation or during several different perturbations of normal cardiac function (e.g. coronary occlusion).

Mechanoreceptors are also located in the vena cavae, the atria and the pulmonary arteries and veins (44, 46). These receptive fields have been described as low-pressure baroreceptors because they sense and respond to the small changes in pressure associated with changes in central blood volume. Bainbridge (13) first described a reflex tachycardia during intravenous infusion of saline into dogs and ascribed this to a reflex withdrawal of vagal tone. Subsequently, this reflex was further defined and was attributed to vagal afferent signals originating in the aforementioned anatomical regions, and synapsing in the cardiovascular centers of the brainstem (254). In contrast, changes, both increases and decreases, in the central venous or cardiac filling pressure did not produce a reflex tachycardia in man (10, 73, 248). This was reported to be due to a lack of
effect of alterations in central venous pressure on arterial pressure, and therefore a lack of effect on the arterial baroreflexes (22,248).

Several studies (2,137,213,267) have demonstrated that the cardiopulmonary baroreflexes produce a graded effect on peripheral and regional vascular resistances in man. Significant vasoconstriction has been observed when the central venous pressure was lowered with simultaneously no change in arterial pressure; whereas, an increase in central venous pressure produced significant vasodilation in the skeletal muscle vasculature. Recently, Essandoh et al. (90) reported that vasoconstriction is significantly greater in arm skeletal muscle than in leg muscle during low levels of LBNP. Thus, as with the arterial baroreflex, there are regional differences in response of the cardiopulmonary reflex. The effects of cardiopulmonary baroreflexes on the venous system are far less conclusive. Although earlier studies implicated a reflex venoconstriction during a decrease in central venous pressure (104,195,237), the more recent investigations suggest that there is a negligible effect on veins (2,88,228).

The cardiopulmonary receptors also appear to reflexly modulate renin release from the kidney. Epstein et al. (84,86) found that water immersion, which increases central blood volume and central venous pressure, produced a decrease in renin activity. Julius and colleagues (138,148)
obtained similar results during lower body positive pressure and also observed significant increases in renin activity during decreases in central venous pressure. They also demonstrated that this effect was not due to the arterial baroreflexes and was blocked by pharmacologic \( \alpha \)-adrenergic blockade. Therefore, they concluded that this effect was due to a sympathetically-mediated reflex from the cardiopulmonary receptors. Aldosterone (86) and vasopressin (83,85) release has also been shown to decrease during increases in cardiac filling pressure; however, the data are less conclusive when considering decreases in the cardiac filling pressure. Goldsmith et al (107) observed no change in plasma vasopressin (AVP) at low and high levels of LBNP, while others have observed increases in AVP at high levels of LBNP (>40 torr) where both the cardiopulmonary and arterial baroreceptors are involved (17,215). Therefore, the degree of contribution of the two baroreceptor fields in the AVP response remains uncertain. These humoral responses occur within minutes after alterations in central venous or arterial pressure occur, and are likely involved, to some degree, in the cardiovascular adjustments to prolonged G stress. The natriuretic hormone (or atrial natriuretic factor) has been implicated in renal and vascular resistance responses to changes in blood volume (133,145,201). However, these responses appear to be slow in developing, requiring several hours for a maximal response to occur, and
therefore are probably not involved in the responses to the transient G stress of orthostasis.

Resetting of the stimulus-response relationship for the cardiopulmonary receptors has been observed (140,180). This phenomenon appears to be similar to the resetting process that occurs in the arterial baroreceptors. Moreover, the time course for this resetting phenomenon is similar to that observed for the arterial baroreflex, with resetting beginning approximately five minutes after an aberration in the central venous pressure. In man, it appears that the cardiopulmonary and arterial baroreflexes produce similar qualitative effects on the peripheral vasculature and kidney, and similar humoral responses. The only exception is the lack of a heart rate effect by the cardiopulmonary reflex. Recent investigations have begun to reveal an interaction between the two reflex arcs. Previous studies in animals imply that both the cardiac (128,168) and cardiopulmonary receptors (167,168) attenuate the gain of the arterial baroreflex. Removal of the afferent input results in an augmented carotid baroreflex gain. Takeshita et al. (248), using LBNP at -20 torr to deactivate the cardiopulmonary receptors and neck suction to stimulate the carotid receptors, found no interactive effect on the heart rate response to the neck suction procedure. Thus, in addition to a lack of a Bainbridge reflex, the cardiopulmonary baroreflex does not appear to affect the normal chronotropic
effects of the arterial baroreflex in man. In similar studies, Bevegard et al. (21,22) demonstrated a significant heart rate response and suggested that an interaction of effects was the cause. However, they used LBNP at -40 torr to deactivate the cardiopulmonary receptors which produces a significant decrease in arterial pressure and would thus affect the arterial baroreceptors. More recently, it was shown that LBNP at -10 torr produced a response that significantly augmented the vasoconstrictor response to neck pressure. This effect was greater than a simple additive effect of the individual vasoconstrictor responses (176). This supports the findings in animals that propose a cardiopulmonary modulation of the arterial baroreflex responses, with the exception that the heart rate response is unaffected.

Endurance Exercise Training and Orthostatic Tolerance

There have been numerous reports in the literature suggesting that increased aerobic fitness or athletic prowess is associated with a decreased orthostatic tolerance (154,155,208,244,245). The data supporting this finding include the greater occurrence of syncope of fainting during head-up tilt (244), LBNP (154) and centrifugation (154) in endurance trained men as compared to untrained men. In addition, other studies have reported a less effective maintenance of blood pressure during LBNP (155,208,251) in endurance trained versus untrained men. This hypothesis has
been challenged by others who found no difference in syncopeal occurrences in men before and after either an eight day cycling (50) or a variable duration running (81) exercise program. However, Stegemann et al. (245) demonstrated that the gain of the arterial baroreflex arc was depressed in a group of endurance trained athletes as compared to non-athletes. They proposed that "the control system of a well-trained athlete seems to be barely adequate" to effectively regulate blood pressure during a gravitational stress. An alteration in autonomic control was postulated to explain this effect.

Interestingly, there have been many investigations showing that endurance exercise training significantly alters the autonomic nervous system. The decrease in resting heart rate (HR\textsubscript{r}) that is usually associated with increased aerobic fitness appears to be due to two adaptations. First, several studies (143, 162, 247) indicated that endurance exercise training induced a decrease in the intrinsic heart rate (HR\textsubscript{0}), or the HR obtained when neural control was abolished. The abolition of autonomic influence on the heart has been accomplished by pharmacologic blockade of both parasympathetic (muscarinic) and sympathetic (beta-adrenergic) receptors. In one study, Katona et al. (143) suggested that the decreased HR\textsubscript{r} of endurance trained men was due exclusively to the decrease in HR\textsubscript{0} (162, 247). Maciel et al. (170) observed no difference in the respir-
atory sinus arrhythmia before and after a 10-week endurance training period, and suggested that this was supportive of Katona's finding (143) of no change in resting parasympathetic activity. However, others have shown that there is an increased parasympathetic resting activity (97,205), while Ekblom et al. (80) proposed an increased parasympathetic activity and concomitant decreased sympathetic activity. Similarly, Lin and Horvath (165) suggested that the resting relative bradycardia in trained rats was due to a decrease in sympathetic activity. More recently, Kenney (146) studied the resting variation in heart period (VHP) of 21 men and women representing a wide range of aerobic power ($V_{O_2,max}$). He found that the VHP was strongly correlated ($r=0.92$) with the aerobic power in a positive manner. The discrepancies within these previous findings are probably explained in part by genetic differences in the endurance trained and untrained subject pools of the different cross-sectional studies. However, several longitudinal studies (80,162,163) in humans and laboratory animals support this hypothesis of increased parasympathetic activity due to aerobic training and suggest that exercise training at appropriate intensities, durations and frequencies can produce demonstrable effects on autonomic control of the cardiovascular system.

In 1967, De Schyver et al. (62) observed a reduced catecholamine concentration in the heart of animals after
exercise training. However, other studies have found varied effects of exercise training on myocardial catecholamine concentration (63,161,193,194), norepinephrine metabolism (194,226), and plasma concentration and urinary excretion of catecholamines (35,122,123,139). Although the effect of exercise training on resting sympathetic activity remains controversial, Williams et al. (263,264) has provided new insight into this question. They have eloquently demonstrated that exercise training does not alter β-adrenergic receptor number or antagonist affinity in cardiac membrane fractions of animals or the lymphocyte β-adrenergic receptor number or affinity in men. These findings have been further substantiated by the work of Moore et al. (183) who found no change in the β-adrenergic receptor density in rat hearts after exercise training.

Since the initial observations of Stegemann et al. (244) that the baroreflex "gain" was attenuated with exercise training, several studies have produced supporting evidence. Tipton et al. (251) found that trained rats demonstrated a reduced baroreflex response to LBNP when compared to untrained rats. Bedford and Tipton (18) found a decreased baroreflex gain in trained rats, as determined using an isolated carotid sinus preparation, and suggested that this was not due to changes in the stress-tissue deformation characteristics of the adventitia surrounding the baroreceptors. In two separate studies (208,241) prior to the current investigation, we found that the change in heart rate per change in blood pressure (ΔHR/ΔSBP) response
to progressive LBNP, used as an index of baroreflex responsiveness, was significantly smaller in the endurance trained subjects versus the untrained subjects. Likewise, Mass et al. (178) found that a 10-week exercise training regimen in dogs resulted in a significant attenuation of the baroreflex chronotropic response to bolus doses of either phenylephrine or nitroprusside. In summary, endurance exercise training appears to alter the normal resting activity of the autonomic nervous system and probably affects the autonomic balance (balance between parasympathetic and sympathetic activities) as well. In addition, evidence has accrued in support of an exercise training-induced attenuation of normal baroreflex responsiveness.

As previously noted, the initial effect of an orthostatic stress is the pooling of a significant volume of blood caudally. Therefore, the degree of pooling is an important determinant of the responses to follow. In a study comparing the responses of runners and non-runners to LBNP, Luft et al. (169) proposed that the fitness-related differences in response were due to the greater changes in leg volume during LBNP of the runners. They suggested that this was indicative of a greater venous compliance. Subsequently, we (209) studied the venous compliance of the legs of endurance trained (ET) and untrained (UT) men by measuring changes in leg volume between leg occlusion pressures up to 100 torr. This confirmed the previous findings
of Raven et al. (208) that leg volume changes during LBNP were not different between trained and untrained subjects. The changes in absolute volume per unit of occlusion pressure were not different between the groups suggesting that there was no difference in venous compliance. Changes in total blood volume or plasma volume could affect the absolute or percent volume of blood shifted during an orthostatic stress. This, in turn, would alter the degree of deactivation of the cardiopulmonary, and possibly the arterial, baroreceptors. This consideration is important because it has been previously shown that active or athletic persons have significantly greater total blood volumes (66,129,192,225). These increases in blood volume are predominantly attributable to increases in plasma volume. However, the influence of changes in blood volume on the reflex response to an orthostatic stress has not been addressed.

Associated with increases in blood volume are significant increases in cardiac output and stroke volume during exercise (234). The chronic employment of this phenomenon with exercise training apparently provides the stimulus for changes in cardiac dimensions. Both radiographic (11,224) and echocardiographic (147,184,200) studies have universally shown that exercise training produces global cardiac hypertrophy. The normal hypertrophic state which develops with endurance exercise (running, cycling, swimming) training has
been termed eccentric hypertrophy. Eccentric hypertrophy is characterized by a marked increase in chamber size and heart volume with minimal increases in myocardial wall thickness (147). The importance of this endurance training-induced adaptation with regard to the mechanisms of response to an orthostatic stress is uncertain and has not been addressed in the literature.

Summary

In review of the literature, a question remains as to whether blood pressure regulation is altered with endurance exercise training. Furthermore, there is a paucity of information describing mechanistic differences of blood pressure regulation between endurance trained and untrained individuals. The importance of the autonomic nervous system in blood pressure control is undeniable. Moreover, there is evidence to suggest that endurance training significantly alters normal autonomic nervous system function at rest. Therefore, the purpose of this investigation was to determine the differences in blood pressure regulation that exist between endurance trained and untrained men. In attempting to explain any observed differences, the following regulatory mechanisms were assessed:

1) The linear portion of the arterial baroreflex function curve during steady-state conditions as assessed during incremental infusion rates of phenylephrine up to a maximum rate of 120 μg/min;
2) The influence of parasympathetic control of the heart on blood pressure regulation during an orthostatic stress as determined by atropine blockade of the parasympathetic system during lower body negative pressure;

3) The influence of sympathetic control of the heart on blood pressure regulation during an orthostatic stress as determined by metoprolol blockade of the cardiac sympathetic system during lower body negative pressure;

4) The role of vasoconstriction in blood pressure regulation during cardiopulmonary stimulation (LBNP to -16 torr) and during simulated one G stress (LBNP to -40 torr);

5) The role of vasoconstrictor capacity in blood pressure regulation during an orthostatic stress as determined by complete cardiac autonomic blockade with atropine and metoprolol during LBNP;

6) The link between blood pressure regulation (as assessed by the experimentation noted above) and resting autonomic activity (as determined from the resting heart rates during selective autonomic blockade and complete cardiac autonomic blockade).
CHAPTER II

METHODS

The specific aims of this investigation were accomplished by analyzing the physiological responses to two different perturbations of arterial blood pressure (progressive LBNP or incremental phenylephrine infusion) in healthy male volunteers. Twenty men, aged 18-35 years, were divided into two subject groups based on the subject's maximal oxygen consumption ($VO_2^{\text{max}}$). Ten endurance exercise trained men with a $VO_2^{\text{max}} > 60$ (ml O$_2$/kg)/min comprised the exercise trained (ET) group, while ten sedentary men with a $VO_2^{\text{max}} < 45$ (ml O$_2$/kg)/min comprised the untrained (UT) group. The cardiovascular responses to progressive LBNP with and without pharmacological autonomic blockade were compared between the groups, STUDY 1. In addition, similar comparisons were made during incremental infusion of the alpha-adrenergic receptor agonist phenylephrine, STUDY 2.

Subjects

Prospective volunteer subjects were recruited from the Dallas-Fort Worth metropolitan area and the student populations of area universities. Each prospective subject was informed of the purpose and experimental procedures to be used and provided signed written consent for each procedure. All procedures conformed to the ethical considerations of
the Helsinki code as approved by the Institutional Review Board of the Texas College of Osteopathic Medicine. Each prospective subject completed a medical history questionnaire and was given an abbreviated physical examination by the collaborating physician (H.M. Graitzer, D.O.). Clinical screening also included a resting 12-lead electrocardiogram and a maximal exercise stress test, during which, the VO$_2$max was determined. Volunteers free of cardiovascular disease and meeting the fitness requirements of the VO$_2$max limits were accepted as subjects for the respective groups according to their fitness level.

