BLOOD PRESSURE REGULATION DURING SIMULATED ORTHOSTATISM PRIOR TO AND FOLLOWING ENDURANCE EXERCISE TRAINING

DISSERTATION

Presented to the Graduate Council of the University of North Texas in Partial Fulfillment of the Requirements For the Degree of

DOCTOR OF PHILOSOPHY

By

Glen H. J. Stevens, B.Sc., M.Sc.
Denton, Texas
May, 1992
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Stevens, Glen, H. J., Blood Pressure Regulation During Simulated Orthostatism Prior to and Following Endurance Exercise Training. Doctor of Philosophy (Biology), May, 1992, 151 pp., 5 tables, 20 illustrations, bibliography, 239 titles.

Cardiovascular responses and tolerance to an orthostatic stress were examined in eight men before and after eight months of endurance exercise training. Orthostatic stress was induced using progressive lower body negative pressure (LBNP) at -5, -15, -25, -35, and -45 torr, followed by -5 torr increments until presyncope. In addition, cardiac autonomic blockade was utilized during LBNP to -45 torr. Cardiopulmonary baroresponsiveness was assessed as the slope of the relationship between forearm vascular resistance (FVR) and central venous pressure (CVP) (utilizing the dependent arm technique) during LBNP < -25 torr. Baroreflex function was further evaluated using progressive intravenous infusion of phenylephrine hydrochloride (PE) to a maximum dose of 0.12 mg·min⁻¹. Following training, maximal oxygen consumption and blood volume were increased, and resting heart rate reduced. Orthostatic tolerance was reduced following training in all eight subjects. Blockade of the parasympathetic cardiac receptors with atropine sulphate resulted in the maintenance
of mean arterial pressure (MAP). Baroreceptor responsiveness, as defined by a change in heart rate (HR) / change in MAP, was not significantly decreased during LBNP, however, the slope of the FVR/CVP relationship was attenuated with training during LBNP. The ΔHR/ΔMAP relationship during PE infusion was attenuated following training, however, when the relationship was plotted as ΔARRI/ΔMAP no significant differences were noted. It was concluded that prolonged endurance training decreased orthostatic tolerance and this decrease in tolerance appeared associated with attenuated baroreflex sensitivity and alterations in autonomic balance secondary to an increased parasympathetic tone noted with training.
ACKNOWLEDGEMENT

This investigation and author were supported by N.I.H. Grant #HL34397 and #HLT32-07652. The period of education and research training resulted in the following publications and abstract presentations.

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<td>Aortic baroreceptors</td>
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<tr>
<td>BP</td>
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<td>BSA</td>
<td>Body surface area</td>
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<td>CSI</td>
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<td>Electromyogram</td>
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<td>Forearm vascular resistance</td>
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<td>Graded exercise test</td>
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MAP  Mean arterial pressure
MCFP Mean circulatory filling pressure
MSNA Muscle sympathetic nerve activity
NP/NS Neck pressure / neck suction
OIT Orthostatic intolerance
OT Orthostatic tolerance
O₂ Oxygen
PₐCO₂ Arterial partial pressure of carbon dioxide
PₐCO₂ Alveolar partial pressure of carbon dioxide
PₑₑCO₂ End tidal partial pressure of carbon dioxide
PE Phenylephrine hydrochloride
PV Plasma volume
PₐCO₂ Mixed venous partial pressure of carbon dioxide
PRU Peripheral resistance units
Q̇ Cardiac output
RRI R wave to R wave interval of time in milliseconds
SV Stroke volume
SBP Systolic blood pressure
TPR Total peripheral resistance
̇VCO₂ Rate of carbon dioxide elimination
̇VO₂ Rate of oxygen uptake
̇VO₂max Maximal aerobic power
VT Ventilatory threshold
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CHAPTER I

INTRODUCTION

"Pour bien comprendre une Science, 
il faut en connaitre l'histoire"
Auguste Comte (1798-1857)

"Those who cannot remember the past
are condemned to repeat it"
George Santayana (1863-1952)

The quest for understanding in science moves forward when questions are asked and an attempt to answer them using the scientific method is made. It is said that science cannot "prove" a hypothesis, but only disprove it. The strongest hypotheses and hence those that last, are the ones that stand the test of time. The questions that initially arise are often born out of anecdotal evidence or per chance by something that is noted in an unrelated experiment. This dissertation will attempt to answer a question in physiology that has a history of strong debate over the past few years both anecdotal and experimentally. The question to be answered involves specifically, the concept of fitness related variations in arterial blood pressure regulation as it pertains to human beings undergoing orthostatic stress. Anecdotally, many athletes involved in endurance training have reported dizziness, nausea and occasional syncope when
moving from a supine or recumbent position to an upright stance. Convertino et al. (50) defined orthostatic tolerance (OT) as "the capacity of the cardiovascular reflexes to maintain arterial pressure so an individual can tolerate the upright, stationary posture". Orthostatic intolerance (OIT) therefore, would be defined as the inability of the cardiovascular reflexes to maintain arterial pressure in the upright posture.

The study of the cardiovascular responses under orthostatic conditions has been used to examine the control of blood pressure in individuals who may undergo exposures to various degrees of change in gravitational force. The primary hemodynamic effect of orthostasis is the translocation of blood from the central veins and heart to the lower extremity with the magnitude of the volume shift related to the physiological responses (24). To study the cardiovascular responses to orthostatic stress various experimental techniques have been utilized including passive standing, passive and active head-up-tilt, lower body negative pressure (LBNP), and centrifugation (+Gz acceleration). The advantage of LBNP over the other techniques is that it allows gravity independent venous volume translocation to the lower extremities with minimal muscular activity, easy instrumentation access and physiological recording. It also allows for accurate step-wise gradations of gravitational stress with the ability to
discontinue the stressor immediately. Lightfoot et al. (124) suggested that OIT can be defined as the onset of presyncope (fainting), evidenced by a drop in mean pressure and a precipitous decrease in heart rate and vascular resistance during an orthostatic challenge. The important question is:

'Is there a subpopulation of individuals who, due to specific characteristics are more prone to orthostatic intolerance, resulting in lipothymia (faintness), and if so, what is/are the specific underlying characteristics of this group?'

In 1974 Stegemann et al. (204) stated that "endurance training reduces the effectiveness of the blood pressure control systems." In 1977 Klein et al. (109) suggested that prior aerobic conditioning could place astronauts at high risk for syncope after their return from microgravity. These reports caused investigators to question whether aerobic training was detrimental to blood pressure control during orthostatism. Since that time, several investigators have suggested, as did Stegemann et al. (204), that endurance training results in attenuated orthostatic reflexes (106-109,128,132,157,165,195-199), while others have reported no such aberrant relationship (47,50,51,89,114,124). It has been suggested that the detrimental relationship between tolerance and fitness was due to attenuation of the arterial baroreflex regulation of blood pressure (165,196,199). Cardiopulmonary baroreflex control of forearm vascular resistance has been reported to be attenuated in high versus
low fit individuals (132,225). Other suggestions include an alteration in leg volume pooling with LBNP (129,157); or perhaps the variations in blood pressure regulation are secondary to alterations in autonomic balance affected by training (196). The concept of a fitness related OIT has been a difficult proposition to accept, since, physical fitness is usually associated with an increase in the ability to withstand stressors. This apparent paradox has been difficult for many to assimilate into current thinking since an increase in fitness results in an increase in plasma volume (48), which should protect against orthostatic intolerance (47). Blomqvist (22), suggested that the paradox is further heightened in that prolonged bed rest, which results in physical deconditioning and a decreased plasma volume, produces OIT.

Blomqvist (22) suggested two principal mechanisms that cause orthostatic intolerance: 1) an abnormal degree of central hypovolemia; and 2) inadequate cardiovascular regulatory responses. Blomqvist further suggested that dual descriptors referring to the volume and autonomic state may better elucidate the underlying mechanisms involved in OIT. Using Blomqvists theory, weightlessness may predispose individuals to a hypovolemic hyperadrenergic form of OIT in which individuals experience large decreases in end-diastolic volume, which can then be linked to either abnormal volume distributions or loss of total body water. A
Hyperadrenergic state is needed to counteract the central hypovolemia. In normovolemic, hypoadrenergic (asymptoticolytic) OIT the adrenergic nervous systems ability to counteract a redistribution in intravascular volume is affected. The hypoadrenergic state may be the result of altered baroreceptor function manifest by altered afferent, efferent, or medullary cardiovascular control center dysfunction, or to end organ failure. In 1986 Harrison (93) suggested that a more complete understanding of autonomic control of the cardiovascular system is required to understand fitness related mechanisms of OIT. It is the intent of this dissertation to define possible mechanisms linking endurance exercise training to OIT.

When examined in total, the studies to date, either for or against a fitness related alteration in OIT, suffer from numerous methodologic variances in variables measured and the type of population used. The single largest deficit, however, may be the cross-sectional designs employed in many of these studies. Unfortunately, cross-sectional descriptions of effects and mechanism raise questions with regard to whether genetic factors makes one susceptible to OIT or whether endurance exercise training 'per se' results in OIT.
Statement of the Problem

The effects of endurance exercise training on orthostatic tolerance are not well delineated and mechanisms are controversial. The present study examines the effect of endurance training on the response of the efferent limbs of the autonomic nervous system of the baroreflex to determine mechanisms of fitness related adaptations of blood pressure regulation. To accomplish this, subjects underwent an endurance exercise training program and prior to and following training were challenged by LBNP to presyncope, and on separate days LBNP under complete selective and combined cardiac autonomic blockade. To characterize the high pressure baroreflex stimulus response curve, the response of the baroreflex was also examined under hypertensive perturbations using phenylephrine hydrochloride (PE).

Hypotheses

1) Orthostatic tolerance is reduced following endurance training as determined by the time to presyncope during graded levels of lower body negative pressure.

2) The gain of the vascular reflex defined as the slope of the linear relationship between central venous pressure, and forearm vascular resistance during selective unloading of the low pressure
baroreceptors is diminished following endurance training.

3) The responsiveness of the arterial baroreceptor reflexes is attenuated following endurance exercise training when individuals are subjected to hypotensive and hypertensive stresses; including LBNP and steady-state infusions of PE.

4) Blood pressure is better regulated following endurance training using either atropine or double cardiac blockade, due mainly to an increased forearm vascular resistance that allows maintenance of blood pressure.

Delimitations of the Investigation

Based on several methodological concerns, the following delimitations of the study were established:

1) The opposing effects of various arterial baroreceptor populations were not controlled. Low pressure (ie. cardiopulmonary) baroreceptors were contrasted with high pressure (ie. arterial) baroreceptors, but carotid versus aortic baroreceptor reflex differentiation was not made.

2) Only young, apparently healthy males were used in the present experiments. No attempt was made to determine differences based on gender, age, or health status.

3) Arterial blood pressure measurements were made utilizing invasive measurements at the radial artery.
Therefore, some peripheral pulse wave amplification was expected. We assumed that changes in radial artery pressures reflected changes in aortic arterial pressures.

4) This study did not examine the role of the humoral system in the control of blood pressure regulation during orthostasis. With the volume expansion induced by endurance exercise training and the volume shifts occurring during LBNP, hormonal alterations may have played a part in regulating arterial blood pressure.
CHAPTER II

REVIEW OF RELATED LITERATURE

Concerns regarding man's ability to handle an orthostatic stress were raised when it was noted that astronauts became syncopal upon returning to earth after sojourns in space. While our understanding of the mechanisms involved in orthostatic tolerance have increased, considerable controversy and lack of understanding of individuals at risk still exists. With this in mind, this review will center on a description and summary of: i) the general cardiovascular responses to orthostasis; ii) reflex control of orthostasis through the arterial baroreflexes; and iii) endurance training and tolerance susceptibility. Baroreflex mediated humoral responses are only briefly considered in this review.