Descriptive Data Collection

Descriptive anthropometric and physiological data were obtained for each subject. Height (cm) and weight (kg) were obtained on the screening day. Fat free weight and lean body mass were determined from the hydrostatic weight. The total blood volume and plasma volume of each subject was obtained using the carbon monoxide (CO) dilution technique of Myhre et al. (186). Administration and equilibration of the CO was performed by having the subject lie supine and breathe into a closed system containing a carbon dioxide (CO$_2$) scrubbing compartment. During the first minute of breathing, 50 milliliters of pure (100%) CO was injected into the breathing system. The subject then continued to breathe into the system for an additional ten minutes to allow for equilibration of the CO bound on the subject's
circulating hemoglobin. Five milliliters of blood was collected from the antecubital vein before and after the breathing procedure. The blood samples were analyzed for hematocrit (Hct) using the microhematocrit method in duplicate and correcting by 4% for trapped plasma (120). Total hemoglobin and carboxyhemoglobin was measured spectrophotometrically using a co-oximeter (Instrumentation Laboratories, model 282) within one hour of collection. The total blood volume ($V_B$) and plasma volume ($V_p$) were calculated as follows:

$$
\text{COHb}_I \ (\text{CO/ml rbc}) = \% \text{COHb pre}/\text{Hct pre}
$$

$$
\text{COHb}_F \ (\text{CO/ml rbc}) = \% \text{COHb post}/\text{Hct post}
$$

$$
\Delta \text{COHb} \ (\text{CO/ml rbc}) = \text{COHb}_F - \text{COHb}_I
$$

$$
V_{rbc} \ (\text{ml}) = \frac{V_{CO}}{\text{COHb}}
$$

$$
V_B \ (\text{ml}) = \frac{V_{rbc}}{\text{Hct}}
$$

$$
V_p \ (\text{ml}) = V_B - V_{rbc}
$$

where $\text{COHb}_I$ = Volumes percent carboxyhemoglobin before CO administration

$\text{COHb}_F$ = Volumes percent carboxyhemoglobin after CO administration

$V_{rbc}$ = Volume of red blood cells

$V_{CO}$ = Volume of CO administered

The coefficient of variation of six blood volume measurements for a 70 kg man was determined to be 3.2% around a mean value of 6.26 liters. The coefficient of variation of the plasma volume for the same measurements was determined to be 2.5% around a mean of 3.91 liters indicating minimal variation in the COHb and Hct measurements.
Graded Exercise Stress Test

The determination of VO\textsubscript{2}max was accomplished using the Bruce maximal exercise stress test protocol (60) on a motor-driven treadmill. During the test, ventilation volumes were determined at thirty second intervals using a computer assisted integration and averaging of calibrated pneumotacographic (Fleisch) breath-by-breath measurements of inspired and expired flow. A continuous measurement of the oxygen and carbon dioxide content in expired air was made using a respiratory gas analyzer mass-spectrometer (Perkin-Elmer Corp. model 1100AB) calibrated against known standard gases. All variables were collected on-line using a dedicated minicomputer (MINC 23, D.E.C.) and a customized software package to account for differences in delay and response time. Calculated oxygen uptake (VO\textsubscript{2}) with standardization of ventilation volumes to STPD and BTPS were made according to the metabolic calculations of Consolazio et al. (47). The appearance of the subject at termination of the test, maximum heart rate and a plateauing of VO\textsubscript{2} during the final stages were used as criteria for determining maximum effort. The maximum VO\textsubscript{2} achieved during the plateauing of this measure was defined as VO\textsubscript{2}max. A multiple lead electrocardiograph system (Cambridge, model VS-4) enabling the minute by minute recording of standard and augmented limb and V\textsubscript{5} leads was used. In addition V\textsubscript{5} lead was continuously monitored on an oscilloscope during the
test. A ten second strip recording was obtained at one minute intervals throughout the test, at test termination and during a five minute walking recovery period. Auscultatory brachial artery blood pressure was determined at three minute intervals during the test and at test termination.

Lower Body Negative Pressure Procedure

In experimental STUDY 1, lower body negative pressure (LBNP) was performed by having the subject in the supine position with his lower extremities inside of a wooden chamber and an airtight seal engaged at the iliac crests. Two rheostat controlled vacuum motors were used to induce and regulate the negative pressure inside of the chamber. A standard LBNP protocol (264) was used in which the level of negative pressure was progressively increased through stages of -8, -16, -32, -40 and -50 torr, see figure 1. During all autonomic blockade conditions the protocol was terminated at the completion of -40 torr of LBNP. All physiological measurements were made during stages of rest, -16 torr, -40 torr and -50 torr, while only heart rate, blood pressures, and leg volume changes were determined at -8 torr and -32 torr. All LBNP procedures were performed in ambient room temperature (25± 1 C at 55± 3% relative humidity). LBNP was performed at a time in which the subjects had no organized physical activity, stimulatory drinks or medications for at least 12 hours prior to the test. Upon preparation of the subject, including the placement of a venous cannula (with
heparin lock) in the antecubital vein for administration of the drugs, a thirty minute rest period was provided.

Fig. 1. Time-related protocol for lower body negative pressure exposure. Measurements of leg circumference, heart rate, and blood pressures were made at -8 torr and -32 torr; (*), time at which all measurements were made.

**Autonomic Blockade Procedures**

Five different autonomic blockade conditions were studied during LBNP. Atropine sulfate was used to block muscarinic receptors of the parasympathetic nervous system at a partial blockade (PA) dose producing a 10% increase in heart rate from rest, and at full blockade (FA) dose (0.04 mg/kg) as previously designated by Jose and Taylor (135). The atropine blockade was tested by having the subject perform a valsalva maneuver by producing an expiration pressure of 60
tort while blowing into a closed system. The phase I response to a valsalva maneuver is a parasympathetic mediated bradycardia; therefore, absence of this early bradycardia (as determined by an increase in the R-R interval of the electrocardiogram) during atropine blockade was considered confirmation of full blockade. This procedure was performed prior to administration of any drug and after full blockade was achieved. In addition, the valsalva was performed post-LBNP to insure that the blockade remained. Under circumstances in which full blockade was not achieved the atropine was titrated to a higher dose and the valsalva maneuver repeated.

Metoprolol tartrate was used to block the $\beta_1$-adrenergic receptors of the sympathetic nervous system at a partial blockade (PM) dose producing a 10% decrease in heart rate from control, and at a full blockade (FM) dose of 0.2 mg/kg or a subsequent titrated dose producing no further decrease in heart rate. The FM blockade was confirmed during the double blockade (DB) condition in which full atropine and metoprolol blockade doses were administered. Confirmation of the block was performed by two tests. First, a valsalva maneuver, as described above, was used with an absence of phase I bradycardia or phase III tachycardia providing evidence for blockade of both muscarinic and $\beta_1$-adrenergic receptor populations. Secondly, the $\beta_1$-adrenergic receptor agonist isoproterenol was given in
stepwise doses from 1 µg to 50 µg with no change in heart rate considered verification of the blockade. No circumstances occurred in which FM blockade was not verified.

Phenylephrine Infusion Procedure

On a separate day, experimental STUDY 2 was performed. The subject was instrumented while lying supine on a hospital bed. A venous cannula with a 12-inch extension tube was introduced into a hand vein and connected to an infusion pump (Sage Instruments, model 351). Sterile isotonic saline was infused at 0.1 ml/min to maintain patency of the cannula line during a thirty minute period of quiet rest. After this period of rest, pre-test control measurements were collected. The infusion syringe was then switched to infuse phenylephrine hydrochloride at 12 µg/min for one minute. If no untoward reactions were observed (note that none were observed in any subject) the infusion rate was increased to 24 µg/min for stage 1. Heart rate and blood pressures were measured every minute until both variables achieved a plateau (approximately 4 minutes) at which time steady-state conditions were assumed and all physiological measurements made. The infusion rate was then increased progressively by stage to a maximum rate of 120 µg/min (see table I) or to an infusion rate producing a systolic blood pressure rise greater than 40 torr from control or an absolute diastolic blood pressure greater than 110 torr. The phenylephrine hydrochloride perfusate was
prepared by diluting 30 mg of phenylephrine hydrochloride in sterile isotonic saline to a 500 ml volume thus producing a concentration of 60 μg/ml. The standard volume infusion rates on the infusion pump were 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, and 2.0 ml/min. Therefore, incremental infusion rates of phenylephrine at 12, 24, 36, 48, 60, 90 and 120 μg/min were achieved with a maximum infused volume of less than 40 ml total.

TABLE I
PROTOCOL FOR PHENYLEPHRINE INFUSION

<table>
<thead>
<tr>
<th>Infusion Rates</th>
<th>Time (min)</th>
<th>Physiological Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 μg/min *</td>
<td>2</td>
<td>HR, SBP, DBP</td>
</tr>
<tr>
<td>24 μg/min *</td>
<td>7</td>
<td>all</td>
</tr>
<tr>
<td>36 μg/min *</td>
<td>7</td>
<td>all</td>
</tr>
<tr>
<td>48 μg/min *</td>
<td>7</td>
<td>all</td>
</tr>
<tr>
<td>60 μg/min *</td>
<td>7</td>
<td>all</td>
</tr>
<tr>
<td>90 μg/min *</td>
<td>7</td>
<td>all</td>
</tr>
<tr>
<td>120 μg/min *</td>
<td>7</td>
<td>all</td>
</tr>
</tbody>
</table>

* Infusion was terminated if systolic blood pressure rose more than 40 torr above rest or an absolute diastolic blood pressure greater than 110 torr was obtained.

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; "all" includes HR, SBP, DBP, forearm blood flow, cardiac output, and calculated variables.
Physiological Measurements

In both studies heart rates and blood pressures were obtained at each minute of the respective protocols. The electrocardiogram was monitored continuously on a cardio-oscilloscope and on a strip chart recorder (Narco Physiograph, model SIX-B). The heart rate for each stage was determined as the mean rate of ten consecutive cardiac cycles during the last minute of each stage. Indirect blood pressure measurements were recorded every minute using a semi-automated electrosphygmomanometer (Narco Biosystems, model 700). Mean arterial blood pressure (MBP) was calculated as diastolic pressure plus one-third pulse pressure.

The following measurements were made during the steady-state condition of each stage of STUDY 2 and at rest, -16 torr and -40 torr during LBNP in STUDY 1. Cardiac output \( Q \) was determined non-invasively using a CO\(_2\) rebreathing technique to derive the variables of the Fick equation. Mean volume of carbon dioxide produced (V\(CO_2\)) and oxygen uptake (V\(O_2\)) were measured over a thirty second period prior to the rebreathing procedure. Subsequently, 15 seconds of end-tidal CO\(_2\) measures were obtained and the mean value used as arterial CO\(_2\) (PaCO\(_2\)). A semi-automated Jones rebreathing valve-bag system was used to switch from room air to the rebreathing bag during which approximately ten breaths were measured and used to extrapolate mixed venous CO\(_2\) content (PvCO\(_2\)) by the asymptotic method of Defares (58). The \( Q \)
was calculated with appropriate corrections for BTPS by the
method described by Klausen (152). The coefficient of
variation for resting measurements was 1.9% around a mean
value of 5.45 l/min as determined from eight serial measure-
ments in a 70 kg man. The concentration of all measured CO₂
was determined by use of a calibrated infrared gas analyzer
(Beckman, model LB-2) and recorded on a multi-channel strip
chart recorder (Soltec, model 1286). The oxygen concen-
tration measurement for VO₂ was made using a calibrated
polarographic oxygen analysis (Beckman, model OM-11) of
expired air in phase with both the CO₂ analysis and venti-
lation volume (Vₑ) determination using a turbine volume
meter (Pneumoscan, model S-301). A heart rate (HR) measure-
ment was made during the rebreathing procedure (HRQ) and was
used to calculate stroke volume (SV) where SV (ml) = Q/HRQ.
Peripheral vascular resistance (PVR) was calculated as
PVR=MBP/Q. The respiratory quotient (RQ) was determined
from the 30 second control measurements made prior to the
rebreathing procedure and calculated as RQ = VCO₂/VO₂.
Lastly, forearm blood flow (BFₕ) was determined using the
plethysmographic technique described by Whitney (260). A
calibrated mercury-in-silastic strain gauge was placed in a
mid-forearm position and connected to a plethysmographic
pre-amplifier (Parks Electronics, model 271). The output
from this pre-amplifier was recorded on the chart recorder
(Narco Biosystems, model SIX-B). For each BFₕ measurement
an occlusion cuff placed around the wrist was inflated to 280 torr to occlude the arterial supply of the hand. This prevented the confounding effect of the anastomotic circulation of the hand on blood flow measures in the forearm. Subsequently, the blood pressure cuff located at the proximal portion of the arm was inflated to 50-60 torr to produce venous occlusion. Thus, the rate of change in forearm circumference was assumed to be proportional to the rate of arterial blood flow into the forearm. The mean rate of change in forearm circumference of triplicate measures was used to calculate \( BF_f \) as follows:

\[
BF_f \ [(ml/100ml)*min] = \frac{2 * C_{FA}}{\Delta C_{FA}} * 100
\]

where \( C_{FA} \) = forearm circumference

\( \Delta C_{FA} \) = the change in forearm circumference per minute during the venous occlusion

Forearm vascular resistance (FVR) was then calculated as \( MBP/ BF_f \).

In addition to the measurements noted above, the following variables were monitored or recorded during LBNP in STUDY 1. The electromyographic activity of the subject's lower extremities and abdominal region were monitored continuously with an integrated biofeedback EMG apparatus (American Biofeedback Corp., Inner Tell model A-7). Placement of the recording electrodes on the inner calf of each leg and at the lateral borders of the abdomen allowed for a peak-to-peak integrated measure of the total EMG activity of
the lower extremities. Pilot work demonstrated that this recording protocol was sensitive to contraction of all leg musculature, trunk musculature, pyramidalis and the family of rectus abdominus muscles. In a previous study (238), we found that moderate muscle tension (5-10% of maximal voluntary contraction) in those regions significantly affected the normal cardiovascular responses to progressive LBNP, apparently due to a somatopressor effect. Therefore, this procedure for monitoring EMG activity was used to insure that the subject was relaxed throughout LBNP and did not engage somatopressor reflexes.

Circumference of the calf was monitored throughout the LBNP procedure using a dual-loop, mercury in silastic plethysmographic strain gauge. The loop was placed in a mid-calf position with one centimeter spacers placed at several locations around the calf to insure uniform placement. The gauge was connected to a pre-amplifier (Parks Electronics, model 271) and the output recorded on the strip chart recorder (Narco, model SIX-B). A calibration curve for each gauge was obtained before and after each LBNP procedure. There were no instances in which the calibration had changed from before to after the LBNP procedure.