Orthostasis: General Cardiovascular Responses:

As outlined in the introduction, lower body negative pressure (LBNP) has been shown to be an effective technique for the study of cardiovascular reflex mechanisms associated with orthostatic intolerance. When humans assume the upright posture the heart is approximately 1.2 to 1.5 meters above the feet. This gravitational stress creates a head-to-foot
hydrostatic pressure gradient with redistribution of blood into the compliant veins (approximately 75% of blood volume). Seventy-five percent of the total blood volume is thus below the level of the pump and must be driven back to the right atrium to maintain ventricular filling pressure. Based on the concept of heterometric autoregulation from the Frank-Starling Length-Tension relationship, the heart itself can do little to overcome the fall in filling pressure seen during orthostatism. Since man does stand and function in the upright position, as well as maintain consciousness under artificially induced gravitational stressors, various mechanical factors and reflex adjustments that regulate arterial pressures and flow in the peripheral circulation, to maintain as an end point cerebral perfusion, must be involved. Lower body negative pressure is an accepted model of orthostasis and one which allows the gradual reduction of central venous pressure. Figure 1 illustrates the basic cardiovascular responses to an orthostatic stress induced by LBNP. In the data presented in the left hand panel (99), the subjects were exposed after a 20 minute rest period to lower body suction of -1 torr·min⁻¹ until a pressure of -50 torr had been established. The aortic pulse pressure, aortic dp/dt, mean pressure or heart rate did not begin to be affected until suction exceeded -20 torr, although right atrial pressure had decreased from +5 to 0 mmHg from 0 to -20 torr of box pressure. The aortic pulse pressure during
this time was maintained by peripheral vasoconstriction of forearm and splanchnic vasculature. Forearm blood flow reduction was altered very little after -20 torr, while only 10% of splanchnic blood flow had decreased from 0 to -20 torr.

**FIG. 1.** Cardiovascular responses to graded lower body negative suction. Panels on the left show the average responses to suction applied at a continuous rate of -1 torr·min⁻¹ for 50 min (99). Panels on the right show cardiovascular responses to -10 torr increments of LBNP (6).

The data by Ahmad et al. (6) (right panel) shows how the aortic pressure was regulated by peripheral vasoconstriction in the face of falling cardiac output and stroke volume. The apparent discrepancy in response up to
and past -20 torr LBNP will be discussed in the following sections along with the influence that training could have on the variables. In summary, the ability to resist orthostasis or gravitational stressors depends on the responsiveness of the cardiovascular reflexes during conditions of central hypovolemia and arterial hypotension. The reflexes emanating from arterial and cardiopulmonary baroreceptors mediate myocardial function, arterial and venous tone, and neuroendocrine secretion as a means of regulating arterial pressure. An understanding of how these reflexes function in individuals of low and high aerobic fitness will be helpful in understanding differences in OIT associated with training. Which of these adaptations may be responsible for predisposing an athlete to OIT has not been clearly determined. In the following sections the various baroreceptor populations will be examined and their role in reflex control of arterial pressure will be discussed. Finally, endurance exercise training and orthostatic tolerance specifically will be examined.

Reflex Control of Orthostasis:

Arterial Baroreflexes:

Three population of mechanoreceptors will be reviewed, these being: i) the high pressure baroreceptors (HPBR) (carotid and aortic); ii) the low pressure baroreceptors or cardiopulmonary baroreceptors (CPBR); and iii) the cardiac receptors.
Carotid Baroreceptors: Effect on Heart Rate:

Stretch receptors located in the adventitia of the carotid sinus (bifurcation of the common carotid arteries) (4), are sensitive to changes in stretch caused by increases and decreases of arterial pressure. Abraham (3) and Willis and Tange (234) noted that this region contains sensory endings with single myelinated fibers that branch into small fibrils and terminate in neurofibrillar end-plates. The carotid baroreceptors (CBR) have been shown to be important in beat-to-beat regulation of arterial pressure. Evidence for the tonic ability of the baroreceptors came initially from Bristow et al. (29). They injected phenylephrine into humans and noted an average lengthening in the R wave to R wave interval (RRI) of 13 msec/mmHg increase in systolic blood pressure during the ramp phase. Similar results have been shown by others during the steady-state phase of drug induced baroreceptor stimulation (112,135). Baroreceptor deactivation with depressor drugs has shown a mean reduction in RRI of 9 msec/mmHg reduction in systolic blood pressure (162). These results support the theory that heart rate control is tonic in nature and the baroreflex is poised to either increase or decrease heart rate during spontaneous fluctuations in blood pressure in humans. A rise in arterial pressure distends the area around the baroreceptors and sensory nerve endings are activated with impulses relayed to the medulla by afferent fibers from the carotid sinus in the
glossopharyngeal nerve (105). Both A-type myelinated afferent fibers (5,56) and C-type unmyelinated afferent fibers have been reported to be active participants in the regulating process. Jones and Thoren (97) have shown that, due to their lower threshold levels, myelinated fibers mediate the majority of normal responses, whereas unmyelinated fibers with higher thresholds fire when the pressures are abnormally elevated. In the medulla, complex interactions through interneuronal connections result in inhibitory reflexes consisting of bradycardia (through sympathetic inhibition, and parasympathetic stimulation), and vasodilatation (through inhibition of adrenergic vasoconstrictor nerves). The bradycardia and vasodilatation act to buffer and reverse the rise in pressure.

The reflex bradycardia is probably secondary to an increased efferent outflow of vagal activity to the sino-atrial (SA) node of the heart. Although fibers from both the right and left vagus nerve innervate the SA node, a greater absolute number of branches are noted emanating from the right vagus and hence it probably contributes more to tonic regulation of heart rate (21,32). It has also been shown that surgical ablation of the right vagus causes a greater change in heart rate than from the left vagus (92). This reflex change in heart rate secondary to alterations in blood pressure in humans has been shown to have a latency of 240-600 msec (27,64), and is eliminated by atropine (113).
Conversely, it is unlikely that the early reflex heart rate response is due to sympathetic inhibition. Some studies evaluating initial heart rate responses to alterations in blood pressure regulation have shown little effect if β-adrenergic blockers are given first (162), while others have disagreed (134,196). The magnitude of cardiac response to either increases (29,112) or decreases (112,135) in arterial pressure is an RRI change of 3-15 msec/mmHg alteration in arterial pressure.

In terms of temporal effects of heart rate control, Coleman (43) has clearly shown that when arterial pressure is elevated for a prolonged period of time (5 minutes), the bradycardia is mediated by the vagus exclusively only during the first 10 seconds. Sympathetic withdrawal takes over after approximately 15 seconds and becomes a more dominant factor. Very similar results have been shown by Wang and Borrison (229).

Due to the above mentioned temporal relationships, the neck chamber system described by Eckberg (64,65) provides a means of evaluating cholinergic carotid baroreflex responses. They have found that neck suction (which mimics carotid hypertension) results in an initial bradycardia that can be blocked by atropine. Hence, neck suction could be used to determine the effectiveness of atropine blockade. Neck pressure (effective carotid hypotension) induced tachycardia is thought to be mediated by vagal withdrawal
(65,104,106). These results seem consistent as long as the
carotid hypotension is < 20 seconds, after which time the
sympathetic activity is also increased (85). Two caveats are
important to remember: 1) these results are reported on
normotensive adults or animals; 2) the age of the subjects
is similar. It has been shown by Bristow et al. (29) and
Gribbon et al. (90) that carotid baroreceptor control is
altered in hypertension. They noted that lengthening of the
RRI secondary to an increase in systolic blood pressure when
phenylephrine was infused at steady-state progressively
decreased in mild to severe hypertensive individuals. Thus
resting arterial pressure is an important variable affecting
reflex control of heart rate. Gribbon et al. (90) also
noted, in a group of individuals aged 19-66 years, that CBR
sensitivity was inversely related to age, and this effect
was independent of the influence of hypertension.

In summary, the cardiac efferent pathway induced by CBR
stimulation or inhibition appears to temporally affect RRI.
The initial responses appear solely related to
parasympathetic stimulation or withdrawal, while prolonged
CBR stimulation or inhibition (>20 seconds) also involves
sympathetic stimulation or withdrawal. Starting age and
baseline arterial blood pressure are also important
variables that need to be factored.

Carotid Baroreceptors: Effect on Atrio-Ventricular Node:

Carotid sinus massage has been shown in some
individuals to result in atrio-ventricular (AV) blockade (38,86) and hence the CBR have the potential to exert a marked influence on AV conduction. Mancia et al. (134) noted that phenylephrine injections (21 mmHg increase in mean arterial pressure) caused a marked lengthening of the RRI but did not alter the atrio-ventricular node interval (A-H), or the time between the His bundle potential and ventricular excitation. If, however, RRI is kept constant by an atrial pacemaker and arterial pressure is altered, then A-H is markedly changed. These results are blocked by atropine. This suggests that A-V conduction control is mediated through cholinergic nerves and is tonic in nature.

The role of the A-V node, however, appears to be to maintain a constant time relationship between atrial and ventricular events during reflex changes in heart rate.

Carotid Baroreceptor: Effect on Contractility:

The role of CBR control of cardiac contractility has long been debated. Sarnof et al. (182) were the first to suggest that baroreceptors could effect contractility. They noted that when carotid artery perfusion was reduced, in an atrial paced dog heart that a rapid rise in cardiac output (\( \dot{Q} \)), and a decrease in left atrial pressure occurred. Since alterations in pre-load and after-load can effect \( \dot{Q} \), and these were not well controlled variables, the work of Sarnoff et al. (182) has been challenged by Salisbury et al. (178). To better answer the critiques of the studies by
Sarnoff et al., DeGeest et al. (54), performed similar experiments but with better control measures. They used a neurally intact canine heart preparation which isolated the heart from the circulation so that pre-load, after-load and heart rate could be controlled. In their experiments, increases in carotid sinus perfusion pressure decreased peak left ventricular systolic pressure resulting in an interpretation of a decrease in contractility which was CBR mediated. Downing and Gardner (61) in experiments similar to those of DeGeest et al. (54), but in a cat model, found that with carotid hypotension, the Starling curve shifted up and to the left, so that for a given pre-load, with after-load and heart rate held constant, increases in stroke volume or stroke work were found, suggesting a positive inotropic effect. Although considerable evidence now exists in support of CBR control of contractility, controversy remains and further work needs to be done.

Carotid Baroreceptor: Control of Venous Circulation:

Carl Ludwig through his interaction with Dittmar and Owssjannikow developed the concept of a vasomotor center in the medulla (145). These concepts have proved fundamental to our modern ideas of tonic vasoconstrictor activity exerted by sympathetic fibers influencing nearly all the regional peripheral circuits. A lack of suitable techniques to assess changes in venous compliance ($\Delta V/\Delta P$) in humans has hampered the interpretation of HPBR control of the venous
circulation. It has been suggested that the first use of the term 'venous tone' was by Richard Lowes in 1669 who used the term 'relaxato venarum tono' (81) and concluded that venous dilation resulted in a feeble pulse because the heart was deprived of its normal venous input. Arterial baroreceptors (HPBR) have not been shown to exert much control of the cutaneous veins in animals (28,33). To examine this in humans, Bevegård and Shepherd (18) studied the responses of the hand vein to carotid neck suction. They used the occlusion technique to monitor venomotor changes, which allows pressure within a vein to be measured while keeping venous volume constant (180a). They found that neck suction up to -60 torr failed to alter venous pressure. Similar findings have also been reported by Epstein et al. (77). They observed no effect on venous pressure to carotid neck suction, or phenylephrine injection which would activate both carotid and aortic baroreceptor populations. Splanchnic vascular beds, however, have been shown to be affected by HPBR (187,188). In humans, stimulation and deactivation of carotid baroreceptors have produced no change in central venous pressure (172) and hence, their role in regulation in humans has been questioned. Greene and Shoukas (88), however, have recently challenged this paradigm. Using a canine model, they monitored mean circulatory filling pressure (MCFP) as carotid sinus pressure was independently altered. They found an inverse relationship between MCFP and
change in perfusion pressure.