Changes in calf circumference (ΔLgC), as percent of the original circumference, were assumed to be representative of changes throughout the leg and were therefore used to calculate the leg volume change (ΔLgV) in milliliters as follows:
\[ \text{LgV} = \left\{ \frac{(CV_x - CV_p)}{CV_p} \times 100 \right\} 	imes \text{LgV} \]

where \( CV_x \) = Calf volume under the gauge during stage \( x \) of LBNP
\( CV_p \) = Calf volume under the gauge before LBNP

The percent blood volume shifted (VOLPER) during LBNP was then calculated as:
\[ \text{VOLPER} = \left( \frac{\text{LgV}}{\text{BV}} \right) \times 100. \]

Other baseline data for each subject was obtained during the blockade conditions. The intrinsic heart rate (HR\(_o\)) was defined as the heart rate obtained during the double blockade condition. The baseline parasympathetic activity was determined by the variation in heart period (VHP) from the control electrocardiogram. The techniques of Kenney (145) were used where VHP was calculated from the low and high R-R intervals obtained during each respiratory cycle. The breathing rate (15-18 breaths per minute) and tidal volume (800-1200 ml) were controlled while measurements were obtained. The VHP was calculated for each respiratory cycle and the mean from fifty consecutive respiratory cycles was used as an individual's VHP.

A modified version of the mathematical model of Rosenblueth and Simeone (215) for determination of resting heart rate, recently used in humans by Katona et al. (142), was used. According to this model resting heart rate (HR\(_r\)) = MNR\(_o\), where M (\( \geq 1 \)) represents a coefficient for the influence of sympathetic activity, N (\( \leq 1 \)) represents a coefficient for the influence of parasympathetic activity and R\(_o\) is the intrinsic rate.
The value of M was determined as $\frac{HR_r}{HR_m}$, where $HR_r$ was the resting heart rate and $HR_m$ was the rate obtained during pharmacological $\beta_1$-adrenergic blockade with metoprolol. Thus, this ratio predicted the influence of sympathetic activity on $HR_r$. The value of N was determined as $\frac{HR_m}{HR_0}$. This ratio represents the ratio of the rate with parasympathetic control alone ($HR_m$) to intrinsic rate ($HR_0$) and thereby, should predict parasympathetic activity at rest. Parasympathetic activity normally predominates under resting conditions. Therefore, to generate an index of autonomic balance that reflects this parasympathetic predominance, the reciprocal of N was used such that increases in parasympathetic activity would be reflected by an increase in the variable. Autonomic balance ($A_{bal}$) was then calculated as $A_{bal} = \frac{1}{N}/M$.

Statistical Analyses

Statistical analysis of the results in STUDY 1 was performed by a three factor (2x6x5) factorial design using an analysis of variance (ANOVA) with repeated measures to discern differences between groups and conditions across stages of LBNP (see figure 2). The differences between the fitness groups or the blockade conditions at rest and at each stage of LBNP was probed with a two factor ANOVA on uncorrelated means with a Student-Newman-Keuls "post hoc" analysis test used to distinguish specific differences when main effect differences were observed.
Fig. 2. Experimental design for studies with LBNP. Independent Variables included blockade condition, fitness level, and LBNP stage. Dependent variables included heart rate, stroke volume, systolic blood pressure, forearm blood flow, diastolic blood pressure, forearm vascular resistance, mean blood pressure, oxygen consumption, cardiac output, HR/ SBP, peripheral vascular resistance, and leg volume changes.

The design for STUDY 2 involved a one way ANOVA across groups for each given phenylephrine infusion rate and a two factor ANOVA for comparison of responses across discrete phenylephrine infusion rates. A general linear models regression analysis was used to describe the heart rate change per change in blood pressure during STUDY 2. Comparison of descriptive data and baseline control data across groups was made using a Student t test. Significance levels for all of the above statistical analyses were set at p<0.05.
CHAPTER III

RESULTS

In the following chapter the mean values and statistical analyses for the descriptive, baseline, and experimental data are presented. In addition, there are graphic illustrations of important differences or similarities between the endurance trained (ET) and untrained (UT) subjects in their responses to the experimental procedures.

Descriptive Comparisons

The descriptive physiological and anthropometric data for the two subject groups are summarized in Table II. The subject groups were not significantly different in age or height (with means of 26.0 ± 1.1 years and 176.4±4.5 cm, respectively). The UT subjects were significantly heavier than the ET subjects (mean weight =79.9±4.0 kg for UT versus 67.2±1.2 kg for ET) and had a greater surface area (SA) with a mean of 1.97±0.05 for UT versus 1.81±0.02 for ET. Furthermore, the UT subjects had significantly greater percent body fat (BF), consequently, the lean body mass (LBM) was similar between the groups (p>0.28), see Table II. The absolute maximal rate of oxygen consumption (VO₂max) was significantly greater in the ET subjects, 4.37±0.12 liters
O$_2$/min versus 3.38±0.20 liters O$_2$/min for the UT subjects.

In addition, the VO$_2$max per body weight or lean body mass was significantly greater in the ET subjects consistent with an exercise training-induced increase in aerobic capacity, see Table II.

**TABLE II**

DESCRIPTIVE PHYSIOLOGICAL AND ANTHROPOMETRIC DATA FOR THE SUBJECT GROUPS

<table>
<thead>
<tr>
<th></th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.8 ±1.3</td>
<td>27.1 ±0.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.3 ±1.5</td>
<td>177.8 ±1.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.2 ±1.1</td>
<td>79.9 ±4.0</td>
</tr>
<tr>
<td>Surface area (m$^2$)</td>
<td>1.81±0.02 *</td>
<td>1.97±0.05</td>
</tr>
<tr>
<td>Total body fat (%)</td>
<td>8.5 ±0.7</td>
<td>17.4 ±1.6</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>61.5 ±1.3</td>
<td>66.0 ±3.0</td>
</tr>
<tr>
<td>VO$_2$max (l/min)</td>
<td>4.37±0.12 *</td>
<td>3.36±0.20</td>
</tr>
<tr>
<td>VO$_2$max [(ml/min)/(kg WT)]</td>
<td>65.0 ±1.7 *</td>
<td>42.4 ±1.1</td>
</tr>
<tr>
<td>VO$_2$max [(ml/min)/(kg LBM)]</td>
<td>71.0 ±1.3 *</td>
<td>50.8 ±2.0</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.
Values represent mean ± S.E.M.

A description and comparison of the blood volumes of the subject groups is summarized in Table III. The total blood volume (BV) and plasma volume (PV) were the same between groups (p>0.92 and p>0.66, respectively). However, when the volumes were expressed as a ratio of body weight or lean body mass, both the BV and PV per mass were significantly greater in the ET subjects; see BV/kg, PV/kg, BV/LBM, and PV/LBM in Table III.
TABLE III
BLOOD VOLUMES AND PLASMA VOLUMES OF THE SUBJECT

<table>
<thead>
<tr>
<th></th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood volume (liters)</td>
<td>6.65±0.29</td>
<td>6.69±0.32</td>
</tr>
<tr>
<td>Plasma volume (liters)</td>
<td>4.29±0.23</td>
<td>4.15±0.21</td>
</tr>
<tr>
<td>BV per body weight (ml/kg)</td>
<td>99.0 ±4.3  *</td>
<td>84.2 ±2.6</td>
</tr>
<tr>
<td>PV per body weight (ml/kg)</td>
<td>63.8 ±3.2  *</td>
<td>52.1 ±1.2</td>
</tr>
<tr>
<td>BV per lean body mass (ml/kg)</td>
<td>108.1 ±1.8 *</td>
<td>101.0 ±1.4</td>
</tr>
<tr>
<td>PV per lean body mass (ml/kg)</td>
<td>69.7 ±1.6 *</td>
<td>62.9 ±1.3</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.
Values represent mean ± S.E.M.

RESTING AUTONOMIC ACTIVITY

Assessment of resting autonomic activity and autonomic balance was performed by several methods as described in the previous chapter. The data obtained for these different measurements are illustrated in Table IV. The variation in

TABLE IV
COMPARISON BETWEEN GROUPS OF THE VARIATION IN HEART PERIOD, PARASYMPATHETIC ACTIVITY, SYMPATHETIC ACTIVITY AUTONOMIC BALANCE

<table>
<thead>
<tr>
<th></th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variation heart period (msec)</td>
<td>180.6 ±7.0</td>
<td>156.0 ±9.6</td>
</tr>
<tr>
<td>Parasympathetic activity (N)</td>
<td>0.61±0.02</td>
<td>0.70±0.03</td>
</tr>
<tr>
<td>Sympathetic activity (M)</td>
<td>1.12±0.01</td>
<td>1.16±0.02</td>
</tr>
<tr>
<td>Autonomic balance (Abal)</td>
<td>1.47±0.06</td>
<td>1.25±0.07</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.
Values represent mean ± S.E.M.
heart period (VHP), measured in milliseconds, was
180.6±9.1 msec for the ET subjects and 156.0±7.0 msec for
the UT subjects with the difference being significant
(p=0.042). The parasympathetic activity (calculated as
N = HR_m/HR_o) was found to be significantly different between
groups with N=0.61±0.02 for the ET subjects and N=0.70±0.03
for the UT subjects. These data indicate that the ET
subjects had a greater parasympathetic activity at rest. In
addition, the autonomic balance (A_{bal} = [1/N]/M) was signifi-
cantly greater in the ET subjects (1.47±0.06 versus
1.25±0.07 for the UT subjects). The sympathetic activity
(calculated as M = HR_r/HR_m) was 1.12±0.01 and 1.16±0.02 for
the ET and UT subjects, respectively. This difference
between the groups was not significant (p=0.052). However,
the trend (0.05<p<0.10) would suggest that the ET subjects
had less sympathetic activity at rest than the UT subjects.

Blockade Effects on Baseline Data

Differences in baseline (resting) values for each phy-
siological variable between each respective blockade con-
dition and control condition are summarized in Table V.
**TABLE V**

**EFFECT OF AUTONOMIC BLOCKADE ON CONTROL DATA**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>PM</th>
<th>FM</th>
<th>PA</th>
<th>FA</th>
<th>DB</th>
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</thead>
<tbody>
<tr>
<td>HR</td>
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<td>S</td>
<td>S</td>
<td>S</td>
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<td></td>
<td>UT</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>SBP</td>
<td>ET</td>
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<td>S</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
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<td>NS</td>
<td>NS</td>
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<tr>
<td>DBP</td>
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<td>FB$_f$</td>
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</tr>
<tr>
<td></td>
<td>UT</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

S= significantly different from control condition (p<0.05); NS= no significant difference from control condition.

PM= partial metoprolol; FM= full metoprolol; PA= partial atropine; FA= full atropine; DB= double blockade.
Baseline heart rate was significantly lower in the ET subjects during all blockade conditions except full atropine (FA), see Table VI. Heart rate for each blockade condition was significantly different from control condition with partial metoprolol (PM) and full metoprolol (FM) values significantly lower than control, and partial atropine (PA), full atropine (FA) and double blockade (DB) values were significantly higher than control, see Table V.

**TABLE VI**

| BASELINE HEART RATE (BEATS/MINUTE) FOR EACH AUTONOMIC BLOCKADE |
|-----------------------------|----------------|----------------|
| Condition                   | ET (n=10)      | UT (n=10)      |
| Control                     | 54.7±3.0       | * 70.2±3.1     |
| Partial Metoprolol          | 50.2±2.8       | * 64.1±2.8     |
| Full Metoprolol             | 47.6±2.6       | * 58.4±3.1     |
| Partial Atropine            | 60.6±3.4       | * 78.8±3.2     |
| Full Atropine               | 100.3±5.4      | 108.6±5.2      |
| Double Blockade             | 79.5±2.8       | * 86.6±2.5     |

* Significant difference between groups, p<0.05. Values represent mean ± S.E.M.

Baseline systolic blood pressure was significantly greater in the ET subjects during control and PM conditions, but was not different between groups during any other condition, see Table VII. The baseline SBP was significantly reduced during FM condition in the ET subjects but was not affected by any other blockade condition for either group, see Table V.
**TABLE VII**

BASELINE SYSTOLIC BLOOD PRESSURE (TORR) FOR EACH AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>126.8±1.2</td>
<td>121.2±1.4</td>
</tr>
<tr>
<td>Partial Metoprolol</td>
<td>123.2±1.2</td>
<td>* 118.4±1.5</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>118.8±2.0</td>
<td>117.2±1.7</td>
</tr>
<tr>
<td>Partial Atropine</td>
<td>125.4±2.0</td>
<td>121.1±1.7</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>129.0±2.8</td>
<td>125.4±1.7</td>
</tr>
<tr>
<td>Double Blockade</td>
<td>127.8±2.1</td>
<td>123.6±1.7</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.
Values represent mean ± S.E.M.

Baseline diastolic and mean blood pressures were not significantly different between groups during any blockade condition (Tables VIII and IX). However, resting DBP and MBP were significantly increased during FA and DB conditions in the UT subjects, while DBP was increased during DB condition in the ET subjects, see (Table V).

**TABLE VIII**

BASELINE DIASTOLIC BLOOD PRESSURE (TORR) FOR EACH AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>77.2±2.9</td>
<td>78.4±2.0</td>
</tr>
<tr>
<td>Partial Metoprolol</td>
<td>75.2±2.3</td>
<td>75.6±2.2</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>77.8±2.4</td>
<td>78.6±1.3</td>
</tr>
<tr>
<td>Partial Atropine</td>
<td>74.6±2.1</td>
<td>75.6±2.0</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>82.0±2.8</td>
<td>84.0±2.1</td>
</tr>
<tr>
<td>Double Blockade</td>
<td>84.4±3.0</td>
<td>86.0±1.6</td>
</tr>
</tbody>
</table>

No significant differences were observed between groups. Values represent mean ± S.E.M.
TABLE IX

BASELINE MEAN BLOOD PRESSURE (TORR) FOR EACH AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>93.7±2.2</td>
<td>92.7±1.0</td>
</tr>
<tr>
<td>Partial Metoprolol</td>
<td>91.5±1.7</td>
<td>89.5±1.3</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>91.5±1.8</td>
<td>92.1±1.8</td>
</tr>
<tr>
<td>Partial Atropine</td>
<td>91.5±2.1</td>
<td>90.7±1.6</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>97.7±2.5</td>
<td>96.5±1.7</td>
</tr>
<tr>
<td>Double Blockade</td>
<td>98.9±3.0</td>
<td>98.5±1.6</td>
</tr>
</tbody>
</table>

No significant differences were observed between groups. Values represent mean ± S.E.M.