In summary, the carotid baroreceptors of humans have not been shown to play a role in maintaining cardiac filling pressure, as they have in animals, by vеноconstriction of the high capacitance beds. It is thought that CBR mediated reflexes primarily affect splanchnic volume via attenuation of vasomotion of the arterioles (175).

Carotid Baroreceptors: Control of Arterial Circulation:

An important physiological question to be asked is whether the carotid baroreceptor reflex provides effective blood pressure control in response to physiological alterations in baroreceptor stimulation. Carotid baroreceptor importance has clearly been shown by studies demonstrating increases in blood pressure after a reduction in carotid transmural pressure of 15 to 20 mmHg (135,172). Conversely, a blood pressure decrement is seen if carotid transmural pressure was decreased 15 to 20 mmHg (18,135). The response time of the carotid reflex is impressive. During carotid neck suction, arterial blood pressure has been shown to respond with a latency of 3 msec after the initiation of the stimulus. The arterial pressure drop reached its nadir in 10 to 20 seconds during a held suction, and then began to rise toward control levels. However, the arterial pressure increase failed to achieve the control levels (18,26,135).

Since the reflex response to alterations in carotid
transmural pressure induced by neck suction or pressure can be elicited, reflex control must be tonic in nature and similar to baroreceptor control of heart rate. The blood pressure reflex demonstrates latency, which when contrasted with the lag time response of the chronotropic response to carotid transmural pressure alterations results in a slower vasomotor response.

Mancia et al. (135) determined the degree of blood pressure buffering provided by the carotid baroreceptors in response to carotid neck suction or pressure. They noted that mean arterial pressure increased an average of 0.68 mmHg per mmHg increase in tissue pressure outside the carotid sinus. Conversely, with hypotension, a reduction in mean arterial pressure of 0.44 mmHg per mmHg reduction in tissue pressure outside the carotid sinus was noted. In summary, the carotid baroreflex control of blood pressure has been shown to buffer $\frac{2}{3}$, or 67% of the blood pressure response to an increase in mean arterial pressure and 50% of the response to a decrease in arterial pressure.

The exact mechanism as to how the hypotension was induced by the carotid baroreceptor stimulation has been raised. Due to the observation of a decreased pulse pressure during electrical carotid nerve stimulation Carlston et al. (37a) argued for a reduction in $Q_c$ as the important variable. While some researchers support this view (17,18), others (19,76) have observed little or no change in $Q_c$. 

during carotid baroreceptor stimulation and have suggested decreases in total peripheral resistance as the mechanism of action. With baroreceptor deactivation, however, the studies show that both $\dot{Q}_e$ and total peripheral resistance are increased (19,221).

It is important to note that atropine doesn’t effect the vascular reflex (26,76). Hence alteration of total peripheral resistance by carotid baroreceptor reflex depends on alterations in sympathetic vasoconstrictor outflow.

Carotid Baroreceptors: Control of Regional Circulation:

Carlsten et al. (37a) originally suggested that the carotid baroreflex influenced skeletal muscle beds. They noted a marked increase in forearm blood flow during electrical stimulation of the carotid sinus nerves, suggesting a vasodilatation. Others have failed to show alterations in forearm vascular resistance with carotid baroreceptor neck suction (1,2), but have shown alterations with unloading of the cardiopulmonary baroreceptors (99,239). Reports summarized by Wallin and Fagius (228) were unable to demonstrate any link between cardiac rhythmicity and bursts of skin sympathetic nerve activity supporting the hypothesis that the skin blood flow is unaffected to any degree by the carotid baroreflex.

Carotid baroreceptors also influence splanchnic blood flow as evidenced by a marked increase in splanchnic vascular resistance when LBNP suction resulted in a
decreased pulse pressure and mean arterial pressure (99). Johnson et al. (99) also demonstrated that low level LBNP that did not affect mean arterial pressure or pulse pressure caused only a moderate reduction in skin blood flow as measured by indocyanine green clearance. Abboud et al. (1) also noted a change in the clearance of indocyanine green in conscious man subjected to -40 torr neck suction during LBNP at -40 torr. The restoration of the carotid transmural pressure eliminated the vasoconstriction resulting from the LBNP induced hypotension.

**Aortic Baroreceptors**

Stretch receptors located in the adventitia of the aortic arch (origin of the brachiocephalic and left subclavian arteries) (149) are sensitive to changes in stretch caused by increases and decreases of arterial pressure. Unlike carotid baroreceptors, there is no decrease in the smooth muscle content of the arterial wall in the region of the baroreceptor (60). This difference in muscle wall content may explain some of the differences in responsiveness between aortic and carotid baroreceptor populations.

Aortic baroreceptor (ABR) isolation in humans is technically difficult, but a number of studies have inferred conclusions. It has been shown that when phenylephrine is infused to increase arterial blood pressure, and positive neck pressure is used to counteract the increase in carotid
sinus transmural pressure (thereby isolating the aortic baroreflex function), the aortic cardiac reflex had a more prominent role than the carotid-cardiac reflex (135,80). In an interesting set of experiments, Mancia et al. (135) estimated the aortic baroreceptor function as the difference in response to phenylephrine (PE) and carotid sinus neck suction (NS), and the response to nitroglycerin and carotid sinus neck pressure (NP). The difference between PE and NS was an increase in RRI of 9.9 msec/mmHg increase in MAP. The difference between nitroglycerin and NP was a decrease in RRI of 5.9 msec/mmHg decrease in MAP. These data suggest that ABR are two times more influential in reflexly affecting HR versus the CBR. These findings are in agreement with animal studies that suggest that the ABR exert a greater influence on HR versus CBR (236).

A second method has been used with some success to determine ABR function in man. Sanders et al. (181) examined muscle sympathetic nerve activity during alterations in aortic perfusion pressure with phenylephrine infusions. Since phenylephrine will increase CBR and ABR pressure, simultaneous neck pressure was utilized to offset the increase in mean arterial pressure. To compensate for changes in right atrial pressure due to phenylephrine, lower body negative pressure was utilized. Muscle sympathetic nerve activity increased by 54% when phenylephrine was infused. Those level decreased to only 46% when neck
pressure was also applied. In examining the heart rate response, PE alone caused a bradycardia of 15% below baseline. When neck pressure was added, however, the bradycardia was only 4% below baseline. These data suggest that ABR affects both HR and vascular resistance, however, the vascular resistance seems to be its primary target.

In animal studies the ABR have been reported to be at a higher operational point than the CBR (121). Pelletier et al. (159) have stated that the operational point for CBR is 62 mmHg, while that of the ABR is 95 mmHg. These results have lead some researchers to suggest that aortic baroreceptors are tonically inactive. Others have shown that with newer surgical preparations and recording equipment that the operational points in animals of the two baroreceptor populations are similar (9).

In summary, the role of the aortic baroreceptor in humans remains unclear. The data, to date, from animal and human experiments would suggest that ABR have a greater overall control of the muscle vascular resistance, while CBR have more effect on heart rate control with arterial pressure alterations.

Cardiopulmonary (Low Pressure) Baroreceptors (CPBR):

Mechanoreceptors are located at the junction of the vena cava, in the pulmonary veins, right atrium, left atrium and within the walls of the heart. These stretch receptors respond to changes in intracardiac pressure (126,152),
central venous pressure, and via afferent vagal pathways, impinge on the cardiovascular centers of the medulla. The presence of cardiopulmonary baroreceptor (CPBR) reflexes suggests that cardiac filling volume or pressure is being regulated by a feed forward mechanism, (i.e., by adjusting arterial pressure, through an interaction at the cardiovascular centers of the medulla with resultant efferent neuronal traffic, a reflex vasoconstriction is produced).

In 1957 Roddie et al. (172) noted that reflex vasodilatation seen in muscle after passive leg raises was not correlated with alterations in arterial pressure and was secondary to the activation of low pressure receptors in the thorax.

Lower body negative pressure (LBNP) has been used in both animal and human models to simulate orthostatic stress and hemorrhage (30,99,220,239) for evaluation of cardiopulmonary baroreceptor function. It has been postulated that during LBNP of less than -20 torr, a decreased central venous pressure (CVP) results, and cardiopulmonary baroreceptors are selectively unloaded (174). This decrease in CVP occurs without a change in aortic blood pressure (174). Despite the decrease in CVP the central hypovolemia is limited, because of a translocation of fluid from low capacitance beds to the great veins as measured by increases in muscle sympathetic nerve activity.
The increased MSNA has been correlated with increases in vascular resistance in both upper and lower extremities (99,224). Zoller et al. (239) suggested that the increased sympathetic activity was mediated by a decrease in the discharge rate of intrathoracic mechanoreceptors (cardiopulmonary receptors), caused directly by the translocation of fluid from the thoracic cavity resulting in a decrease in central venous pressure. Evidence for the necessity of cardiac afferent nerve involvement comes from human cardiac transplant data. Mohanty et al. (142) showed a marked attenuation of the forearm vascular resistance response to LBNP after cardiac transplantation. Further evidence to support this reflex as independent of CBR comes from the work of Abboud et al. (1). They reported that stimulation of carotid baroreceptors by neck suction alone fails to cause alterations in forearm vasodilatation, while passive leg raises cause a marked vasodilation in these subjects. The role of the CPBR in control of the cutaneous circulation is fairly conclusive. Roddie and Shepherd (172) demonstrated that hand blood flow failed to increase during passive elevation of the legs. Low levels of LBNP have also failed to produce increases in hand blood flow (139). In the experiments outlined in the introduction by Johnson et al. (99) it was noted that at -20 torr LBNP, splanchnic blood flow had decreased despite arterial pressure not being altered. The splanchnic blood
flow decrease, however, was only -11%, while forearm blood flow decreased -33%.

In summary, evidence exists to suggest that CPBR primarily control muscle sympathetic nerve activity and hence, limb blood flow. Secondarily they regulate splanchnic blood flow in a minor fashion. They have no effect on cutaneous circulation.

Cardiac Receptors:

Bainbridge (12) reported a reflex tachycardia in dogs secondary to intravenous infusions of saline and suggested that this was due to a reflex withdrawal of vagal tone. In man, however, increases or decreases in CVP with changes in cardiac filling pressure have failed to produce this reflex tachycardia (10,62,210). This lack of effect has been thought to be secondary to an inability of the altered CVP to effect arterial pressure and hence HPBR (210).

Another reflex thought to exist in the heart is the cardiac mechanoreflex, which is similar to the arterial baroreflex. The receptors responsible for this reflex are thought to be located in the posterior wall of the left ventricle (214). Nerve endings in the ventricle may be activated mechanically either by cardiac distension, stretching, or by vigorous forceful and rapid systolic contraction. The triggered activity is relayed to the medulla by afferent fibers in the vagus nerve and results in an inhibitory reflex producing bradycardia and
vasodilatation (214). Veratridine or nicotine are chemicals that have been shown to activate this so called Bezold-Jarisch Reflex (44). Clinically, this reflex has been noted during coronary arteriography (69). The importance of this reflex, however, in day to day control of blood pressure and cardiovascular function is uncertain. The Bezold-Jarisch reflex may, however, have some clinical value. When veratridine was injected into the circumflex coronary artery of the dog (which supplies the posterior inferior wall), the reflex bradycardia and hypotension were greater than if it had been injected into the descending coronary artery supplying the anterior wall (226). In agreement with this response is the finding that bradycardia and hypotension are more common in dogs during inferior versus anterior ischemia (215). This reflex may help to explain the high incidence of nausea and vomiting in the early stages of inferoposterior myocardial infarction.