Baseline cardiac output (Q) was not significantly different between groups during any blockade condition (Table X). The cardiac output was affected only by the FA condition where Q was significantly increased above control condition in both groups (Table V).

TABLE X

BASELINE CARDIAC OUTPUT (L/MIN) FOR EACH AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.81±0.39</td>
<td>5.95±0.25</td>
</tr>
<tr>
<td>Partial Metoprolol</td>
<td>5.67±0.37</td>
<td>5.72±0.31</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>5.24±0.25</td>
<td>5.24±0.19</td>
</tr>
<tr>
<td>Partial Atropine</td>
<td>5.68±0.24</td>
<td>5.32±0.27</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>6.50±0.27</td>
<td>7.12±0.40</td>
</tr>
<tr>
<td>Double Blockade</td>
<td>5.33±0.12</td>
<td>5.59±0.21</td>
</tr>
</tbody>
</table>

No significant differences between groups were observed. Values represent mean ± S.E.M.

The baseline stroke volume was significantly greater in the ET subjects during all conditions except for FA and DB, see Table XI. Control stroke volume was affected only by
the FA and DB conditions in which the values were significantly lower in both groups (Tables V and XI).

TABLE XI

BASELINE STROKE VOLUME (ML) FOR EACH AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>95.2±7.5</td>
<td>80.7±3.9</td>
</tr>
<tr>
<td>Partial Metoprolol</td>
<td>100.2±7.1</td>
<td>85.5±3.6</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>102.2±8.8</td>
<td>86.1±4.9</td>
</tr>
<tr>
<td>Partial Atropine</td>
<td>90.8±5.1</td>
<td>71.5±3.2</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>64.7±3.7</td>
<td>65.2±4.4</td>
</tr>
<tr>
<td>Double Blockade</td>
<td>68.0±2.5</td>
<td>65.5±4.1</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.
Values represent mean ± S.E.M.

The baseline oxygen consumption (VO₂) was not significantly different between groups during any blockade condition, see Table XII. In addition, all pharmacological blockade conditions had no effect on the baseline VO₂ (Tables V and XII). In addition, the calculation of
arterial-venous oxygen difference, where $a-vO_2$diff = $V_0^2/Q$, was not affected by any autonomic blockade. These data indicate that autonomic blockade had no effect on metabolic drive.

The baseline forearm blood flow ($BF_f$) was not significantly different between groups for each blockade condition except during DB condition where the $BF_f$ was significantly greater in the ET subjects (Table XIII). Only the $FB_f$ during FA condition was significantly different (greater) from the control condition, with the other blockade conditions not affecting resting $BF_f$ (Tables V and XIII).

**TABLE XIII**

BASELINE FOREARM BLOOD FLOW [(ML/MIN)/100 ML] FOR EACH AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.19±1.02</td>
<td>4.39±0.76</td>
</tr>
<tr>
<td>Partial Metoprolol</td>
<td>5.13±0.80</td>
<td>4.42±0.75</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>4.58±0.78</td>
<td>4.17±0.21</td>
</tr>
<tr>
<td>Partial Atropine</td>
<td>5.41±0.85</td>
<td>4.82±0.29</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>7.25±1.08</td>
<td>6.37±0.80</td>
</tr>
<tr>
<td>Double Blockade</td>
<td>6.49±1.21</td>
<td>* 4.27±0.27</td>
</tr>
</tbody>
</table>

* Significant difference between groups, $P<0.05$. Values represent mean ± S.E.M.

Resting forearm (FVR) vascular resistance was not significantly different between groups during any blockade condition (Table XIV). Likewise, the peripheral vascular resistance was not significantly affected by any blockade
TABLE XIV

BASELINE FOREARM VASCULAR RESISTANCE (PRU) FOR EACH AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>23.0±4.0</td>
<td>24.8±3.5</td>
</tr>
<tr>
<td>Partial Metoprolol</td>
<td>23.8±4.1</td>
<td>23.5±2.9</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>23.8±3.1</td>
<td>23.1±1.8</td>
</tr>
<tr>
<td>Partial Atropine</td>
<td>20.0±3.6</td>
<td>21.5±1.2</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>17.2±3.4</td>
<td>17.3±1.5</td>
</tr>
<tr>
<td>Double Blockade</td>
<td>21.3±4.4</td>
<td>24.5±1.4</td>
</tr>
</tbody>
</table>

No significant differences were observed between groups. Values represent mean ± S.E.M.

condition (Table XV). Furthermore, only the FVR, for the FA condition, and PVR, for the DB condition, in the UT subjects were significantly different (lower) from the control condition (Tables V, XIV and XV).

TABLE XV

BASELINE PERIPHERAL VASCULAR RESISTANCE (PRU) FOR EACH AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (n=10)</th>
<th>UT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>16.6±0.8</td>
<td>15.9±0.8</td>
</tr>
<tr>
<td>Partial Metoprolol</td>
<td>16.6±0.9</td>
<td>16.1±0.9</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>17.9±1.1</td>
<td>17.6±0.7</td>
</tr>
<tr>
<td>Partial Atropine</td>
<td>16.3±0.6</td>
<td>17.4±0.8</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>15.3±0.7</td>
<td>14.6±0.8</td>
</tr>
<tr>
<td>Double Blockade</td>
<td>18.2±0.5</td>
<td>17.8±0.7</td>
</tr>
</tbody>
</table>

No significant differences between groups. Values represent mean ± S.E.M.
Physiological Responses to Lower Body Negative Pressure

The physiological responses to lower body negative pressure (LBNP) during each autonomic blockade condition are presented in Tables XIX-XXIV. The data are presented for stages 0 Torr, -16 Torr, and -40 Torr only since all measurements were made at these respective stages. Physiologically, these stages represent rest (0 Torr), stimulation of cardiopulmonary baroreceptors alone (-16 Torr), and stimulation of both arterial and cardiopulmonary baroreceptors (-40 Torr). Significant differences between groups are indicated by a "*" at each stage. Figures 3-16 present the change (in units and percent) in HR, SBP, FVR, PVR, Q, SV and BF\(_f\) from 0 to -16 torr and 0 to -40 torr LBNP for each blockade condition. In addition, the differences between the changes across different stages of LBNP for each group and blockade condition are summarized in Table XVI.

**Heart Rate Responses to LBNP**

During all blockade conditions except for double blockade, HR increased significantly at -40 Torr in both groups, consistent with a reflex tachycardia (see appendix I, Table XIX). The unit change in HR from 0 torr to -40 torr was significantly greater than the change from 0 torr to -16 torr for both groups during all blockade conditions except double blockade. The actual values were significantly different between the groups at all stages during control
<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>PM</th>
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<th>PA</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>ET</td>
<td>UT</td>
<td>ET</td>
<td>UT</td>
</tr>
<tr>
<td>HR</td>
<td>0-16</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0-40#</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>S</td>
</tr>
<tr>
<td>SBP</td>
<td>0-16</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
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<td>NS</td>
<td>NS</td>
<td>*</td>
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<tr>
<td>Q</td>
<td>0-16</td>
<td>-</td>
<td>NS</td>
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<td>-</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>*</td>
</tr>
<tr>
<td>SV</td>
<td>0-16</td>
<td>*</td>
<td>S</td>
<td>*</td>
<td>NS</td>
<td>NS</td>
</tr>
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</tr>
<tr>
<td>BF&lt;</td>
<td>0-16</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td></td>
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<td>PVR</td>
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<tr>
<td></td>
<td>0-40#</td>
<td>-</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Blockade conditions are: C=control; PM=partial metoprolol; PM=full metoprolol; PA=partial atropine; DB=double blockade. Variables are: HR=heart rate; SBP=systolic blood pressure; Q=cardiac output; SV=stroke volume; BF<forearm blood flow; FVR=forearm vascular resistance; PVR=peripheral vascular resistance. 0-16= change from 0 to -16 torr of LBNP. 0-40= change from 0 to -40 torr of LBNP. * significant difference between groups. # significant differences between 0-16 and 0-40. NS=not significant from control; S=significantly different from control.
and partial metoprolol conditions (Tables I and II, appendix I), while significant differences between groups were observed only at stages 0 and -16 torr during full metoprolol and partial atropine (Tables XXI and XXII, appendix).

During full atropine blockade no difference in HR was observed between groups at any stage of LBNP. The HR did not change during LBNP during the double blockade condition consistent with the complete ablation of nervous control of HR. The unit changes in HR from 0 torr to -16 or -40 torr were not significantly different between the groups during any blockade condition, see figure 3 and Table XVI. The HR

![Heart rate responses to LBNP](image)

**Fig. 3.** Heart rate responses to LBNP are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the unit change from 0 torr to -40 torr LBNP, while the hatched portion represents the unit change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade. Measurements represent means±S.E.M.
change from 0 torr to -40 torr was significantly reduced during full metoprolol, in the UT subjects, and double blockade in both subject groups, see figure 3 and Table XVI. The HR response was augmented in the ET subjects during partial atropine blockade. Similar trends in the HR responses are illustrated by the percent changes (figure 4).

![Heart rate responses to LBNP](image)

**Fig. 4.** Heart rate responses to LBNP (in percent change) are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the percent change from 0 torr to -40 torr LBNP, while the hatched portion represents the percent change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade.
Systolic Blood Pressure Responses to LBNP

During all blockade conditions the SBP decreased significantly at -40 torr in both groups, see Tables XIX-XXIV, appendix I. The unit change in SBP from 0 to -40 torr was significantly greater than the change from 0 to -16 torr during all blockade conditions for both groups (figure 5 and Table XVI). No significant group differences in absolute SBP.

Fig. 5. Systolic blood pressure responses to LBNP are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the unit change from 0 torr to -40 torr LBNP, while the hatched portion represents the unit change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade. Measurements represent means+S.E.M.
were observed during all conditions except for the full metoprolol condition, where SBP was lower in the ET subjects at -40 torr (Table XXI, appendix I). The greater SBP response to LBNP in the ET subjects during the control and metoprolol blockade conditions is clearly illustrated by the percent changes observed (figure 6). The unit change from 0

![Diagram](image)

**Fig. 6.** Systolic blood pressure responses to LBNP (in percent change) are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the percent change from 0 torr to -40 torr LBNP, while the hatched portion represents the percent change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade.
to -40 torr was significantly different between groups only
during the control and full metoprolol conditions. During
these two blockade conditions, SBP fell more dramatically in
the ET subjects (figure 5 and Table XVI).

**Cardiac Output Responses to LBNP**

During all blockade conditions, $Q$ decreased signifi-
cantly at -16 torr and -40 torr in both groups, (Table XXI,
appendix I) consistent with a significant reduction in
venous return during LBNP. The actual values were not
significantly different between groups at stage 0 or -16
torr during all blockade conditions (Table XXII, appendix
I). However, $Q$ was significantly different between groups
(ET and UT) at -40 torr during the control and both meto-
prolol blockade conditions (Table XVI).

The unit change in $Q$ from 0 to -40 torr was signifi-
cantly greater than the 0 to -16 torr change during all
blockade conditions for both groups (figure 7 and Table
XVI). The unit change in $Q$, from 0 to -40 torr, was signi-
ificantly different between groups during the full metoprolol
(ET > UT) and full atropine (ET < UT) blockade conditions,
while no group differences were observed during any other
blockade condition (figure 7 and Table XVI). The unit
change in $Q$ from 0 to -40 torr was significantly greater
than control conditions during full atropine blockade (in
both groups) and during double blockade (in UT subjects
only), see figure 6 and Table XVI. The change from 0 to -16
torr was significantly different from control condition only during full atropine blockade in the UT subjects.

Fig. 7. Cardiac output responses to LBNP are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the unit change from 0 torr to -40 torr LBNP, while the hatched portion represents the unit change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade. Measurements represent means+S.E.M.

The fall in Q during LBNP was 8-10% greater in the ET subjects than the UT subjects during the partial and full metoprolol blockade conditions and approximately 12% greater in the UT subjects (as compared to the ET subjects) during full atropine (figure 8).
Fig. 8. Cardiac output responses to LBNP (in percent change) are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the percent change from 0 torr to -40 torr LBNP, while the hatched portion represents the percent change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade.

**Stroke Volume Response to LBNP**

Stroke volume (SV) decreased significantly at all stages of LBNP during all conditions (Tables XIX-XXIV, appendix) consistent with a progressive reduction in venous return during LBNP. The change from 0 to -40 torr was signifi-
cantly greater than the 0 to -16 torr change during all blockade conditions (figure 9 and Table XVI). Although SV was significantly different between groups at rest during several conditions (as illustrated in Table XI), there were no group differences at -16 torr or -40 torr during any blockade condition.

Fig. 9. Stroke volume responses to LBNP are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the unit change from 0 torr to -40 torr LBNP, while the hatched portion represents the unit change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade. Measurements represent means+S.E.M.
The unit fall from 0 to -16 torr in SV was significantly different between groups during the control (ET > UT) and partial metoprolol (ET < UT) conditions (see figure 9 and Table XVI). The change from 0 to -40 torr was significantly different between the groups only during partial atropine blockade (ET > UT). Percent changes, relative to rest values, were not remarkably different and uniformly reflected the unit changes observed (figure 10). The SV

Fig. 10. Stroke volume responses to LBNP (in percent change) are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the percent change from 0 torr to -40 torr LBNP, while the hatched portion represents the percent change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade.
change (from 0 to -16 and -40 torr) during full atropine and double blockade were significantly less than the changes observed during control in the ET subjects (figure 9 and Table XVI). This latter finding reflected the remarkable decrease in resting SV in the ET subjects.

Blood Volume Shifts During LBNP

The percent shift in blood volume into the lower extremities is represented by VOLPER in Tables XIX-XXIV, appendix I. This measurement increased significantly at -16 torr and -40 torr, consistent with progressive pooling of blood in the lower extremities. The percent change was not significantly different between groups at any stage during any blockade condition. This is suggestive of a consistent effect of LBNP on volume shifts during the procedure regardless of blockade condition.

Forearm Blood Flow Responses to LBNP

The BF<sub>f</sub> decreased significantly at -16 torr and -40 torr of LBNP during all conditions in both groups (Table XIX, appendix I). The unit change in BF<sub>f</sub> from 0 to -40 torr was significantly greater than the 0 to -16 torr change only in the UT subjects during the full atropine blockade condition. Actual BF<sub>f</sub> values were significantly different between groups at -40 torr during the partial and full atropine blockade conditions (Tables XXII and XXIII).

Group differences in response (change in BF<sub>f</sub>) were
observed only for the 0 to -40 torr change during the double blockade condition (ET > UT), see figure 11 and Table XVI.