In summary, the heart appears to be a reflexogenic organ capable of inducing severe hypotension and bradycardia. This reflex appears to play a role in myocardial ischemia and may be important in regulating coronary flow. The Bainbridge reflex may be active in animals but does not appear to play an important role in man.

Interaction of Cardiopulmonary and Carotid Reflexes:

The ability of CPBR to modulate CBR was initially
demonstrated in experiments by Koike et al. (110). They demonstrated that transection of the CPBR afferent nerves in dogs augmented the vasoconstrictor effects elicited by carotid sinus hypotension. However, it appears that the modulation effect of the CPBR on CBR efferent outflow does not involve chronotropic alterations. Takeshita et al. (210) reported that alterations in CVP from 1 to 9 mmHg did not alter carotid baroreflex control of heart rate. These results, however, are contrasted to those of Billman et al. (20) who noted that head-down-tilt and volume augmentation in rhesus monkeys decreased the change in RRI invoked by bolus injections of phenylephrine. Others suggest that CPBR when deactivated augmented the gain of carotid baroreflex control of vascular resistance in humans as well as experimental animals (156).

In summary, CPBR have been shown to interact with CBR and appear to be involved more with the regulation of vascular resistance rather than with chronotropic responses.

Fitness and its Relationship to Orthostatic Tolerance

Chronic endurance training has been shown to alter autonomic nervous system function; decrease resting heart rate; and increase cardiac size, maximal oxygen consumption ($\dot{V}O_{2max}$), blood volume, maximal cardiac output ($\dot{Q}$), and vascular conductance. These various parameters will be discussed with emphasis on their possible relationship to alteration in orthostatic tolerance in the following
Autonomic Nervous System (ANS): Effect of Training:

Because the ANS is an integral component of blood pressure regulation, an exercise training-induced alteration in autonomic function could account for the differences in blood pressure control observed between endurance trained and untrained men. Smith et al. (196) found that blood pressure was maintained primarily by augmented vasoconstriction equally in trained and untrained subjects during complete cardiac and atropine blockade during LBNP. They also noted that blood pressure decreased to a greater extent in trained subjects during unblocked and metoprolol blockade conditions secondary to an attenuated vasoconstriction and chronotropic response to LBNP. Mangseth and Bernauer (136) have also suggested that endurance training may be associated with a reduced capacity to increase peripheral resistance during an orthostatic stress (passive head-up-tilt). Similar results have been shown during LBNP experiments (165,167). The exact mechanism accounting for the lower vasoconstrictor tone is unknown. The possibility of a decreased sympathetic tone following endurance training is possible, although SNA recorded at the peroneal nerve has not been shown to be altered with training (208). If the vasoconstrictor effect is not central in origin, it is possible that alterations may occur at the cellular level. If the sensitivity of the vascular
α-adrenergic receptors were altered, then a given rate of sympathetic outflow would produce less vasoconstrictor effect. The results from these studies have been inconclusive, showing reductions with NE injections of systolic and diastolic blood pressure in athletes versus nonathletes (154), and lower peripheral resistance using an α-adrenergic agonist in unfit versus fit subjects (167). Hypersensitivity of the blood vessels to β-adrenergic stimulation has also been hypothesized to be a potential mechanism, however, the evidence must still be regarded as inconclusive (47).

In summary, it is possible that alterations in ANS function are responsible for the differences seen in subjects exposed to an orthostatic stress. Further research, however, is required to elucidate the underlying mechanisms.

Heart Rate: Effect of Training:

Studies investigating the effects of endurance exercise have demonstrated reductions in resting heart rate (RHR) post-training (72,222,238). Some investigators suggest that the training induced bradycardia (TBR) at rest is due to an alteration in autonomic tone (197). Using atropine and propranolol blockade alone and in combination Ekblom (72), found that training bradycardia (ie. at rest) was the result of increased parasympathetic (PAR) and decreased sympathetic (SYM) tone to the heart. Others have suggested that a decreased intrinsic heart rate (IHR) either alone (102) or
in combination with PAR increases (197) are responsible for the TBR. In 1934, Rosenblueth and Simeone (173) completed the first quantitative studies examining cardiac SYM-PAR interactions. They were the first to present the concept of accentuated antagonism: that being, that a given level of vagal stimulation evokes a greater absolute reduction in heart rate in the presence of a constant level of SYM activity, than in the absence of SYM tone. It is possible therefore, that the resting bradycardia could be the result of altered SYM-PAR interactions, i.e., accentuated antagonism. In a 1991 review article of the "Athletic Heart Syndrome", George et al. (83) suggested that the exact mechanism underlying training induced bradycardia is controversial and not well delineated.

Levy (117,118) has previously shown that one measure of cardiac end-organ responsiveness at rest (i.e., heart rate) is a non-linear function of the relationship between SYM and PAR input to the myocardium. This non-linear function could be the result of:

(a) central nervous system neuronal regulation (i.e., central command),
(b) direct vagal-sympathetic interactions between the afferent nerves,
(c) alterations in cardiac autonomic receptor numbers or binding parameters, and/or
(d) alteration of the coupling (i.e., G proteins) or amplification processes within the cell.

As outlined above, the possible mechanisms involved in training induced resting bradycardia are many and no clear
picture has emerged.

Our understanding of the control of heart rate has progressed since Otto Louis first described the inhibitory effects of acetylcholine on heart rate. The ANS, through complex interactions of the adrenergic and cholinergic reflex system, exerts major functional control on the heart. The heart is specifically controlled by the sympathetic nervous system (SNS) through stellate ganglion stimulation and norepinephrine (NE) release, whereas the parasympathetic nervous system is controlled by cholinergic (Vagal) stimulation with Ach release. The time frame of response between these two limbs of the ANS are very different. The SNS exerts effects which are relatively slow 'on' and dissipate over a long period of time, versus the effects of vagal stimulation which arise faster and dissipate faster. Hence, the vagal effects may have run their course while simultaneously stimulated SNS stellate ganglia may still be in its latency. Three possible mechanisms have been proposed for the slower responding SNS:

1. NE terminal dispersion is slower versus Ach (120).
2. Slower junctional cleft removal of NE. The NE removal from nerve terminals is reuptake or washout into the coronary system (119) versus Ach, which is quickly hydrolyzed by acetylcholinesterase. The net effect of this is probably a longer lasting response for the SNS.
3. The second messenger systems are different:
At the heart, NE after release from nerve terminals binds β-adrenergic receptors which are coupled to adenylate cyclase through a guanine nucleotide binding protein (G<sub>s</sub>) (84). The net result of this interaction is an increase in intracellular c-AMP levels (206). The resultant c-AMP activates protein kinases that phosphorylate cellular substrates that then mediate physiologic effects.

The PNS effects occur through Ach binding to muscarinic receptors (M) which are linked to a number of cellular processes. One mechanism suggests that M receptors are directly coupled to specific sarcolemmal K<sup>+</sup> channels (147) by guanine nucleotide binding proteins (G<sub>i</sub> or G<sub>0</sub>) (161). The net result of the activation of the K<sup>+</sup> channel is a membrane hyperpolarization occurring within 100 msec of vagal stimulation (177). The M receptors are also coupled to adenylate cyclase by the guanine nucleotide binding protein (G<sub>i</sub>) which acts to inhibit the enzyme (201). This decrease in c-AMP decreases the flow of Ca<sup>2+</sup> ions (170). Muscarinic receptors are also thought to increase phosphatidylinositol turnover (31,209).

The control of heart rate, however, may not be a simple function of SNS-PNS activity, rather a differential based on interactions at the cellular level. Pre-junctional and post-junctional interactions are known to exist. It has been reported that pre-junctional Ach inhibits NE release from neighboring adrenergic nerve terminals (211). Conversely,
neuropeptide Y released from adrenergic nerve terminals with NE inhibits Ach from cholinergic nerve terminals (230).

Post-junctional interactions between SNS and PNS activity are secondary to sarcolemmal receptor interactions and the resulting interaction of G proteins and ion channel fluxes.

In summary, the ANS control of heart rate is very complex and involves both efferent limbs of the ANS, as well as intrinsic cardiac receptor second messenger systems.

Cardiac Adaptations: Effect of Training

With exercise training humans show marked cardiac adaptations (23). Using various scanning measures it has been shown that endurance training results in cardiac hypertrophy (103, 143, 160, 180). The increased heart size results in an increase in overall heart size without concentric hypertrophy (160). The role that cardiac hypertrophy plays in alterations in baroreceptor function is not known. Recently, however, Levine et al. (114-116) reported that high fit subjects have greater myocardial compliance than average or low fit subjects and therefore, have greater decreases in cardiac filling volumes for a given amount of LBNP stress. This altered Frank-Starling relationship results in a more marked drop in stroke volume during LBNP and appears associated with high fit subjects reduced LBNP tolerance.

Limb Compliance: Effect of Training:

Luft et al. (129), examined the limb compliance of five
competitive runners and five untrained men and correlated limb compliance with LBNP tolerance. They found that the runners exhibited a reduced orthostatic tolerance and an increased limb compliance ($\Delta$leg volume$\%$-$\Delta$torr'). The correlation between the two parameters was $r=0.72$ for $\dot{V}O_{2max}$ and limb compliance and a significant negative correlation was found between limb compliance and LBNP tolerance ($r=-.75$). Their conclusion was that the increased limb compliance seen in runners was the reason behind the decreased tolerance to LBNP. Similar results have also recently been reported by Levine et al. (114). They noted that maximal calf vasodilator conductance obtained at rest was a primary factor for predicting LBNP tolerance.

**Orthostatic Tolerance: Testing Techniques:**

Two techniques have been used to the greatest extent to determine the effect of training on orthostatic tolerance; LBNP and head-up tilt (HUT). Both of these techniques rely on peripheral redistribution of blood volume and thereby decreased venous return, stroke volume and blood pressure. While both techniques represent effective perturbations for inducing orthostasis, each has distinct characteristics that provide different information about the cardiovascular system and its reflex mechanisms responsible for blood pressure regulation. Another potential problem is that many of the studies that make statements regarding OT and fitness have no defined or poorly defined criteria for tolerance.
During passive HUT the subject lies on a table and is tilted to various degrees while supported by a saddle or harness to allow the legs to hang passively. One disadvantage is that this technique is limited to producing no greater than one gravitational stress. Several studies have failed to define if the subjects weight was supported or not. It has been shown that the use and activity of leg muscles can markedly effect venous pressure, and volume of distribution (164).

While LBNP does not involve tilting, muscle activity must again be determined. Smith et al. (194) showed that isometric activity during LBNP augments venous return and more importantly activates the somato-pressor reflex (140) and reflexly maintains blood pressure despite a falling cardiac filling pressure. Keeping these points in mind, a critical review of the relevant experiments that have examined fitness and tolerance is presented.

**Carotid Baroreceptors and Tolerance:**

When humans stand, both central venous and arterial pulse pressures fall. Therefore, it is difficult to know which of the pressure signals accounts for most of the neuro and humoral adjustments to upright posture (163). The only way to effectively act on the carotid baroreceptors alone in humans is through the application of positive or negative pressure applied directly to the neck to reduce or increase carotid sinus transmural pressure without altering central venous pressure. Wallin and Eckberg (227) have demonstrated
that when systemic hypertension was simulated by using neck suction and hence, stimulation of the carotid sinus receptors that peroneal sympathetic nerve traffic was decreased. When systemic hypotension was stimulated by utilizing neck pressure the carotid sinus receptors, were deactivated and an increase in sympathetic nerve traffic was noted. Stegemann et al. (204) were one of the first groups to use the neck pressure/suction device and make comparisons based on fitness level. They used a specially designed upper body pressure box with an airtight seal around the shoulders. They examined the heart rate, blood pressure responses to chamber pressures ranging from -60 to +60 torr in 25 endurance trained and 25 sedentary control subjects. They reported an attenuation in the heart rate response for a given blood pressure response to a given stimulus of neck pressure or suction suggesting reduced sensitivity in the carotid baroreflex with training (Figure 2). In figure two the open-loop gain has been plotted for the neck pressure neck suction (NP/NS) experiments for the trained versus untrained athletes. One of the criticisms of Stegemanns et al.'s. data (204) was that when the carotid transmural pressure was decreased below 80 mmHg in the unfit subjects, the open-loop gain became infinite, and hence the reported data has been questioned.
FIG. 2. The calculated open-loop gain of the blood pressure control system. Untrained subjects (dashed line), trained subjects (solid line) (204).

Similar results have also been reported for endurance trained rats (220). Barney et al. (13) reported greater RRI changes at each neck pressure in trained versus untrained subjects, suggesting an increase in baroreceptor sensitivity. Falsetti et al. (79), however, found no differences in HR or blood pressure responses in trained subjects, in this case swimmers, to carotid stimulation. Finally, in another study, baroreflex sensitivity was not found to be altered by 10 weeks of daily exercise in dogs (90a).

In summary, carotid baroreceptors have been reported to be attenuated with endurance training and may be responsible for the decrease in tolerance reported by some groups after endurance training.
Aortic Baroreceptors and Tolerance:

Several cross-sectional studies have recently suggested that CBR are not responsible for the attenuation of baroreceptor control of heart rate in exercise trained individuals (114,155). Similar results have recently been proposed for longitudinal studies (112,183). Shi et al. (186) suggested that the closed loop gain of the ABR cardiac reflex control of heart rate was significantly decreased in high fit subjects during steady-state increases in arterial blood pressure. In their study, the CBR gain of the average fit subjects was $4.1 \pm 0.6$ msec/mmHg (35% of total gain) and ABR gain was $7.9 \pm 1.0$ msec/mmHg (65% of total gain). The ABR gain in the HF subjects was $2.2 \pm 1.4$ msec/mmHg (39% of total gain) while the CBR gain of $4.7 \pm 2.5$ msec/mmHg (65% of total gain) was not affected. The possible mechanism for the decreased ABR responsiveness can be explained as follows. Endurance exercise training results in an increased blood volume, left ventricular hypertrophy and improved cardiac contractile function at rest in humans (55,70,100). With these morphological and functional changes a sinus bradycardia ensues. Cardiac filling time and hence, stroke volume increased. The increased stroke volume at rest could chronically impact on the aortic vasculature by producing a greater pulsatile deformation in the area of the ABR, which may significantly dissipate at the locus of the carotid baroreceptor. This prolonged period of increased pulsatile
stretch of the aortic vasculature during rest may result in the ABR resetting or down regulation (39). Hence, while technically difficult to isolate, indirect evidence suggests that aortic BR function may be altered with endurance training. Certainly the question of altered sensitivity of the ABR with endurance training has not been well delineated and further work needs to be performed.

**Cardiopulmonary Baroreceptors and Tolerance:**

Endurance training has been shown to increase resting blood volume 8-16% due primarily to protein retention and consequent plasma volume expansion. (48,184). The role of volume expansion seen with endurance training produces an interesting paradox. The volume expansion should provide greater protection against orthostatic hypotension in athletes. Conversely, it may cause greater cardiac filling with stimulation of the CPBR and an autonomic "resetting". In animal experiments, with volume loading, it has been shown that CPBR tonically oppose carotid baroreflexes (1). In a recent investigation from our lab, Pawelczyk and Raven (155), observed that the maximum gain of the heart rate mean arterial pressure stimulus response curves were linearly and inversely related to central venous pressure, suggesting that CPBR tonically inhibits carotid baroreceptor responsiveness in man. There is evidence to suggest that circulatory responses to changes in thoracic blood volume are different in aerobically trained athletes and non-
athletes. Boening and Skipkas (25) showed significantly less diuresis in endurance trained individuals after 6 hours of water immersion. They suggested that the reduced immersion diuresis could be due to either a decreased shift of blood volume out of the atria, decreased sensitivity of volume receptors, or an alteration in the central mechanism involved in volume regulation. Since Epstein (73–75) has shown that activation of the CPBR by loading, inhibits antidiuretic hormone and the renin-aldosterone system release, the lesser diuretic effect with water immersion in athletes may be secondary to lower CPBR sensitivity.

Cardiopulmonary baroreceptor responsiveness has also been recently examined with training by utilizing the slope of the relationship between forearm vascular resistance and central venous pressure when CVP is decreased from 0 to -20 torr LBNP. The slope has been shown to be reduced in a cross-sectional study (132). Takeshita et al. (210), however, have reported that the slope of the FVR/CVP relationship was increased in a group of athletes. In the Takeshita study, however, the athletes were former football players. It has been shown by Claybaugh et al. (42) that different groups of athletes have differences in diuretic responses to water immersion. Smith and Raven (199) have also shown that blood pressure control during LBNP differed among athletes, depending on their training regimen (ie. distance runners versus weight lifters). Takeshita et al. 
(210) also evaluated the characteristics of the CPBR control of FVR using LBNP to -40 torr which would result in unloading of both the CPBR and HPBR. Finally, Charles and Richardson (40) found that FVR was maintained better in non-runners versus runners to 10 degrees head-up-tilt. They concluded that the reduced responsiveness to CPBR would result in less reflex elevation in systemic peripheral resistance at any given drop in venous pressure. Hence, the aerobically conditioned athlete with the less responsive CPBR system would be more susceptible to an orthostatic stress.

Overview of Studies Against or For a Role for Fitness Alterations in Orthostatic Tolerance:

The belief that orthostatic tolerance was associated with aerobic fitness may have evolved initially from the crew of Skylab 4 Apollo space mission. It was noted that the application of LBNP inflight resulted in a greater incidence of presyncopal and syncopal symptoms in two of the three astronauts. It was noted that the more tolerant commander had a $\dot{V}O_{2max}$ that was approximately 10 ml/kg/min less than the two pilots. These data lead Luft to state that 'highly competitive forms of (preflight) endurance exercises primarily involving the lower extremities should be avoided' (129). Since that time there have been many proponents for (132,157,165-167,196,225), and against (47,50,51,124,210) an association for aerobic fitness and orthostatic tolerance.
This review will focus on some of those studies, and attempt to provide insight into why such disparagent results have persisted.

Studies Against a Role for Endurance Exercise and Orthostatic Intolerance:

In 1968, Shvartz (189) studied 18 physical education students during 70° HUT. They found that the four fainters in their study could do fewer pushups and situps per minute, and had slower times in the mile. In a follow-up study by Shvartz and Meyerstein (192) they reported on 34 men exposed to 70° HUT for 20 minutes or until they fainted. Group mean \( \dot{V}O_{2\text{max}} \) was 44 ml/kg/min. They found that the \( \dot{V}O_{2\text{max}} \) between fainters and nonfainters was not significantly different, and tolerance was not significantly correlated to \( \dot{V}O_{2\text{max}} \) (\( r=-.31 \)). In a third study Shvartz (191) used a cohort of 12 trained subjects and 16 untrained subjects and demonstrated that 10% of trained subjects fainted versus 25% fainting episodes in untrained men during an orthostatic stand test under five conditions. Based on these three studies, Shvartz and his colleagues suggest that increased fitness relates to a greater orthostatic tolerance. In the Shvartz studies, however, many of the subjects could be said to be isometrically trained. Smith et al. (199) has shown that isometric training increases orthostatic tolerance.

Orthostatic tolerance has been shown to increase following cycle training (50,89). The suggested mechanism of action is
that of an increased muscle mass around the legs with a resultant decrease in leg compliance (133). These data, however, have been challenged by Convertino et al. (47) who examined the physiologic responses to graded LBNP between groups of subjects of varying levels of aerobic fitness and strength. They failed to note differences in hemodynamic responses to LBNP and stated that only one subject from the high aerobic fitness and average strength group became syncopal. The major criticism of their study, however, was that they were not taking all their subjects to a syncopal end point and hence inferences regarding syncopal tendency are tenuous. Convertino et al. (51) used a stepwise linear regression analysis to investigate the relationship between fitness and orthostatic tolerance. They noted that aerobic fitness was a very poor predictor, while leg compliance, and blood volume were very strong predictors of orthostatic tolerance.

Thus data from several cross-sectional studies to determine orthostatic tolerance and fitness have provided evidence that fitness is not related to orthostatic intolerance. It is difficult, however, to ascertain the influence of endurance exercise training on orthostatic intolerance with simply cross-sectional designed studies. Perhaps the physiologic adaptations associated with regular physical activity can affect tolerance. Sheldahl et al. (185) reported results of a six month endurance exercise
training program on 12 middle aged men and monitored their responses to HUT. They noted that orthostatic tolerance to short-term postural stress was not reduced with training. They, however, did not take all of their subjects to syncope. They did notice, however, that stroke volume index decreased more during tilt after training. In general, the few longitudinal studies that have been performed have not usually looked specifically at orthostatic tolerance as it relates to syncope. (16,51a,185). Invariably, those studies that report an increase in tolerance used cycling as their mode of endurance training (191,190,50,89).

Studies Supporting a Role for Endurance Exercise and Orthostatic Intolerance:

A number of the studies supporting the concept of a link between fitness and orthostatic intolerance have already been discussed and will not be repeated. Several investigational groups have tried to infer that because aerobic training reduced the effectiveness of the blood pressure control systems (based on altered hemodynamic responses to an orthostatic stress), that orthostatic tolerance was also reduced (40,165,167,218). Only with the use of specific tests designed to induce a syncopal endpoint can these types of statements be made. Convertino (47) found only three studies (128,130,136) that tried to answer this question and states that the 'hypothesized inverse relationship between aerobic fitness and orthostatic
intolerance that they perpetuate, are misleading, since the majority of evidence in the literature does not support these theses’ (47).

Summary

Based on this review, a question remains as to whether endurance exercise training increases an individual’s susceptibility to orthostatic intolerance. There exists a paucity of information using controlled training longitudinal designed studies aimed specifically at addressing the above question. There is evidence both for and against the role that fitness plays in blood pressure regulation during orthostasis. To answer these questions, the following assessments were attempted:

1) Through the use of an endurance exercise training program, induce a change in aerobic fitness of at least 15%, and blood volume of 10%;

2) Objectively determine orthostatic tolerance before and after the training program using lower body negative pressure and direct measurements of arterial pressure;

3) Determine the HR and blood pressure responses to steady-state infusions of phenylephrine up to a maximum of 120 ug·min⁻¹, and during lower body negative pressure;

4) The role of vasoconstriction in blood pressure regulation during cardiopulmonary inhibition (LBNP to -15 torr), and during LBNP to -45 torr;
5) The influence of parasympathetic and sympathetic control of blood pressure regulation during an orthostatic stress as determined by atropine blockade, and metoprolol blockade.
CHAPTER III

PROCEDURES AND METHODS

The specific aims of this investigation were accomplished by analyzing the blood volume and blood pressure responses to lower body negative pressure (LBNP) with and without cardiac autonomic blockade of eight healthy male subjects prior to and following an eight month aerobic training program. In addition, the subjects cardiovascular responses to a hypertensive stimulus were determined using constant rate infusions of Phenylephrine hydrochloride (PE). Finally, each subject's orthostatic tolerance to LBNP was determined prior to and following eight months of endurance exercise training.

Outline of experimental protocols:

The experimental protocol consisted of five separate testing days (per subject) before and after eight months of aerobic training.

Day One: During the first test day volunteers where provided with background information on the study and informed consent was obtained. Each subject was evaluated and screened using a medical history questionnaire; a resting 12 lead electrocardiogram (ECG); resting blood
and a breath-by-breath maximum exercise stress test (for determination of $\dot{V}O_{2\text{max}}$) on a motor driven treadmill. Subjects accepted into the study proceeded to day two of the testing protocol.