![Diagram](image)

**Fig. 11.** Blood flow responses to LBNP are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the unit change from 0 torr to -40 torr LBNP, while the hatched portion represents the unit change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade. Measurements represent means±S.E.M.

The BF$_f$ changes from 0 to -40 torr were significantly greater than control condition during full atropine (both groups) and double blockade (ET only), see figure 11 and Table XVI. The percent changes in BF$_f$ further illustrate...
the greater vasoconstrictor (decrease in blood flow) response that occurred during full atropine and double blockade, see figure 12.

![Blockade Condition Diagram](image)

**Fig. 12.** Blood flow responses to LBNP (in percent change) are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the percent change from 0 torr to -40 torr LBNP, while the hatched portion represents the percent change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade.

**Forearm Vascular Resistance Responses to LBNP**

Forearm vascular resistance (FVR) increased at stages -16 torr and -40 torr during all blockade conditions (Tables
XIX, appendix I). The increase in FVR from 0 to -40 torr was significantly greater than from 0 to -16 torr during full metoprolol in the ET subjects, and during the partial atropine, full atropine and double blockade conditions in the UT subjects, see figure 13 and Table XVI. The actual FVR values were not significantly different between groups during any blockade condition at any stage of LBNP (Tables XIX-XXIV).

![Fig. 13. FVR responses to LBNP are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the unit change from 0 torr to -40 torr LBNP, while the hatched portion represents the unit change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade. Measurements represent means±S.E.M.](image-url)
The unit change in FVR was significantly different between groups form 0 to -16 torr during the full atropine and double blockade conditions (figure 13 and Table XVI). The increase in FVR from 0 to -40 torr was significantly greater than control conditions in the ET subjects during full atropine and double blockade, and during the partial atropine, full atropine and double blockade conditions in the UT subjects. In addition, the FVR increase from 0 to -16 torr was significantly greater than control condition in the UT subjects during full atropine and double blockade (figure 13 and Table XVI). These greater vasoconstrictor responses (as indicated by the increase in resistance) are also illustrated by the greater percent change in FVR during the atropine and double blockade conditions, see figure 14.
Peripheral Vascular Resistance Responses to LBNP

The PVR increased significantly at both -16 torr and -40 torr during all blockade conditions in both groups (Table XIX, appendix I). The unit change in PVR was significantly greater from 0 to -40 torr only in the UT subjects during full atropine and double blockade, see figure 15 and Table XVI. The actual PVR values were not significantly
different between groups at any stage during any blockade condition (Tables XIX-XXIV).

Fig. 15. PVR responses to LBNP are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the unit change from 0 torr to -40 torr LBNP, while the hatched portion represents the unit change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade. Measurements represent means±S.E.M.

The change from 0 to -16 torr was significantly greater during partial atropine in the ET subjects and during double blockade in the UT subjects than that observed during control condition (figure 15 and Table XVI). The 0 to -40 torr change was significantly greater during both the full
atropine and double blockade conditions (in both groups) than during the control condition. These data further support the occurrence of a greater vasoconstrictor response during the full atropine and double blockade conditions. This is also illustrated by the greater percent change in PVR observed during these two blockade conditions, see figure 16.

![Graph](image)

**Fig. 16.** PVR responses to LBNP (in percent change) are represented for endurance trained (E) and untrained (U) subjects. Total bars (hatched plus open portions) represent the percent change from 0 torr to -40 torr LBNP, while the hatched portion represents the percent change from 0 torr to -16 torr. Blockade conditions are: C=control; PM=partial metoprolol; FM=full metoprolol; PA=partial atropine; FA=full atropine; DB=double blockade.
Orthostatic Tolerance During LBNP

The occurrence of pre-syncopal symptoms and early termination of the LBNP procedure can be used to evaluate subject tolerance to the orthostatic challenge. Pre-syncopal symptoms were observed during control condition in six ET and three UT subjects. The calculation of tolerance (torr x min), as based on the time at which each subject terminated the test, was significantly greater in the UT subjects, see Table XVII. Chi-square analysis of the incidence of pre-syncopal symptoms did not demonstrate a significant difference between the groups (Table XVII). However, with an n of 10 per cell, this test of association can not be considered a powerful statistic. Remembering that during the blockade conditions the LBNP procedure was taken only to -40 torr, pre-syncopal incidents occurred in only two ET subjects during the partial and full metoprolol blockade conditions.

TABLE XVII

ORTHOSTATIC TOLERANCE DURING LBNP

<table>
<thead>
<tr>
<th></th>
<th>ET</th>
<th>UT</th>
<th>X²</th>
<th>t</th>
<th>p value</th>
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<td>Pre-syncopal incidents</td>
<td>6</td>
<td>3</td>
<td>1.82</td>
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<tr>
<td>torr x minutes</td>
<td>479±43</td>
<td>593±22</td>
<td>-</td>
<td>-2.36</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Values for torr x minutes are mean±S.E.M.
Physiological Responses to Phenylephrine

The basic physiological responses to the progressive infusion rates of phenylephrine for each group are illustrated in figures 17-19. Systolic (SBP), diastolic (DBP), and mean (MBP) blood pressures increased progressively with increasing infusion rates, see figure 17.

![Graph showing blood pressure responses to phenylephrine infusion](image)

Fig. 17. Systolic (SBP), diastolic (DBP), and mean (MBP) blood pressure responses during phenylephrine (PE) infusion in endurance trained (open circles) and untrained (solid circles) subjects. * indicates significant difference between groups (P<0.05).
The only significant differences between groups were observed in SBP at 24 µg/min and 36 µg/min, where SBP was greater in the ET subjects. In addition, the degree of change in each blood pressure measurement was approximately the same between groups. Forearm blood flow ($BF_f$) decreased progressively with no significant differences observed between the groups (figure 18). Similarly, both forearm

Fig. 18. Forearm blood flow ($BF_f$) and vascular resistance (FVR), and peripheral vascular resistance (PVR) responses during phenylephrine (PE) infusion in endurance trained (open circles) and untrained (solid circles) subjects. No significant differences between groups were observed.
vascular resistance (FVR) and peripheral vascular resistance (PVR) increased progressively with increasing infusion rates (figure 18). Again, no significant group differences were observed at any infusion rate. Similar to the blood pressure responses, the degree of change in BFf, FVR and PVR was similar between groups. Therefore, the vasoconstrictor effect of the phenylephrine produced similar blood pressure and resistance increases, and BFf decreases in the two subject groups.

Cardiac output (Q) decreased slightly during the phenylephrine procedure, but was not significantly different between groups at any stage of the procedure (figure 19). Stroke volume (SV) changes were more variable with SV increasing in the UT subjects and remaining unchanged in the ET subjects, see figure 19.

Consistent with a reflex bradycardiac response to the increase in blood pressure, heart rate (HR) decreased progressively in both subject groups (figure 19). No significant group differences were observed at any stage other than rest. However, the change from rest to 120 μg/min was significantly greater in the UT subjects (26.3±1.4) than the ET subjects (12.4±1.0), see figure 19. This finding implies a greater baroreflex responsiveness existed in the UT subjects.
Fig. 19. Heart rate (HR), cardiac output (Q), and stroke volume (SV) responses during phenylephrine (PE) infusion in endurance trained (open circles) and untrained (solid circles) subjects. No significant differences between groups were observed.

Regression analyses of HR against SBP (figure 20) or MBP (figure 21) confirmed this hypothesis. In each case, the slope of the line-of-best-fit was significantly greater in the UT subjects. The analysis of HR versus SBP resulted
in the linear regression equations $y = -0.45x + 112.6$ for the ET subjects and $y = -0.81x + 162.8$ for the UT subjects.

Fig. 20. Regression analyses of heart rate versus systolic blood pressure during phenylephrine infusion for endurance trained (dashed line) and untrained (solid line) subjects. The equation of the line-of-best-fit was $y = -0.45x + 112.6$ ($r=0.91, P<0.01$) for the ET subjects and $y = -0.81x + 162.8$ ($r=0.93, P<0.01$) for the UT subjects. The slopes were significantly different ($P<0.05$).

The significant correlation coefficients obtained were 0.91 and 0.93 ($P<0.01$) for the ET and UT subjects, respectively,
indicating that a linear regression model was appropriate for this analysis. The analysis of HR versus MBP resulted in the regression equations $y = -0.57x + 110.6$ for the ET subjects and $y = -0.91x + 148.5$ for the UT subjects.

Fig. 21. Regression analyses of heart rate versus mean blood pressure during phenylephrine infusion for endurance trained (dashed line) and untrained (solid line) subjects. The equation of the line-of-best-fit was $y = -0.57x + 110.6$ ($r=0.92, P<0.005$) for the ET subjects and $y = -0.91x + 148.5$ ($r=0.96, P<0.005$) for the UT subjects. The slopes were significantly different ($P<0.05$).
The significant correlation coefficients obtained were 0.92 and 0.96 ($P<0.005$) for the ET and UT subjects, respectively, indicating that the linear regression model was appropriate. Analysis of the slopes revealed a significantly lower slope in the ET subjects for both regression analyses.
CHAPTER IV

DISCUSSION

In the following chapter the baseline and experimental data will be interpreted and discussed in light of fundamental concepts of physiology, and previous experimental observations and discussions found in the literature. The chapter will be divided into three subsections including: 1) a discussion of the descriptive and baseline data in the two subject populations, 2) a discussion of the physiological responses to a relative hypotensive or hypertensive stress and the implications in cardiovascular regulation, and 3) a summary and discussion of direction for future investigations pertinent to these findings.

Group Differences in Descriptive and Baseline Data

Anthropometric Comparisons

The subject groups were matched for age and height, however, the untrained (UT) subjects had a significantly greater weight, body surface area and total body fat (Table II). The lean body mass was similar between the groups, therefore, the greater weight in the UT subjects was due primarily to the greater body fat (Table II). This finding is consistent with the accepted tenet that exercise training is associated with a reduction in body fat.
It is important to note that the subject groups were matched for age and height as these two variables can affect the physiological responses to an orthostatic challenge. Several studies have shown that orthostatic intolerance, as evidenced by abnormally large falls in systolic blood pressure (SBP) upon standing, is more prevalent in the elderly population (37,197). The mechanisms explaining this loss of blood pressure control in the elder subject are not well understood (232). Therefore, it is not known at what age this phenomenon begins to occur or what aspect of the aging process accounts for this phenomenon. Hence, the matching of subject groups for age eliminated the possibility of this effect confounding the experiment. The height of an individual will affect the hydrostatic pressure gradients observed throughout the body during orthostasis. Therefore, gradations in lower body negative pressure (LBNP) would not be expected to produce identical changes in blood volume distribution in subjects with significantly differing heights. This effect does not complicate the data from this study since the groups were matched for height.

**Aerobic Capacity**

Maximal oxygen uptake (VO₂ max) has been used as an index of aerobic capacity for many years (182). This variable is highly reproducible when appropriate criteria for maximal effort are attained (16,80,219,250). These criteria include achievement of maximum heart rate, a pla-
teau of oxygen uptake (VO₂) as indicated by final stage increases of < 100 ml/min, and the appearance and pallor of the subject. Heart rate increases in a linear fashion with increasing workloads until a maximum workload is achieved (11). Most individuals are capable of functioning at even greater workloads (supra-maximal) for short periods of time. This phenomenon allows a subject to work at or near their VO₂max for two or more minutes and attain a plateau in VO₂ (41). In this study, every subject achieved a heart rate that was maintained for more than two minutes. This plateauing of the HR indicates that a maximum was attained. Likewise, a final stage increase in oxygen uptake of < 100 ml/min was obtained in each subject.

The absolute VO₂max, in ml/min, of the ET subjects was significantly greater than the UT subjects (p<0.01), as would be expected. However, since the groups were not matched for body weight, it is more appropriate to compare the VO₂max of each group in relation to their body weight or lean body mass. These calculations also revealed a significantly greater VO₂max per kilogram of body weight (p<0.001) or lean body mass (p<0.005) in the ET subjects. Drinkwater (74) reviewed the differences in VO₂max observed between men and women. She noted that VO₂max per body weight was usually greater in men than in women by 20 to 25 percent. This difference was reduced to less than ten percent in most populations studied when the calculation of VO₂max was cor-
rected with lean body mass. The logic of this observation is sound as it is the skeletal and cardiac muscle tissues that are primarily responsible for the remarkable increase in metabolic demand. Blood flow to subcutaneous adipose tissue in humans has been found to increase up to 400 percent during prolonged exercise (36). However, this marked rise in blood flow in the fat tissues does not appear to reflect a metabolic demand as the overall increase in VO$_2$ was unaffected. Therefore, it follows that evaluation of VO$_2$max relative to lean body mass is appropriate when comparing different subject populations. The fitness of the ET subjects was clearly greater than the UT subjects, regardless of whether the absolute VO$_2$max, VO$_2$max per body weight, or VO$_2$max per lean body mass was used to compare the groups. This complies with the aerobic capacity differences expected as based on the daily activity requirement of the subject group selection.

**Blood Volume**

Evidence has accrued over recent years supporting the tenet that total blood volume increases with endurance exercise training (48,49,192,212). These reports have been demonstrated in both cross-sectional (212) and longitudinal (48,49,192) designs using several different volume measurement techniques. These findings are in contrast to the previous report by De Bass et al. (57) who suggested that exercise training has no effect on blood volume. De Bass
et al. (57) suggested that earlier findings demonstrating a blood volume increase with training were in error due to a technical problem associated with using the carbon monoxide technique. De Bass et al. (57) proposed that the greater muscle mass, and thus greater myoglobin, was not corrected for and resulted in erroneously high blood volume values. In this study, the total blood volume and plasma volume was similar between the groups. However, when the volumes were corrected for body weight, the ET subjects demonstrated a significantly greater total blood volume and plasma volume than the UT subjects. Furthermore, when the concerns of De Bass et al. (57) were considered by correcting for lean mass, an expanded blood volume was observed in the ET subjects as compared to the UT subjects, and, regardless of how BV or PV were expressed, differences between the groups were consistent. The differences in blood volume and plasma volume between groups were similar. Therefore, it appears that the greater total blood volume of the ET subjects was to be exclusively due to a greater plasma volume. This finding is consistent with the earlier findings of Convertino et al. (49) and Rocker et al. (212).

**Baseline Physiology**

The role of physical activity and endurance exercise training in maintaining or improving cardiovascular health has been primarily attributed to the improvement in cardiovascular responses to stress (exercise or other).
Clausen (41) eloquently reviewed the effects of exercise training on the cardiovascular responses to exercise. In general, these effects result in an improved efficiency in the delivery and utilization of oxygen during exercise. In addition, there is a growing body of evidence suggesting that exercise training results in an improved tolerance of psychological stresses (28,144,216). Although a thorough scientific treatment of the latter effect has not been completed, Rosch (216) has stated that anecdotally, "the facts are quite clear that exercise reduces stress, anxiety and depression for a large majority of individuals."