**Day Two:** The second day of testing familiarized the subjects with the equipment to be used during the experiments. Each subject was exposed to LBNP to -50 torr and experienced the carotid neck pressure/suction ramp protocol that would be utilized to verify the cardiac autonomic blockade.

**Day Three:** On the third test day each subject underwent multi-stage steady-state infusion dosages of PE ranging from 12 to 120 ug min$^{-1}$. Following the hypertensive challenge each subject was challenged with progressive increments of -10 torr LBNP after the initial level of -5 torr to -45 torr LBNP, and then five torr increases in LBNP every two minutes to objectively determine tolerance to LBNP (presyncope). Finally, complete selective cardiac $\beta_1$-adrenergic blockade was achieved utilizing metoprolol tartrate followed by progressive increases of LBNP to -45 torr.

**Day Four:** On the fourth test day, each subject was infused with atropine sulfate until complete cardiac muscarinic blockade was achieved, followed by progressive LBNP to -45 torr. Subsequently, the subjects were again selectively and completely $\beta_1$-adrenergic blocked using metoprolol tartrate, which in combination with the atropine sulphate blockade provided complete cardiac autonomic blockade. Each subject
was once again subjected to progressive LBNP to -45 torr.

**Day Five:** On the last test day blood volume was determined by the carbon monoxide technique, followed by an indirect measure of change in central venous pressure (CVP) during progressive LBNP to -45 torr.

Following completion of the five days of preliminary studies, the subjects performed an eight month individually designed aerobic training program. At the end of the eight months of endurance training the same experimental procedures were repeated by each subject.

**Subjects:**

Eight Caucasian men (ages ranging from 22 to 34 yrs.) were recruited from the Dallas-Fort Worth Metroplex area to participate in the study. All subjects were informed in writing as to the nature of the experiment and signed a subject consent form as approved by the Institutional Review Board for Use of Human Subjects at the Texas College of Osteopathic Medicine. Criterion for inclusion in the study included completion of a medical history questionnaire, an abbreviated physical examination by the collaborating physicians (H.M. Graitzer, D.O., or B.H. Foresman, D.O., both board certified internists), a normal resting 12 lead electrocardiogram, echocardiogram, and adequate ulnar and radial artery perfusion based on the Allen test. In all subjects, a graded exercise test to volitional fatigue was performed for determination of electrocardiographic
abnormalities and changes in maximal aerobic power pre- and post-training. Volunteers free of cardiovascular disease and meeting the prerequisites to enter an endurance exercise training program were accepted as subjects for the study. Each subject was reimbursed $200.00 at the end of the investigation.

**Procedures:**

**Graded Exercise Stress Test (GXT):**

A treadmill (Quinton 24-72) ramp protocol was used to determine parameters of metabolism during the GXT (231). The GXT was conducted according to guidelines established by the American College of Sports Medicine (8). On test day one, after the subjects had familiarized themselves with the treadmill, they walked at 3.5 mph at grades of 5%, 7.5%, and 10% for two minutes each per stage as the initial warm-up. Auscultatory blood pressure was recorded from the brachial artery during the last 30 seconds of each two minute stage, and heart rate during the last 15 seconds of each minute. An anterior (lead II), inferior (lead aVF), and a lateral lead (V6) ECG were continuously monitored during the test from an oscillographic system (Quinton 633). After the initial six minute warm-up period the grade was reduced to 0% and the speed increased to between 5.0 and 7.0 mph for four minutes (the speed chosen was based on the subjects predicted $\dot{V}O_{2max}$). After this period the control of the treadmill was then switched to an automatic programmer.
(Quinton 644) that increased speed 0.15 mph min$^{-1}$ and grade 1.5% min$^{-1}$ until volitional fatigue. Subjects were instructed to complete each stage until unable to do so, even with strong verbal encouragement. Test termination and objective criteria of Taylor et al. (213) were used to quantitatively and qualitatively determine if the subject had made a maximum effort. A determination of $\dot{V}O_{2\text{max}}$ was accepted if a plateau of $\dot{V}O_2$ was achieved or a change < 100 ml min$^{-1}$ for the final minute of the test was demonstrated. When a plateau was not obtained, discontinuous supramaximal stages were administered until a plateau was obtained. Oxygen uptake was determined using a dedicated breath-by-breath analysis system incorporating a mass spectrometer (Perkin-Elmer MGA 1100-AB) to determine gas concentrations ($O_2$ and $CO_2$ and $N_2$), and a turbine flowmeter (Alpha Technologies VMM-2) to measure tidal volume and minute ventilation. All variables were collected on-line using a dedicated minicomputer (Digital Equipment Corporation MINC-23) and a customized software package to account for differences in delay and response time. The mass spectrometer was calibrated before each test using known standard gases. The ventilatory threshold (VT) was determined as the work rate at which ventilation increased disproportional from a linear increase in the mechanical work rate (52). This measure was used to determine and monitor the exercise training heart rate.
Prior to the GXT, steady-state heart rates were determined for each subject pre- and post-training. With the treadmill set at 3.5 mph and 5% grade, subjects rested standing and straddling the treadmill belt while a two minute ECG record was made. At the end of the two minutes the subject was instructed to step onto the treadmill and begin walking. The subjects walked at this steady-state level for 10 minutes after which time the treadmill was stopped and the subjects stood quietly for a further two minutes.

**Lower Body Negative Pressure (LBNP) Induced Central Hypovolemia:**

LBNP was used to induce a central hypovolemia by having the subjects lie in the supine position within a plexiglass and plywood box (LBNP chamber) with an airtight seal engaged around the subjects iliac crests. Variable autotransformers that regulated voltage to two vacuum motors connected to the LBNP chamber were used to control the degree of suction applied to the subjects. A saddle support was provided in the box to help subjects maintain their position in the box when exposed to maximum negative pressures. A digital pressure read-out was supplied by a pressure meter (BioTek Instruments DP-1) accurate to ± 1 torr, that was connected directly to the LBNP chamber. Subjects were exposed to progressively increasing levels of LBNP through stages of control (0), -5, -15, -25, -35, and -45 torr, during the
experiments utilizing cardiac autonomic blockade, and the measurement of central venous pressure. Following the Control LBNP to -45 torr (Day three), the orthostatic tolerance test was accomplished by reducing the box pressure an additional -5 torr every two minutes, until signs and symptoms of presyncopal conditions occurred: nausea, sweating, a rapid decrease in HR or BP, a sustained decrease in systolic blood pressure to < 90 mmHg, or diastolic blood pressure < 50 mmHg. LBNP tolerance was defined as the sum of the products of negative pressure applied and the time spent at each level (i.e., \(\Sigma -5 \cdot 6 + -15 \cdot 6 + -25 \cdot 2\) etc., expressed in torr·min) and was termed the cumulative stress index (CSI) (129) (See Figure 3).

**FIG. 3. LBNP Protocol-Tolerance Test: Subjects were sealed in a LBNP box and pressure was lowered in the box until presyncopal symptoms arose. The stars denote times when heart rate (HR), blood pressure (BP), forearm blood flow, cardiac output, and leg volume (LgV) were measured. At all other times only HR, BP, and LgV were recorded.**
Changes in heart rate and blood pressure were monitored continuously from the electrocardiogram and a radial catheter, respectively, during all the control LBNP and tolerance tests as well as the \( \beta_1 \)-adrenergic blockade experiments. Electromyographic (EMG) signals of the rectus femoris and vastus medialis along with the rectus abdominis were monitored continuously to ensure that straining maneuvers or muscle contraction were not being performed (194). All physiological measurements were made during the stages of Control, -5, -15, -35, and -45 torr, while only HR, leg volume, and arterial blood pressure were determined at -25 torr and post -45 torr LBNP. All LBNP procedures were performed in an ambient environment of 24° to 26°C dry bulb temperature and 40% to 60% relative humidity. LBNP was performed at a time when subjects were at least two hours post-prandial and free from physical activity or any stimulants from the previous 12 hours. Prior to any subject measurements, a 30 minute rest period was provided to allow equilibration of body fluid volumes in the supine position.

Autonomic Blockade Procedure:

Three different cardiac autonomic blockade conditions were studied during LBNP. On LBNP test day three, the cardiovascular responses of each subject to progressive lower body negative pressure were studied during control conditions and during complete \( \beta_1 \)-adrenergic receptor blockade with metoprolol tartrate. On test day four,
occurring 2-5 days after test day three, to assure complete clearance of the metoprolol, the responses to LBNP were studied during complete muscarinic receptor blockade with atropine sulfate and during complete cardiac autonomic blockade with metoprolol and atropine. The metoprolol was individually titrated in 0.05 mg/kg increments into a venous cannula placed in an arm vein. The metoprolol was titrated to a dose of 0.2 mg/kg or until a subsequent 0.05 mg/kg increase in dose produced no further decrease in heart rate. The atropine was also individually titrated in 0.004 mg/kg increments to a dose of 0.04 mg/kg body weight (98) or until a subsequent 0.004 mg/kg increase in dose produced no further increase in heart rate. Complete cardiac autonomic blockade was achieved by infusing the same metoprolol dose previously given into an atropinized subject. The competency of the atropine blockade was assessed by two methods:

1) The subject performed a Valsalva maneuver producing an expiration pressure of +40 torr. The phase I response is a parasympathetic mediated bradycardia, therefore, absence of this bradycardia was considered full atropine blockade.

2. Full atropine blockade was also confirmed by the absence of R-R Interval response to ramped neck suction, which has been determined previously to be mediated by the parasympathetic nervous system (66,68).
The metoprolol and atropine blockade were confirmed during complete cardiac blockade by having the subject perform a Valsalva maneuver, again producing an expiratory pressure of +40 torr. Absence of the autonomic-mediated chronotropic changes during the Valsalva maneuver provided evidence for complete blockade of both β1-adrenergic and muscarinic populations. Metoprolol cardiac blockade alone was confirmed by an absence of phase III tachycardia to the Valsalva maneuver.

Following the administration of each blocking dose two minutes were allowed for equilibration before collecting an average HR over the next 30 seconds. Heart rates were rounded to the nearest whole number for analysis.

Carotid Neck Suction/Pressure:

A rapid neck pressure and suction protocol outlined by Sprenkle et al. (202), was used to confirm the presence of atropine sulfate blockade. This method allows for non-invasive stimulation of the carotid baroreceptors on a beat-to-beat basis. The subject, while in the supine position had a neck collar device applied around the anterior 2/3rd of his neck. Pulses were delivered to the neck for 600 msec during held expiration precisely 50 msec after the R wave of the ECG. Prior to initiation of the first pulse, the computer program scanned the subjects ECG and would not initiate the first pulse until the R-R Interval (RRI) changed less than 30 msec for three
consecutive beats. Pressure and suction were delivered from vacuum sweeper motors and timed using large bore (2.5 cmID) two-way solenoid valves (Asco Model 8215B Florham Park NJ). To minimize baroreceptor resetting, the neck chamber was vented between each pressure and suction pulse. Baroreceptor responsiveness was determined as a change in RRI/change in carotid transmural pressure. At least five trains (12 pulses from +40 to -65 torr) were obtained. Laboratory custom designed software was developed for collection of data on a mini-computer (Digital Equipment Corporation MINC-23).

Phenylephrine Infusion Procedure:

Baroreceptor responsiveness was also determined by using bolus steady-state infusions of phenylephrine HCL (PE) a non-selective \( \alpha_1 \)-adrenergic agonist. The subject was instrumented while in the supine position. Antecubital venous and radial arterial catheters were placed. After a 30 minute control period, PE was administered using a 12 inch extension tube connected from the venous catheter to an infusion pump (Sage Instruments Model 15T). After control physiological measurements were taken, the subject began stage one of infusion (12 ug min\(^{-1}\)). If no untoward effects were noted with this dose then the subjects progressed to the next stage. At approximately three minutes of each stage, when arterial pressure and heart rate were at steady-state, all physiological measures were recorded. The infusion rate was then increased progressively by dose every
six minutes through standard infusion rates of 0.4, 0.8, 1.0, 1.5, and 2.0 ml min' to a maximum rate of 120 ug min' (TABLE I), or until systolic pressure increased >40 mmHg from control, and/or a diastolic pressure of >110 mmHg, and /or arrhythmic ECG patterns were observed.