In addition to these effects, exercise training causes changes in basal physiology. Among these changes is a reduction in resting heart rate (80,162,163,165). Consistent with these previous investigations, the ET subjects had a significantly lower resting heart rate than the UT subjects. A more thorough analysis of the mechanisms explaining this difference will be formulated in the following section (Autonomic Control at Rest). The effect of exercise training on blood pressure is still a debated issue. However, in a recent review of this question and its application to hypertension, Tipton (252) stated that the majority of longitudinal studies "indicate that training would be associated with lower systolic blood pressures (ranging from 5 to 25 mmHg) and lower diastolic blood pressures (ranging from 3 to 15 mmHg)." In the present study,
systolic blood pressure was significantly greater in the ET subjects (126.8±1.2 torr versus 121.2±1.4 torr for the UT subjects) while mean and diastolic blood pressures were not different between groups. This difference may be due to genetic differences between the two subject populations. However, it is important to note that on a separate experimental day the control blood pressures observed prior to the phenylephrine infusion were not significantly different (see figure 17). Hence, the difference observed during the control period prior to the LBNP procedure is more likely an anecdotal difference in the measurements obtained on the day in which the control measurements were made. If a difference in blood pressure were found, a difference in either total blood volume, cardiac output, or resistance would be expected. However, there were no significant differences in total blood volume, cardiac output, or forearm blood flow. In their reviews, Raven and Smith (210) and Clausen (41) indicated that both resting cardiac output and total peripheral resistance do not change significantly with exercise training. Therefore, the results from the present study are consistent with previous findings.

Consequent to the lower resting heart rate in the ET subjects, cardiac filling time and stroke volume (SV) were greater than in the UT subjects. As resting cardiac performance does not appear to be altered by training (39,111, 214), this greater SV at rest in the ET subjects is probably
due exclusively to the Starling effect. During exercise stress, the SV remains higher in endurance athletes due to enlarged cardiac dimensions (89,130,224) and an improved cardiac performance (202,231). Thus, it is only at rest that the greater stroke volume in ET subjects is due to Starling effects alone consequent to a lower heart rate.

**Autonomic Control at Rest**

Endurance exercise training is usually accompanied by a decrease in resting HR after a training period as previously noted (80,162,165). In addition, resting HR is usually significantly lower in trained athletes when compared to sedentary individuals (143,146,163). Similarly, the ET subjects in the present study had a significantly lower resting HR than their UT counterparts (54.7±3.0 beats/min versus 70.2±3.1 beats/min). Analysis of the mechanisms responsible for this difference revealed that the intrinsic heart rate (HR_{o}) was significantly lower in the ET subjects (79.5±2.8 beats/min versus 86.6±2.5 beats/min for the UT subjects). However, this lower HR_{o} does not fully explain the lower HR_{r} observed in the ET subjects. Using the methods of Katona et al. (143) the resting sympathetic and parasympathetic coefficients were determined for each subject. The parasympathetic activity was found to be significantly greater in the ET subjects (p=0.045). The sympathetic activity was slightly, but nonsignificantly (p=0.052), lower in the ET subjects. However, this slight difference appeared
to accentuate the significant difference in autonomic balance, which was significantly greater in the ET subjects (p=0.018). This difference in autonomic balance is indicative of a greater parasympathetic dominance at rest in the ET subjects when compared to the UT subjects. These findings are in agreement with the study of Ordway et al. (192) who demonstrated that cardiac denervation in dogs prevents the endurance exercise training-induced decrease in heart rate. These findings are in contrast to the observations of Katona et al. (143), who suggested that the difference between their ET and UT subjects in HR$_I$ was attributable to a difference in HR$_0$ alone. The ET subjects in Katona's study were oarsmen. The exercise regimen practiced by these athletes involves considerable resistive exercise by the upper extremities, which may produce a unique alteration in autonomic control of the heart. In a recent study in this laboratory, no significant differences in parasympathetic or sympathetic activity were observed between a group of competitive power lifters and the UT subjects (unpublished data). The ET subjects in the present study were exclusively runners or triathletes who practiced only minimal resistive exercise training. This difference in the ET subject populations between the study of Katona et al. (143) and our ET subjects may explain the difference in results from the two investigations. Furthermore, genetic differences in autonomic control between the groups involved in the two studies cannot be discounted as a possible explanation for these differences. If these differences are
due to an exercise training adaptation, a far more intriguing question is conceived regarding the stimulus for and mechanisms of the resulting change in control.

The significantly greater parasympathetic activity observed in the ET subjects is in agreement with several previous investigations demonstrating a similar effect of exercise training (80, 97, 205). Recently, Kenney (146) found that individuals with greater aerobic capacity had significantly greater parasympathetic activity at rest as indicated by a greater variation in heart period (VHP). The VHP of the ET subjects in this study was significantly (p=0.042) greater than the UT subjects. This is in agreement with the observations of Kenney (146) and the calculation of parasympathetic activity noted above.

**Blood Pressure Regulation**

Since the earlier reports of Stegemann et al. (244, 245) and Cooper and Leverett (51), that blood pressure regulation was altered by exercise training, there have been a variety of studies attempting to confirm or reject this hypothesis (50, 81, 154, 155, 208). Most of the previous investigations have not scientifically attempted to determine mechanistic explanations of this possible exercise-induced alteration of blood pressure regulation. Rather, the investigative concerns have been primarily with the issue of whether exercise training can affect one's tolerance to an orthostatic
stress. Previously, it was suggested that exercise training was associated with a decrease in baroreflex responsiveness \((18,245,251)\). This hypothesis implies a change in normal autonomic nervous system control of the cardiovascular system. Hence, the design of the present study was to discern differences in baroreflex function and normal autonomic control of the cardiovascular system between ET and UT individuals. These differences and similarities in cardiovascular regulatory function between the groups will be discussed in the remaining sections of this chapter.

An orthostatic challenge, such as LBNP, presents the cardiovascular system with a relative hypotensive and hypovolumic stress. The stimulus for these stresses is the pooling of blood volume in the lower extremities. The absolute blood volume shifted into the legs was similar between the groups at stage \(-50\) torr during the control condition \((512 \pm 32 \text{ ml for the ET subjects versus } 520 \pm 28 \text{ ml for the UT subjects})\). Furthermore, when this measurement was used to predict the percent of the total blood volume shifted during LBNP, the two subject groups demonstrated similar percentage shifts in total blood volume. It should be noted that the measurement of leg volume, and subsequent calculation of volume changes, does not take into account the pooling of blood in the abdominal veins. In the present study the volume of pooling was assumed to be the same in each group since the volume shifts into the legs was the
same. This finding is in contrast to the data of Klein et al. (154) who suggested that limb compliance was greater in trained individuals which results in greater pooling of blood during an orthostatic stress. However, previously we (209) demonstrated that limb compliance, using passive venous occlusion plethysmography, was not different between ET and UT subjects. These observations confirmed the earlier findings of Raven et al. (208) who found no differences in leg volume responses between ET and UT subjects during progressive LBNP to -50 torr. Therefore, it appears that the LBNP stress presented a similar stimulus to the two subject groups. This finding also was observed during each of the autonomic blockade conditions.

In the present investigation, during the control condition the ET subjects did not maintain blood pressure as effectively as the UT subjects. This was evident by both a greater fall in SBP from rest to -50 torr and a lower absolute SBP at -50 torr in the ET subjects. This occurred in spite of the stimulus (degree of blood pooling) being equivalent between the groups as noted above. In addition, the electromyographic activity of the lower limbs and abdominal muscles was monitored throughout the LBNP procedure. Therefore, it can be concluded that differences in the response of the two subject groups can not be attributed to somato-pressor reflexes which have been shown to significantly affect the responses to LBNP (240). It then follows that
the observed differences between groups in response to LBNP reflect differences in the normal control mechanisms. The primary control mechanisms that are employed during an orthostatic stress include the arterial and cardiopulmonary baroreflexes, which mediate both cardiac and vasomotor responses.

**Reflex Responses**

The arterial baroreflexes provide regulation of blood pressure on a beat-to-beat basis within a finite pressure range. These actions serve to buffer against wide fluctuations in pressure during acute variations in arterial pressure.

**Cardiac Responses:** Stegemann et al. (245) were the first to suggest that baroreflex chronotropic responses were affected by endurance training. They used a neck and head chamber to apply suction or pressure to the neck region in order to stretch the baroreceptors. The effective transmural pressure of the carotid sinus was assumed to be the difference between the arterial pressure and the applied pressure (or negative pressure). They found that highly trained individuals had a smaller mean arterial pressure and heart rate response to a given change in calculated transmural pressure. Although the apparatus was a crude ancestor to the sophisticated neck suction devices of today, the results were obtained with minimal assumptions other than the accuracy of the estimation of carotid sinus pressure.
Since Stegemann's study, few investigations have addressed the question of how exercise training affects the baroreflex chronotropic response. Bedford and Tipton (18) isolated the carotid sinus of endurance trained and sedentary rats. They then evaluated the systemic pressure responses to changes in carotid perfusion pressure and found that the trained rats had a significantly less responsive baroreflex.

Raven and Smith (209) evaluated two groups of men, one group was trained and the other sedentary, in terms of their HR responses to a stepwise infusion of phenylephrine to an infusion rate of 60 μg/min. The baroreflex responses, reported as ΔHR/ΔBP, of the trained men were significantly (p<0.01) less than the sedentary men. This study was limited in that the 60 μg/min infusion rate produced an average increase in mean blood pressure of only nine torr in the trained subjects. This result left questions regarding the nature of the response to the drug. In particular, did the response observed reflect the linear portion of the baroreflex function curve?

The typical baroreflex function curve is represented in figure 22. Point T represents the threshold pressure, above which, reflex responses are observed. The pressure at point 0 represents the operational pressure or the normal pressure during homeostasis. The pressures above point S represent saturation pressures at which further increases produce no further increase in response.
Fig. 22. Arterial baroreflex function curve. Point "T" represents threshold pressure, the pressure at which heart period responses begin to occur; point "O" represents operational or resting mean pressure; point "S" represents saturation pressure, the pressure at which no further increases in heart period occur with further increases pressure.

In this illustration, the operational pressure occurs in the middle of the linear portion of the function curve. However, Eckberg (77) has proposed that the average human operates in or close to the curvilinear portion near the threshold of the function curve during rest. If this is the case, the stimulus needed to assess the linear portion of the curve must be large enough to achieve a significant shift up (to the right) the function curve. For this reason, the maximum phenylephrine infusion rates used (120 μg/min) in the present investigation were double that
used in the previous study (209). In the regression analyses, the correlation was strong ($r>0.90$ in each case) and highly significant ($P<0.01$ in each case). The mean slope of the line, based on either the systolic or mean blood pressure, was significantly less in the ET subjects than the UT subjects. This finding is in support of the previous observations from other investigations (18,209,245). In addition, the $\Delta HR/\Delta SBP$ calculation for the control LBNP procedure was $0.91\pm0.30$ for the ET subjects and $1.62\pm0.28$ for the UT subjects. The difference between the groups was significant ($p=0.033$) and is consistent with the finding that the slope of the regression analysis of HR versus SBP during the phenylephrine infusion was significantly less in the ET subjects as compared to the UT subjects. However, it is interesting to note that the SBP fell up to 30 torr during the LBNP procedure. This contradicts Eckberg's proposal that the operational point lies very close to the threshold. Furthermore, if Eckberg is correct in his assessment of the normal baroreflex function curve, then the data of the present study suggest that the alteration of cardiopulmonary baroreceptor activity imposed by LBNP, altered the normal functional pressure range of the arterial baroreflex. This effect would appear as either a shift of the entire function curve to the left, or a lowering of the threshold pressure. There is evidence that cardiopulmonary baroreceptor activity modulates the arterial baroreflex
(128,156,168,248); however, there is no evidence in the literature to suggest that a shift in the function curve is produced. Although a cardiopulmonary baroreceptor-mediated shift in the arterial baroreflex function curve is an interesting possibility, it can not be discerned from the present data as the threshold pressure was not obtained.

Recently, two studies have proposed that endurance training results in an augmentation of the baroreflex chronotropic response (15,25). Billman et al. (25) observed an increase in the heart rate response to a bolus dose of phenylephrine after a six-week exercise training period in post-infarcted dogs. However, demonstration of a training effect was not accomplished; therefore, it is uncertain whether the exercise was responsible for the change in baroreflex responsiveness. Similarly, Barney et al. (15) found that the slope of the baroreflex function curve was significantly greater in trained men and in untrained men. In Barney's study, a combination of neck suction and neck pressure was used to manipulate the arterial baroreceptors. The differences between the studies of Billman et al. (25) and Barney et al. (15) and the data obtained in the present study probably reflect a procedural difference. In the two studies showing an increase in baroreflex responsiveness, the stimulus-response data were obtained during a stimulus period of less than ten seconds. In Billman's study (25), the measurements were
obtained from consecutive heart beats during the initial rise in blood pressure until the SBP had risen 30 mmHg. This initial rise normally occurs within ten to fifteen seconds. With the neck suction procedure, data were obtained within five seconds of the initiation of suction. In each of these studies the increase in responsiveness was attributed to an increase in parasympathetic activity associated with the endurance training. The heart rate response to graded neck suction appears to be mediated exclusively by parasympathetic mechanisms, as cholinergic blockade with atropine eliminates the chronotropic responses while beta-adrenergic blockade with propranolol does not affect the normal response (76). Moreover, the baroreflex HR responses to neck suction were augmented by increasing parasympathetic activity with low dose atropine or scopolamine (65). In contrast, Bedford and Tipton (18) demonstrated that exercise trained rats had an attenuated baroreflex HR response to carotid sinus pressure manipulations. Likewise, Mass et al. (178) found that trained dogs had an attenuated baroreflex HR response to phenylephrine and nitroprusside injections. Stegemann et al. (245) demonstrated an attenuated baroreflex HR response using a neck suction procedure; however, the protocol used, allowed three minutes for a steady-state condition to be achieved before measurements were obtained. In the phenylephrine procedure used in the present study, 3-5 minutes were needed to attain steady-
state. Moreover, the data collected during LBNP were obtained at steady-state between minutes three and four of each stage. The heart rate response was not eliminated by either the atropine or metoprolol blockade (Table XVIII),

Table XVIII

<table>
<thead>
<tr>
<th></th>
<th>ET</th>
<th>UT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.65±0.22</td>
<td>1.54±0.31</td>
<td>0.035</td>
</tr>
<tr>
<td>Full Metoprolol</td>
<td>0.64±0.20</td>
<td>0.83±0.12</td>
<td>0.525</td>
</tr>
<tr>
<td>Full Atropine</td>
<td>0.89±0.30</td>
<td>1.25±0.24</td>
<td>0.330</td>
</tr>
</tbody>
</table>

Values represent mean ±S.E.M.

and thus indicates that the control responses involved both a parasympathetic and sympathetic response. It is interesting to note that the ΔHR/ΔSBP response was significantly attenuated by the metoprolol blockade in the UT subjects, suggesting that the control response was mediated predominantly by sympathetic effects. This hypothesis is consistent with the finding that the heart rate response to prolonged parasympathetic stimulation 'fades' back toward the control heart rate (177). Furthermore, it has been shown that the heart rate response to prolonged hypotension was mediated by a combined sympathetic and parasympathetic response (233,258) or an exclusively sympathetic response (106). These previous findings suggest that the HR responses
obtained during the phenylephrine or LBNP procedures used in the present study reflect a combined response of the two limbs of the autonomic nervous system. Therefore, the investigations of Billman et al. (25) and Barney et al. (15) indicated that the rapidly occurring parasympathetic baroreflex HR responses were augmented by exercise training. In contrast, the present investigation and other investigations (209,245) indicated that the integrated HR responses (involving both sympathetic and parasympathetic effects) to prolonged changes in pressure were attenuated by exercise training.

The HR change during LBNP was significantly greater during the partial atropine condition than the control condition in the ET subjects (Table XVI). In addition, the HR/ΔSBP was slightly (although insignificantly) greater during the full atropine condition as compared to the control condition for the ET subjects. These findings suggest that removal of parasympathetic control in the ET subjects improves the reflex HR response. Therefore, the increased parasympathetic activity observed in ET individuals, as discussed above, resulted in an attenuated reflex HR response during prolonged perturbations of the system. Whereas, an increased parasympathetic activity due to endurance exercise training appears to have resulted in an augmentation of the HR response to brief or transient perturbations (15,25,65).
Previously, it has been reported that contractility is unchanged during LBNP to -40 torr (8,188). In these two studies blood pressure and heart rate changed minimally; hence, the arterial baroreceptors were not remarkably altered. Although there remains a debate as to whether the arterial baroreflexes affect contractility, the data has mounted in support of this hypothesis (59,71,72). Since heart rate changes alone can not alter cardiac output or blood pressure (stroke volume would change inversely to HR to maintain a constant Q according to Starling mechanism), a concomitant change in contractility would be a teleologically sound response. A combined HR and contractile response would effectively alter Q and blood pressure relative to any changes in preload or afterload. If this does not occur, the baroreflex HR response would appear to be futile in nature.

In the present study, no controlled measurements of contractility were made. However, if preload (similar degree of blood pooling), and afterload (similar peripheral vascular resistances) were assumed to be the same between groups, the difference in Q observed at -40 torr during the control condition would be suggestive of a difference in contractility. This also was observed during the partial and full metoprolol conditions. Again, there appeared to be a significantly lower cardiac response in the ET subjects when parasympathetic control was intact; and, removal of
parasympathetic control resulted in the elimination of groups differences observed during the control condition. This interpretation is highly speculative, as it is based on two assumptions. Therefore, a contractility effect will not be considered as an explanation for the group differences in blood pressure control.

Vasomotor Responses: Among the normal cardiovascular adaptations to an orthostatic stress is a multi-regional vasoconstriction. LBNP is known to produce significant reflex increases in peripheral sympathetic nerve traffic relative to the level of LBNP (246). This effect is associated with vasoconstriction of the vasculature of the skeletal muscle of the legs and arms (137,221,246). Vasoconstriction of the vasculature of the skin (179,239,253), splanchnic circulation (137,221), and kidney (105) have also been demonstrated during LBNP.

Previously, it was reported that the vasoconstrictor response (as indicated by smaller rise in peripheral vascular resistance) to LBNP was lower in ET subjects when compared with UT subjects (208). In the present study, the PVR change was similar between the groups. In addition, the decrease in forearm blood flow ($BF_f$) and rise in forearm vascular resistance (FVR) was the same in both groups. In the previous study the difference appeared to be related to a greater PVR at rest in the UT subjects, whereas in the present study the resting resistances were virtually iden-
tical. Furthermore, since the systolic blood pressure fell more dramatically in the ET subjects, thereby producing a greater stimulus for a vasoconstrictor response, it appears that the vasoconstrictor response of the ET subjects was attenuated in comparison to the UT subjects.

The vasoconstrictor responses occurred predominantly at the earlier stages of LBNP. This was evident by the minimal increases in resistance and decrease in BF$_f$ from -16 torr to -40 torr. This is consistent with previous investigations which report that the changes in BF$_f$ are near maximum at -20 torr of LBNP (137,253). Tripathi and Nadel (253) also made measurements of skin blood flow and extrapolated out the vasoconstrictor effects on both the skin and muscle blood flow of the forearm. They concluded that the decrease in muscle blood flow was maximized by -20 torr, while the skin blood flow decreased progressively with decreasing lower body pressures. These responses at the early stages of LBNP have been attributed exclusively to effects of the cardiopulmonary baroreflexes (2,137). The control data from the present investigation are in agreement with these previous findings. Both the BF$_f$ and resistance responses increased minimally from -16 torr to -40 torr of LBNP.

Blockade of the $\beta_1$-adrenergic receptors with metoprolol did not affect the vasoconstrictor responses to LBNP. Nor did the metoprolol affect the trends in responses between the groups. However, the BF$_f$ and resistance responses during
the full atropine and double blockade conditions were significantly augmented in both groups in comparison to the control condition. The FVR response was significantly greater in the ET subjects, as compared to the UT subjects, at -16 torr during these two conditions. In addition, the 0 torr to -40 torr responses were significantly greater in both groups during these two conditions. These effects indicate that removal of parasympathetic control unmasked a greater potential for vasoconstriction. This effect was significantly greater in the ET subjects which supports the hypothesis, presented above, that the enhanced resting parasympathetic activity in the ET subjects buffered the reflex responses to LBNP. An alternative explanation could be that atropine blocked a cholinergic vasodilator response in the periphery. This response has been demonstrated in the muscle vasculature of cats (249) and dogs (211). However, this effect did not appear to be present at rest as resistances were decreased rather than increased (as would be expected). Furthermore, if a vasodilator system was intact but dormant at rest, one would not expect reflex vasodilation to occur during a hypotensive stress.

Since the cardiac response mechanisms are eliminated with double blockade, the vasoconstrictor responses to LBNP during this condition should represent the reserve capacity for baroreflex-mediated vasoconstriction. Indeed, the degree of response and the absolute BF obtained were far
more dramatic during the double blockade condition. The change in BF$_f$ was greater in the ET subjects; however, the absolute BF$_f$ attained at -40 torr was not different between the groups. The vasoconstrictor reserve was similar between the groups, or perhaps slightly greater in the ET subjects. Hence, the question is raised as to why this vasoconstrictor reserve was not tapped more effectively in the ET subjects when blood pressure fell rapidly during the latter stages of LBNP. Similarly, the $\alpha$-adrenergic receptor sensitivity appeared to be the same between the groups. When BF$_f$ was plotted against the dose of phenylephrine (corrected for plasma volume), the slopes of the responses of the two groups were the same, see figure 23. This is in contrast with the findings of Hasser et al. (124) who found that the peak pressor effect of a bolus dose of the alpha receptor agonist methoxamine was greater in exercise trained rats. This difference may reflect a difference in the rapid responses to acute alpha receptor stimulation versus the steady-state response to chronic stimulation of the receptors.
Fig. 23. Relation of forearm blood flow response and phenylephrine dose rate. Dose rate is corrected for plasma volume. The line-of-best-fit for the endurance trained (dashed line) subjects was $y = -0.091x + 5.90$, and $y = -0.102x + 5.11$ for the untrained subjects (solid line). The slopes were not significantly different between the groups ($p>0.05$).

Conclusions

In summary, blood pressure regulation was less effective during lower body negative pressure (LBNP) in the endurance trained (ET) individuals. This was evident by a greater fall in systolic blood pressure (SBP) during LBNP and a lower absolute SBP at the final stages of LBNP. The autonomic reflex mechanisms involved in blood pressure control are illustrated in figure 24. There is reciprocal
Fig. 24. ANS cardiac efferent pathways.
innervation of the heart with depressor (parasympathetic) and accelerator (sympathetic) components. In addition, there is sympathetic innervation of the vasculature providing control over the resistance of the system. All of these avenues of reflex adaptation can be engaged by either or both of the baroreflex systems (arterial and cardiopulmonary). During rapid and transient changes in arterial pressure, the HR responses are mediated by the parasympathetic system alone (65). However, with prolonged pressure changes, in excess of 30 seconds, the compensatory responses are mediated by all limbs of the autonomic nervous system (203,235).

In this study, the stimulus was the same between the two subject groups, yet blood pressure maintenance was reduced in the ET subjects. This implies a difference in some component of the autonomic effector system. A difference in autonomic regulation could involve a difference in 1) the baroreceptor tissues, 2) the integration of baroreflex afferent signals, or 3) the effector organs. The arterial baroreflex heart rate (HR) response was reduced in the ET subjects as compared to the UT subjects. There were no group differences in the vasoconstrictor responses, nor were any differences observed in the vasoconstrictor reserve capacity (as determined by the vasoconstrictor response during complete blockade of the heart). In addition, when phenylephrine was infused the two subject groups had similar
vasoconstrictor responses relative to the dose of phenylephrine. \( \beta_1 \)-adrenergic blockade did not affect significantly the differences in responses between the groups. However, cholinergic blockade (which eliminates the parasympathetic control of the heart) eliminated the group differences in response to LBNP. Furthermore, the vasoconstrictor response was significantly augmented in the ET subjects. This also resulted in an improved blood pressure maintenance in the ET subjects.

The autonomic nervous system is considered redundant in nature. It is a multi-faceted reflex system with both duplication and reciprocality of effects. However, these data suggest that the redundancy does not function to maintain universal homeostasis regardless of which components of the system are left intact. This was evident by the improvement in blood pressure control observed in the ET subjects during the atropine blockade conditions. The ET subjects had an elevated parasympathetic activity at rest. This altered autonomic balance appears to depress the normal cardiovascular adjustments that occur during an orthostatic stress such as LBNP. The reflex HR response was attenuated in these subjects and the vasoconstrictor capacity was not adequately engaged to maintain blood pressure. The mechanisms explaining this effect of an elevated parasympathetic activity on normal blood pressure regulation would appear to lie within the integration processes of the brainstem. One
hypothesis that is apparently viable in light of these data, is that a temporal hierarchy of reflex responses exist within the neuronal network of the brainstem. This hierarchy dictates parasympathetic withdrawal or augmentation as the initial response. Sympathetic effects would follow as the parasympathetic responses failed to maintain homeostasis. This would hold only for the arterial baroreflex arc as the cardiopulmonary baroreflex responses did not appear to be different between the subject groups. Differences in the humoral responses to LBNP may also be contributory. However, our present ignorance of the humoral responses does not dilute the observations that were obtained.

These data are suggestive of important alterations in autonomic regulation induced by exercise training. However, the cross-sectional design that was used does not conclusively implicate exercise training in the effects observed. Therefore, a longitudinal design is necessary to better elucidate the effect exercise training has on blood pressure regulation. Orthostatic hypotensive problems have been anecdotally and experimentally documented. Therefore, the impetus to pursue this question is evident. Differences in humoral responses to an orthostatic stress may also contribute to the reduced blood pressure regulation observed in the ET subjects and should be investigated. In conclusion, the answers to several questions were uncovered; however,
many new questions have arisen. Thus, it is apparent that an age old proverb appropriately expresses the findings of this study.

"The more we know, the more we realize how little we know." anonymous
APPENDIX
### APPENDIX I

#### TABLE XIX

**PHYSIOLOGICAL RESPONSES TO LBNP DURING CONTROL CONDITION**

<table>
<thead>
<tr>
<th>LBNP STAGE (TORR)</th>
<th>0</th>
<th>-16</th>
<th>-40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET</td>
<td>54.7±2.0</td>
<td>56.4±2.0</td>
<td>73.1±3.7</td>
</tr>
<tr>
<td>UT</td>
<td>70.4±3.5 *</td>
<td>73.3±3.4 *</td>
<td>92.3±3.2 *</td>
</tr>
<tr>
<td><strong>SBP (Torr)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET</td>
<td>126.8±1.2</td>
<td>121.8±2.1</td>
<td>97.4±4.6</td>
</tr>
<tr>
<td>UT</td>
<td>121.2±1.4 *</td>
<td>120.2±2.2</td>
<td>107.0±1.0 *</td>
</tr>
<tr>
<td><strong>MBP (Torr)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET</td>
<td>93.7±2.2</td>
<td>94.5±2.3</td>
<td>80.9±3.7</td>
</tr>
<tr>
<td>UT</td>
<td>92.7±1.0</td>
<td>93.1±1.3</td>
<td>88.5±1.0 *</td>
</tr>
<tr>
<td><strong>DBP (Torr)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET</td>
<td>77.2±2.9</td>
<td>80.8±3.2</td>
<td>72.6±3.6</td>
</tr>
<tr>
<td>UT</td>
<td>78.4±2.0</td>
<td>79.6±2.2</td>
<td>79.2±1.2</td>
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<tr>
<td><strong>Q (l/min)</strong></td>
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<tr>
<td>ET</td>
<td>5.75±0.4</td>
<td>4.59±0.4</td>
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<tr>
<td>UT</td>
<td>5.95±0.3</td>
<td>5.14±0.3</td>
<td>4.55±0.2 *</td>
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<tr>
<td><strong>SV (ml)</strong></td>
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<tr>
<td>ET</td>
<td>96.6±8.2</td>
<td>65.3±6.7</td>
<td>55.1±9.0</td>
</tr>
<tr>
<td>UT</td>
<td>80.7±3.9 *</td>
<td>62.6±3.0</td>
<td>47.3±2.9</td>
</tr>
<tr>
<td><strong>VOLPER (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET</td>
<td>--</td>
<td>3.5±0.6</td>
<td>7.8±0.8</td>
</tr>
<tr>
<td>UT</td>
<td>--</td>
<td>3.8±0.5</td>
<td>7.6±0.8</td>
</tr>
<tr>
<td><strong>BF&lt;sub&gt;f&lt;/sub&gt; [(ml/min)/100 ml]</strong></td>
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<td></td>
<td></td>
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<tr>
<td>ET</td>
<td>5.19±1.0</td>
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<td>UT</td>
<td>4.39±0.7</td>
<td>2.94±0.3</td>
<td>2.54±0.3</td>
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<tr>
<td><strong>FVR (PRU)</strong></td>
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<td></td>
</tr>
<tr>
<td>ET</td>
<td>23.0±4.3</td>
<td>33.5±4.7</td>
<td>37.5±5.1</td>
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<tr>
<td>UT</td>
<td>24.8±3.5</td>
<td>34.8±4.5</td>
<td>37.8±4.3</td>
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<tr>
<td><strong>PVR (PRU)</strong></td>
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<td></td>
</tr>
<tr>
<td>ET</td>
<td>16.7±1.0</td>
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<td>20.1±0.1</td>
</tr>
<tr>
<td>UT</td>
<td>15.9±0.8</td>
<td>18.8±1.1</td>
<td>19.8±1.0</td>
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</table>

* Significant difference between groups, p<0.05.