TABLE I

<table>
<thead>
<tr>
<th>Infusion Rates</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 ug min'</td>
<td>2</td>
</tr>
<tr>
<td>24 ug min'</td>
<td>6</td>
</tr>
<tr>
<td>48 ug min'</td>
<td>6</td>
</tr>
<tr>
<td>60 ug min'</td>
<td>6</td>
</tr>
<tr>
<td>90 ug min'</td>
<td>6</td>
</tr>
<tr>
<td>120 ug min'</td>
<td>6</td>
</tr>
</tbody>
</table>

Infusion was terminated if systolic blood pressure (SBP) > 40 mmHg above rest or an absolute diastolic blood pressure (DBP) >110 mmHg was obtained. Heart rate (HR), SBP, DBP, mean pressure, and forearm blood flow measures were determined at each infusion from dose 24 ug min' on. Only HR and BP were determined at 12 ug min'.

Exercise Training Program:

The training program was approximately eight months in duration and was aimed at producing a 20-25% increase in \( \dot{V}O_{2\max} \). A supervised conditioning program was prescribed for each subject requiring the subject to exercise a minimum of four times per week. The training consisted of a walk or jog
protocol that would allow the subject to exercise at a HR that was calculated just below each individual's determined ventilatory threshold (VT). Most of the training was conducted on treadmills, however, some individual's trained on athletic tracks at indoor and outdoor athletic facilities. A GXT was performed approximately 6-8 weeks into the training program to re-determine training heart rate. Each subject's training session was monitored by the principal investigator.

Techniques of Measurement

Cardiac output

Cardiac output (\(\dot{Q}_c\)) was determined non-invasively using an indirect Fick method carbon dioxide (CO\(_2\)) rebreathe, which required the estimation of the arterial and mixed venous CO\(_2\) concentrations. The equation for \(\dot{Q}_c\) is given by the Fick principle:

\[
\dot{Q}_c = \frac{\dot{V}CO_2}{(Cv-Ca)O_2}
\]

Where:

\(\dot{Q}_c\) = cardiac output in 1 min

\(\dot{V}CO_2\) = CO\(_2\) production in ml min

\((Cv-Ca)CO_2\) = venous-arterial CO\(_2\) concentration difference in ml dl blood

Arterial CO\(_2\) Concentration:

Since the time of Haldane and Priestly (1905) alveolar CO\(_2\) tension (P\(_A\)CO\(_2\)) has been thought to closely approximate arterial CO\(_2\) tension (P\(_a\)CO\(_2\)). Response time of the analyzer
and breathing frequency may have some effects on the estimation of $P_aCO_2$ (96), however, these problems were avoided by utilizing a respiratory gas analyzer mass spectrometer (Perkin Elmer Corp Model 1100A) calibrated against known standard gases.

**Mixed Venous CO$_2$ Concentration:**

The mixed venous CO$_2$ tension ($P_vCO_2$) was estimated using the method of Defares (53) and a continuous sampling procedure. After monitoring the pressure of end-tidal CO$_2$ ($P_{ET}CO_2$) for approximately 20 seconds, a semi-automated Jones rebreathe valve-bag system was used to switch the subject from room air to a 5 liter anesthesiology balloon filled to approximately 1 1/2 to 2 liters with 4% CO$_2$ in 96% O$_2$ (131). A signal was given by the subject at the end of an expiration (functional residual capacity) and the subject was switched to the bag containing 96% O$_2$ in 4% CO$_2$. Subjects inspired at a rate of 30 breaths per minute (131). To avoid recirculation of the blood the rebreathing procedure was limited to 15 seconds (91). The mixed venous CO$_2$ was calculated using a computer curve fitting program which determined the asymptotic point of a regression line for the mixed venous values. All CO$_2$ tensions were converted to concentrations using a standard CO$_2$ dissociation curve for oxygenated whole blood (45). Arterial CO$_2$ partial pressure was also converted to a concentration using the same curve. The coefficient of variation for resting
measurement was 1.9% around a mean value of 5.45 l/min as determined from eight serial determinations on a 70 kg man. The fractional concentration of CO₂ in the measured gases was determined by using a calibrated mass spectrometer and recorded on a multi-channel strip chart recorder (Soltec, Model 1286).

Measurement of Blood Volume:

The total blood volume (red blood cell volume (V_rbc) and plasma volume (PV)) of each subject was determined using the carbon monoxide (CO) dilution technique of Myhre et al. (144). The CO dilution technique uses the strong affinity of CO for hemoglobin (Hb) to label the red blood cells. Administration and equilibration of the CO was performed by having the subject lie supine for 30 minutes. After equilibration of the body fluids an initial 5 ml. venous blood sample was drawn, after which the subject was connected to a closed system containing a carbon dioxide scrubber and 100% oxygen. After one minute, 50 mls. of pure (100%) carbon monoxide was injected into the breathing system. The subject continued breathing on the system for 10 minutes to allow equilibration of CO to bind to the subjects Hb. Following the 10 minute equilibration period a 50 ml. gas sample was taken from the system to determine the level of residual CO within the system. A final 5 ml. venous blood sample was obtained following completion of the 10 minutes of rebreathing. The blood samples were immediately
analyzed for hematocrit (Hct) using the microhematocrit method in quadruplicate. The Hct was corrected for trapped cell volume and central venous versus peripheral venous differences (146). Total hemoglobin and carboxyhemoglobin (COHb) were measured spectrophotometrically using a co-oximeter (Instruments laboratory, model 282).

The total blood volume (BV) and PV were calculated as follows:

\[
\text{COHb}_I = \frac{\% \text{ COHb}_{\text{pre}}}{\text{Hct}_{\text{pre}}} \\
\text{COHb}_F = \frac{\% \text{ COHb}_{\text{post}}}{\text{Hct}_{\text{post}}} \\
\text{COHb} = \text{COHb}_F - \text{COHb}_I \\
V_{rbc} = \frac{[V_{CO} - (10^4 \times \text{Residual})]}{\text{COHb}} \\
\text{BV} = \frac{V_{rbc}}{\text{Hct}} \\
\text{PV} = \text{BV} - V_{rbc}
\]

where:

\[
\text{COHb}_I = \text{Carboxyhemoglobin concentration before administration of carbon monoxide.} \\
\text{COHb}_F = \text{Carboxyhemoglobin concentration after carbon monoxide administration.} \\
\text{Residual} = \text{Residual CO concentration in the rebreathing system (volume} = 10^4 \text{ ml)} \\
V_{CO} = \text{Volume of carbon monoxide administered} \\
V_{rbc} = \text{Volume of red blood cells}
\]

The coefficient of variation of six BV measurements carried out in our laboratory for a 70 kilogram man was
determined to be 3.2%, around a mean value of 6.26 liters. The coefficient of variation for PV for the same measurements was determined to be 2.5% around a mean value of 3.91 liters, indicating minimal variation in the COHb and Hct measures. Data were calculated using a computer program written in BASIC (94) for a personal computer (International Business Machines PC/XT).

Central Venous Pressure Procedure (Peripheral):

On a separate day (day five) a measure of central venous pressure (CVP) was determined on each subject during progressive LBNP to -45 torr. The "dependent arm" technique of Gauer and Sieker (82) was utilized. Briefly, the subject was asked to lie in the right lateral decubitus position after having a 1/4" 20 gauge over-the-needle teflon catheter inserted into an antecubital vein of the right arm. With the subject lying with his right arm through a port in the base of the LBNP device (dependant arm), and sealed at the iliac crests, the catheter was connected to sterile tubing and transducer (Hewlett Packard 1280C, Waltham MA) assembly. In this position, peripheral venous pressure (PVP) is the sum of CVP and the hydrostatic column from the measurement of the right atrium to the transducer. The CVP was estimated and the hydrostatic column effect eliminated by zeroing the pressure transducer to the subjects mid-sternal line. In all experiments a prominent CVP wave was observed, and verified by passively raising the legs or performing a Valsalva
maneuver and noting the rapid effect on the CVP waveform. A catheter in an antecubital vein of the dependant right arm used to record changes to PVP has been shown to be closely related to changes in central venous pressure (82,132).

**Physiological Measurements:**

In all studies the electrocardiogram was obtained from a lead II recording and was continuously monitored on a cardioscope (HP-304) and a strip chart recorder (Narco Physiograph Model Six B). During the neck suction / pressure sequences, to determine blockade effects, beat-to-beat determinations of RRI were used and stored on-line utilizing a minicomputer (DEC MINC-23). Heart rate was determined by counting the number of cardiac cycles during a two minute period and dividing by two. Indirect blood pressures were recorded continuously and non-invasively by means of an optico-mechanical plethysmographic system (Finapres, Ohmeda Inc). Instantaneous changes in vascular volume in the second finger were detected by a light source and photoelectric cell incorporated into an inflatable cuff surrounding the digit. A fast servo pump inflated and deflated the cuff to maintain vascular volume during each pulse. The cuff pressure, therefore, equaled the arterial pressure. Measurements were taken in the supine position with the right hand of the subject horizontal to the level of the heart. In those experiments in which a direct invasive measure of arterial pressure were recorded from radial
arterial catheter was used. A 1.1 mm ID 3.2 cm long teflon catheter was inserted under local anesthesia (1% Lidocaine) into the radial artery at the wrist of the right arm. The catheter was connected to a sterile tubing and transducer (Hewlett Packard 1280, Waltham, MA). The catheter was kept patent with a continuous heparinized (2U/ml) saline flush connected to a pressurized system. Direct arterial pressures were recorded on line using the laboratory mini computer (MINC 23 D.E.C.). One minute averages of SBP and DBP were obtained during steady-state while MAP was obtained by one minute averages of the integrated pressure wave form.

**Forearm Blood Flow**

Forearm blood flow (FBF) was measured by venous occlusion plethysmography technique described by Whitney (232). A calibrated mercury-in-silastic strain gauge was placed in a mid-forearm position of the left wrist and connected to a plethysmographic preamplifier (Parks Electronics, model 271). The output from the preamplifiers was recorded on the chart recorder (Narco Biosystems, model SIXB). For each FBF measured, an occlusion cuff placed around the wrist was inflated to +300 mmHg to occlude the arterial supply to 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 upper arm was inflated to 50-60 mmHg 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. An index of forearm vascular resistance (FVR), in peripheral resistance units (PRU), is then calculated by dividing mean arterial pressure (MAP) by FBF. The mean rate of change in forearm circumference of triplicate measures was used to calculate the blood flow as follows:

\[
\begin{align*}
\text{FBF} &= 2 \frac{C_{FA}}{\Delta C_{FA}} \times 100 \\
\text{FVR} &= \frac{\text{MBP}}{\text{FBF}}.
\end{align*}
\]

Where:

\[
\begin{align*}
\text{FBF} &= (\text{ml 100ml}^{-1}) \text{ min} \\
\text{FVR} &= \text{Peripheral Resistance Units (PRU)} \\
C_{FA} &= \text{the forearm circumference}. \\
\Delta C_{FA} &= \text{the change in forearm circumference per minute during the venous occlusion.}
\end{align*}
\]

Calculations were performed using a computer program written in BASIC (94) for a personal computer (International Business Machines PC/XT).