Values represent mean ± S.E.M. HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; Q=cardiac output; SV=stroke volume; VOLPER=percent blood volume shifted; BF<sub>f</sub>=forearm blood flow; FVR=forearm vascular resistance; PVR=peripheral vascular resistance.
### TABLE XX

**PHYSIOLOGICAL RESPONSES TO LBNP DURING PARTIAL METOPROLOL BLOCKADE**

<table>
<thead>
<tr>
<th></th>
<th>LBNP STAGE (TORR)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<td>-40</td>
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<tr>
<td><strong>HR</strong> (beats/min)</td>
<td>ET 50.4±2.0</td>
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<tr>
<td></td>
<td>UT 64.1±2.8</td>
<td>70.8±3.7</td>
<td>82.8±2.7</td>
</tr>
<tr>
<td><strong>SBP</strong> (Torr)</td>
<td>ET 123.2±1.3</td>
<td>115.2±2.3</td>
<td>97.2±3.7</td>
</tr>
<tr>
<td></td>
<td>UT 118.4±1.5</td>
<td>113.8±1.4</td>
<td>103.2±1.3</td>
</tr>
<tr>
<td><strong>MBP</strong> (Torr)</td>
<td>ET 91.2±1.8</td>
<td>88.8±2.1</td>
<td>80.4±2.3</td>
</tr>
<tr>
<td></td>
<td>UT 89.5±1.3</td>
<td>91.7±1.6</td>
<td>87.6±1.2</td>
</tr>
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<td><strong>DBP</strong> (Torr)</td>
<td>ET 75.2±2.3</td>
<td>75.6±2.3</td>
<td>72.0±2.1</td>
</tr>
<tr>
<td></td>
<td>UT 75.0±1.9</td>
<td>80.6±2.3</td>
<td>79.8±1.7</td>
</tr>
<tr>
<td><strong>Q</strong> (1/min)</td>
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<td>UT 5.72±0.3</td>
<td>4.86±0.3</td>
<td>4.16±0.2</td>
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<td><strong>SV</strong> (ml)</td>
<td>ET 100.2±7.0</td>
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<tr>
<td></td>
<td>UT 85.5±4.6</td>
<td>65.0±4.2</td>
<td>48.0±2.5</td>
</tr>
<tr>
<td><strong>VOLPER</strong> (%)</td>
<td>ET --</td>
<td>3.5±0.4</td>
<td>7.1±0.6</td>
</tr>
<tr>
<td></td>
<td>UT --</td>
<td>3.3±0.3</td>
<td>6.7±0.6</td>
</tr>
<tr>
<td><strong>BF&lt;sub&gt;f&lt;/sub&gt; [(ml/min)/100 ml]</strong></td>
<td>ET 5.13±1.0</td>
<td>3.22±0.7</td>
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<td>UT 4.42±0.8</td>
<td>2.85±0.3</td>
<td>2.54±0.3</td>
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<tr>
<td><strong>FVR</strong> (PRU)</td>
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<td>35.9±6.0</td>
<td>37.5±7.7</td>
</tr>
<tr>
<td></td>
<td>UT 23.5±3.0</td>
<td>34.1±2.8</td>
<td>37.7±4.1</td>
</tr>
<tr>
<td><strong>PVR</strong> (PRU)</td>
<td>ET 16.6±0.9</td>
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<td>22.1±0.7</td>
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<td></td>
<td>UT 16.1±0.9</td>
<td>19.8±1.5</td>
<td>21.4±1.3</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.

Values represent mean ± S.E.M.  
HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; Q=cardiac output; SV=stroke volume; VOLPER=percent blood volume shifted; BF<sub>f</sub>=forearm blood flow; FVR=forearm vascular resistance; PVR=peripheral vascular resistance.
TABLE XXI

PHYSIOLOGICAL RESPONSES TO LBNP DURING FULL METOPROLOL BLOCKADE

<table>
<thead>
<tr>
<th></th>
<th>LBNP STAGE (TORR)</th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-16</td>
<td>-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>ET</td>
<td>47.6±1.7</td>
<td>53.0±1.8</td>
<td>64.3±3.5</td>
</tr>
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<td></td>
<td>UT</td>
<td>58.4±2.9</td>
<td>62.5±3.3</td>
<td>71.6±2.6</td>
</tr>
<tr>
<td>SBP (Torr)</td>
<td>ET</td>
<td>118.8±2.0</td>
<td>113.4±2.0</td>
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</tr>
<tr>
<td></td>
<td>UT</td>
<td>117.2±1.7</td>
<td>111.8±1.2</td>
<td>100.6±1.7</td>
</tr>
<tr>
<td>MBP (Torr)</td>
<td>ET</td>
<td>91.5±1.8</td>
<td>91.3±1.8</td>
<td>76.7±4.4</td>
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<td>89.1±2.0</td>
<td>85.1±1.1</td>
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<td>DBP (Torr)</td>
<td>ET</td>
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<td>80.2±2.2</td>
<td>68.4±4.6</td>
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<td>UT</td>
<td>78.6±1.6</td>
<td>77.8±2.7</td>
<td>77.4±1.4</td>
</tr>
<tr>
<td>Q (l/min)</td>
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<td>5.38±0.3</td>
<td>4.39±0.2</td>
<td>3.75±0.2</td>
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<td>UT</td>
<td>5.24±0.2</td>
<td>4.29±0.2</td>
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</tr>
<tr>
<td>SV (ml)</td>
<td>ET</td>
<td>104.8±9.7</td>
<td>77.7±5.6</td>
<td>57.3±5.9</td>
</tr>
<tr>
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<td>UT</td>
<td>86.1±4.9</td>
<td>67.0±3.2</td>
<td>55.8±4.1</td>
</tr>
<tr>
<td>VOLPER (%)</td>
<td>ET</td>
<td>--</td>
<td>3.7±0.4</td>
<td>7.8±0.7</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>--</td>
<td>3.9±0.3</td>
<td>6.8±0.5</td>
</tr>
<tr>
<td>BF&lt;sub&gt;f&lt;/sub&gt; [(ml/min)/100 ml]</td>
<td>ET</td>
<td>4.58±0.8</td>
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<td>UT</td>
<td>4.17±0.2</td>
<td>2.67±0.4</td>
<td>2.31±0.3</td>
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<tr>
<td>FVR (PRU)</td>
<td>ET</td>
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<tr>
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<td>UT</td>
<td>23.1±1.8</td>
<td>36.8±4.3</td>
<td>40.1±4.3</td>
</tr>
<tr>
<td>PVR (PRU)</td>
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<td>17.1±0.9</td>
<td>20.8±0.9</td>
<td>21.6±1.2</td>
</tr>
<tr>
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<td>UT</td>
<td>17.6±0.7</td>
<td>20.7±0.9</td>
<td>20.9±0.8</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.
Values represent mean ± S.E.M. HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; Q=cardiac output; SV=stroke volume; VOLPER=percent blood volume shifted; BF<sub>f</sub>=forearm blood flow; FVR=forearm vascular resistance; PVR=peripheral vascular resistance.
TABLE XXII

PHYSIOLOGICAL RESPONSES TO LBNP DURING PARTIAL ATROPINE BLOCKADE

<table>
<thead>
<tr>
<th>LBNP STAGE (TORR)</th>
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<th>-16</th>
<th>-40</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>ET</td>
<td>60.6±3.4</td>
<td>65.0±5.3</td>
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<tr>
<td></td>
<td>UT</td>
<td>80.4±2.8</td>
<td>82.4±2.5</td>
</tr>
<tr>
<td>SBP (Torr)</td>
<td>ET</td>
<td>125.4±2.0</td>
<td>120.6±2.4</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>121.1±2.4</td>
<td>115.6±3.0</td>
</tr>
<tr>
<td>MBP (Torr)</td>
<td>ET</td>
<td>91.5±2.0</td>
<td>88.7±3.9</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>90.7±1.6</td>
<td>91.6±2.5</td>
</tr>
<tr>
<td>DBP (Torr)</td>
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<td>74.6±2.1</td>
<td>77.8±2.6</td>
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<tr>
<td></td>
<td>UT</td>
<td>75.6±2.0</td>
<td>79.6±2.8</td>
</tr>
<tr>
<td>Q (l/min)</td>
<td>ET</td>
<td>5.68±0.2</td>
<td>4.31±0.4</td>
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<td>UT</td>
<td>5.32±0.3</td>
<td>4.45±0.2</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>ET</td>
<td>90.8±5.1</td>
<td>69.0±3.8</td>
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<td>UT</td>
<td>71.5±3.2</td>
<td>56.7±3.6</td>
</tr>
<tr>
<td>VOLPER (%)</td>
<td>ET</td>
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<td>4.2±0.8</td>
</tr>
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<td>UT</td>
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<td>4.0±0.5</td>
</tr>
<tr>
<td>BF_f [(ml/min)/100 ml]</td>
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<td>5.61±0.9</td>
<td>3.57±0.6</td>
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<td>UT</td>
<td>4.32±0.3</td>
<td>2.73±0.2</td>
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<tr>
<td>FVR (PRU)</td>
<td>ET</td>
<td>20.0±3.6</td>
<td>34.4±6.7</td>
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<tr>
<td></td>
<td>UT</td>
<td>21.5±1.2</td>
<td>34.4±2.8</td>
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<tr>
<td>PVR (PRU)</td>
<td>ET</td>
<td>16.3±0.6</td>
<td>22.0±0.7</td>
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<tr>
<td></td>
<td>UT</td>
<td>17.4±0.8</td>
<td>21.0±1.0</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.

Values represent mean ± S.E.M. HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; Q=cardiac output; SV=stroke volume; VOLPER=percent blood volume shifted; BF_f=forearm blood flow; FVR=forearm vascular resistance; PVR=peripheral vascular resistance.
### TABLE XXIII

**PHYSIOLOGICAL RESPONSES TO LBNP DURING FULL ATROPINE BLOCKADE**

<table>
<thead>
<tr>
<th>LBNP STAGE (TORR)</th>
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<th>-40</th>
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</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>ET</td>
<td>100.6±5.7</td>
<td>108.0±5.6</td>
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<td>108.6±5.0</td>
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<td>SBP (Torr)</td>
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<td>129.0±2.8</td>
<td>124.6±3.0</td>
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<td>125.4±1.7</td>
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<td>MBP (Torr)</td>
<td>ET</td>
<td>97.7±2.5</td>
<td>95.7±2.7</td>
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<td>100.9±1.8</td>
<td>96.2±2.2</td>
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<td>DBP (Torr)</td>
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<td>65.2±4.4</td>
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<td>VOLPER (%)</td>
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<td>3.9±0.4</td>
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<td>BF_f ([ml/min]/100 ml]</td>
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<tr>
<td></td>
<td>UT</td>
<td>17.3±1.5</td>
<td>30.2±2.5</td>
</tr>
<tr>
<td>PVR (PRU)</td>
<td>ET</td>
<td>15.3±0.7</td>
<td>19.6±0.8</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>14.6±0.8</td>
<td>19.4±1.1</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.

Values represent mean ± S.E.M. HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; Q=cardiac output; SV=stroke volume; VOLPER=percent blood volume shifted; BF_f=forearm blood flow; FVR=forearm vascular resistance; PVR=peripheral vascular resistance.
### TABLE XXIV

**PHYSIOLOGICAL RESPONSES TO LBNP DURING DOUBLE BLOCKADE**

<table>
<thead>
<tr>
<th>LBNP STAGE (TORR)</th>
<th>0</th>
<th>-16</th>
<th>-40</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>ET</td>
<td>79.6±2.8</td>
<td>79.6±2.9</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>86.6±2.5 *</td>
<td>86.6±2.5 *</td>
</tr>
<tr>
<td>SBP (Torr)</td>
<td>ET</td>
<td>127.8±2.1</td>
<td>115.2±1.9</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>123.6±1.7</td>
<td>113.0±2.4</td>
</tr>
<tr>
<td>MBP (Torr)</td>
<td>ET</td>
<td>98.9±2.4</td>
<td>94.4±2.3</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>98.5±1.6</td>
<td>94.5±1.0</td>
</tr>
<tr>
<td>DBP (Torr)</td>
<td>ET</td>
<td>84.4±3.0</td>
<td>84.0±3.2</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>86.0±1.6</td>
<td>85.2±1.3</td>
</tr>
<tr>
<td>Q (l/min)</td>
<td>ET</td>
<td>5.33±0.1</td>
<td>3.97±0.3</td>
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<td></td>
<td>UT</td>
<td>5.59±0.2</td>
<td>4.40±0.2</td>
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<tr>
<td>SV (ml)</td>
<td>ET</td>
<td>68.0±2.5</td>
<td>50.1±3.3</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>65.5±4.1</td>
<td>51.1±2.3</td>
</tr>
<tr>
<td>VOLPER (%)</td>
<td>ET</td>
<td>--</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>--</td>
<td>3.8±0.4</td>
</tr>
<tr>
<td>BFf [(ml/min)/100 ml]</td>
<td>ET</td>
<td>6.50±1.4</td>
<td>3.13±0.7</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>4.27±0.3</td>
<td>2.64±0.2</td>
</tr>
<tr>
<td>FVR (PRU)</td>
<td>ET</td>
<td>21.3±4.4</td>
<td>41.7±4.0</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>24.5±1.4</td>
<td>37.4±2.8</td>
</tr>
<tr>
<td>PVR (PRU)</td>
<td>ET</td>
<td>18.2±0.5</td>
<td>24.7±1.4</td>
</tr>
<tr>
<td></td>
<td>UT</td>
<td>17.8±0.7</td>
<td>21.9±0.9</td>
</tr>
</tbody>
</table>

* Significant difference between groups, p<0.05.

Values represent mean ± S.E.M.  HR=heart rate; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; Q=cardiac output; SV=stroke volume; VOLPER=percent blood volume shifted; BFf=forearm blood flow; FVR=forearm vascular resistance; PVR=peripheral vascular resistance.
REFERENCES


201. Plunkett, W.C., P.M. Hutchins, K.A. Gruber, and V.M.