**Change in Calf Circumference and Leg Volume**

The circumference of the calf was monitored throughout LSNP using a dual-loop mercury-in-silastic plethysmographic strain gauge. The loop was placed in a mid-calf position with 1 cm spacers placed at several locations around the calf to ensure uniform placement. The gauge was connected to a preamplifier (Parks Electronics, Model 271), and the output recorded on a strip chart recorder (Narco, Model SIX-
B). A calibration curve for each stage 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. The initial circumference of the calf was measured so that changes in leg circumference could be expressed as changes in leg volume. This change was assumed to be proportional to the segmental volume of the subject's leg. Therefore, a series of 12 circumferences were determined before the experiment at defined positions along the subject's leg, and summed to determine the volume of the leg using the following equation:

$$V_t = \sum_{i=1}^{11} \frac{(C_i + C_{i+1})}{2} L_t$$

This procedure is similar to one described by Thorton et al. (216) for use during the Apollo and Skylab missions. Changes in leg volume were then calculated from changes in calf circumference using a computer program written in BASIC (94) for a personal computer (International Business Machines PC/XT). Changes in calf circumference ($\Delta LgC$) as a percentage of the original circumference, were assumed to be representative of changes throughout the leg and were therefore used to calculate the leg volume change ($\Delta LgV$) in milliliters (mls), as follows:

$$\Delta LgV = LgV \times 100 \left( \frac{C_x - CV_p}{CV_p} \right) CV_p^{-1}$$
where:  

\[ CV_x = \text{calf volume under gauge during stage } x \text{ of LBNP} \]

\[ CV_p = \text{calf volume under gauge before LBNP} \]

**Anthropometric Measurements:**

Descriptive anthropometric and physiological data were obtained for each subject. Height was measured (Holtain Standiometer) to within 0.1 cm and weight (Health-o-Meter) to within 0.2 kg. A measure of the subject’s weight was taken prior to each experiment. These measures were then used to calculate body surface area (BSA), according to the formula of Dubois and Dubois (1916), as cited by Consolazio et al. (46). Percentage body fat and lean body mass were determined pre- and post-training by measuring skin fold thickness. Body fatness was determined by measuring skinfold thickness at 12 defined sites, including the cheek, chin, chest, bicep, tricep, subscapular, juxtanipple, abdominal, suprailiac, knee, calf, and thigh regions. These values were input into a computer program written in FORTRAN (58) that calculated the body fatness using published equations for prediction of body fatness or body density (7,95,101,235). Body density values were converted to body fatness using standard equations (34). The mean of the body fatness values was reported as body fatness.
**Statistical Analysis:**

Pre- to post-training changes in subject characteristics and orthostatic tolerance were analyzed using a paired Student "t" test. Differences in responses to LBNP (0 to -45 torr) under the unblocked state alone were analyzed using a 2-factor (2 X 5) analysis of variance with repeated measures pre- to post-training and at each level of LBNP. Results of the blockade studies were performed by a 3-factor (2 X 6 X 4) analysis of variance with repeated measures (Figure 4) to discern differences between groups and conditions across stages of LBNP. A Student-Newman-Keuls 'post-hoc' analysis test was used to distinguish main effect differences.

The design for the phenylephrine data involved the use of a 2-factor analysis of variance for comparisons across infusion rates pre- versus post-training.

Significant levels for analysis for all variables was set at $p < 0.05$. 
FIG. 4. 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 arterial pressure, cardiac output, peripheral vascular resistance and leg volume changes.
CHAPTER IV

RESULTS

The major goals of this investigation were to i) determine if endurance training alters orthostatic tolerance; ii) determine the relative contribution of the autonomic nervous system to orthostatic stress with training. This chapter provides a summary of results of the program of prolonged endurance exercise training on the cardiovascular responses to orthostatic stress as designed to answer the primary questions of the investigation.

Descriptive Anthropometric and Physiologic Data

The descriptive physiologic and anthropometric data for the subjects before and after eight months of an endurance training program are presented in Table II. The subjects had a mean age of 27.6 ± 4.0 yrs entering into the study. Training produced a significant decrease in weight of -4.3% (p=0.046), but did not significantly alter percentage body fat, lean body mass, or body surface area. Training produced a significant decrease in both resting and maximal heart rate. A significant increase in maximal oxygen consumption ($\dot{V}O_{2max}$) both absolute (+21%) and per kg body weight (+26%) (p<0.0001) were noted with training. During the graded
TABLE II: DESCRIPTIVE PHYSIOLOGICAL AND ANTHROPOMETRIC DATA FOR THE SUBJECT GROUPS

<table>
<thead>
<tr>
<th></th>
<th>UT (N=8)</th>
<th>ET (N=8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.6 ± 4.0</td>
<td>--.--</td>
<td>--</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>182.5 ± 5.4</td>
<td>84.4 ± 14.5</td>
<td>*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.3 ± 14.4</td>
<td>84.4 ± 14.5</td>
<td>*</td>
</tr>
<tr>
<td>Body Surface Area (m²)</td>
<td>2.1 ± 0.15</td>
<td>2.1 ± 0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Lean Body Mass (kg)</td>
<td>70.1 ± 8.9</td>
<td>69.2 ± 9.1</td>
<td>NS</td>
</tr>
<tr>
<td>Total Body Fat (%)</td>
<td>20.0 ± 5.7</td>
<td>17.6 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Rate-Rest (bpm)</td>
<td>68.4 ± 9.3</td>
<td>58.9 ± 11.0</td>
<td>#</td>
</tr>
<tr>
<td>Heart Rate-Max. (bpm)</td>
<td>200.3 ± 11.7</td>
<td>191.4 ± 9.1</td>
<td>**</td>
</tr>
<tr>
<td>( \dot{V}O_2_{max} ) (l/min)</td>
<td>3.95 ± 0.56</td>
<td>4.79 ± 0.60</td>
<td>#</td>
</tr>
<tr>
<td>( \dot{V}O_2_{max} ) (ml/kg/min)</td>
<td>45.20 ± 6.12</td>
<td>57.46 ± 7.85</td>
<td>#</td>
</tr>
<tr>
<td>Time to ( \dot{V}O_2_{max} ) (min)</td>
<td>15.56 ± 1.57</td>
<td>18.11 ± 1.45</td>
<td>#</td>
</tr>
</tbody>
</table>

Values represent Mean ± Standard deviation (SD). Significant differences between groups: NS = Not Significant, * = p<0.05, ** = p<0.01, # = p<0.0001.

exercise stress test treadmill performance time was also significantly increased with training by 2.5 minutes, p<0.01.

Further evidence of an exercise training effect was found when comparing the heart rate (HR) response during the maximal treadmill stress test (Figure 5). Prior to and following the endurance exercise training program the average submaximal HR obtained during the graded treadmill test was reduced 15 beats per minute (p<0.01) with training. The data presented in Figure 5 also depicts the lower resting (-14.4%) and maximal HR (-4.3%), along with the
increased performance time post-training as identified in Table II.

FIG. 5. Heart rate responses during the maximal exercise stress test prior to (solid circles) and after (solid triangle) 8 months of aerobic training. Values represent mean ± S.E.M.

Training also resulted in a significant increase in blood volume (Figure 6) expressed as either absolute or per lean body mass (+15.8% \( p=0.013 \)). The majority of the increase in blood volume was secondary to an increase in plasma volume.

**LBNP Tolerance:**

Training resulted in a significant decrease in orthostatic tolerance (for individual data see Figure 7) as
FIG. 6. Blood volume changes in untrained (UT) and after 8 months of endurance training (ET). Values represent mean ± S.E.M.

defined by the cumulative stress index. Training resulted in a mean tolerance reduction of 24% from a pre-training mean of 1123.4 ±126.7 torr min, to a post-training mean of 806.2 ±111.1 torr min.

As non-invasive measurements closely represented direct measurements of arterial pressure throughout the experiment (Figure 8), the use of the non-invasive measurement of blood pressure during LBNP to -45 torr experiments with full muscarinic and combined β,-adrenergic and muscarinic blockade was justified.

Responses to LBNP: Prior to and following endurance exercise training the hemodynamic responses to progressive increases in LBNP from 0 to -45 torr were qualitatively similar (See Table III). However, post-training responses
FIG. 7. The individual and group means ± standard error of the means of the subjects cumulative stress index (torr min) to pre syncope, prior to and following the endurance exercise training program.

were significantly different for all variables measured across all stages of LBNP (See Table III). With one exception, this being the changes in leg volume (LgV), there were no statistically significant interactions between training status and cardiovascular responses to any of the stages of LBNP. The post-training changes in LgV during LBNP were greater at -5 torr, $p<0.02$ and approached significance at -15 torr LBNP, $p<0.08$.

Significant main effects with respect to discrete stages of LBNP were observed for HR, stroke volume (SV), cardiac output ($Q_c$), peripheral vascular resistance (PVR), mean arterial pressure (MAP) and systolic blood pressure (SBP). Cardiac output decreased linearly with increasing LBNP, and was significantly less than control at all levels
of LBNP. In addition, each stage of LBNP produced a further significant drop in \( Q_c \), from one stage to the next. Stroke volumes at 0 and -5 torr were not significantly different despite an average decrease of 9 ml/beat from 0 to -5 torr LBNP. However, SV measured at -45 torr and -35 torr were significantly less than at -15, -5 and 0 torr LBNP. The SV between -45 torr and -35 torr LBNP were not different \((p>0.05)\), while the SV at -15 torr LBNP was less than that measured at 0 torr LBNP. There was no difference in HR measured at 0, -5, -15 and -25 torr LBNP \((p>0.05)\), however, the HR at -35 torr LBNP was significantly greater than the HR at -15, -5 and 0 torr LBNP, yet was not different than the HR at -25 torr or -45 torr LBNP \((p>0.05)\). The HR at -45 torr LBNP was significantly greater than the HR at -25,-15,-5 and 0 torr LBNP.

![FIG. 8. A typical pen recording trace of directly measured radial arterial blood pressure at pre-syncope compared with a non-invasive (Finapress) measure of blood pressure during progressive LBNP.](image)
Mean arterial pressure was unchanged (p>0.05) from 0 to -35 torr LBNP. However, MAP at -45 torr LBNP was significantly less than that measured at -5 and 0 torr. Systolic blood pressure at -45 torr LBNP was significantly decreased below that measured at -35, -15, -5 and 0 torr, while SBP at -35 torr was less than SBP at -15, -5, and 0 torr LBNP, p<0.05. The slight increase in diastolic blood pressure observed from 0 to -45 torr LBNP prior to training was not significantly different, however, the decrease in DBP from 0 to -45 torr LBNP following training was significantly different than that observed pre-training. Consequently, calculated pulse pressures were significantly different pre- to post-training and reflected the same stage differences across LBNP as reported for the changes in systolic blood pressure.

Prior to training the average decrease in SBP from 0 to -45 torr was 14.5 ± 4 mmHg (p<0.009) and produced 16.6 ± 1.9 beat/min increase in HR (p<0.0001) and a ΔHR/ΔSBP ratio of 1.8 ± 0.5 beats/min/mmHg, p<0.008, following training the decrease in SBP from 0 to -45 torr LBNP was 15.5 ± 1.9 mmHg (p<0.0001) and resulted in a 11.9 ± 1.9 beats/min increase in HR (p<0.0004) and a ΔHR/ΔSBP ratio of 0.8 ± 0.2 beats/min/mmHg, p<0.001.
TABLE III: CARDIOVASCULAR RESPONSES TO LBNP
PRIOR TO AND FOLLOWING ENDURANCE TRAINING

<table>
<thead>
<tr>
<th>Dependent Measures</th>
<th>Training Status</th>
<th>0</th>
<th>Lower Body Negative Pressure (torr)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-5</td>
<td>-15</td>
<td>-35</td>
</tr>
<tr>
<td>( \dot{V}_{C} )</td>
<td>UT</td>
<td>5.7±0.13</td>
<td>5.1±0.11</td>
<td>4.7±0.13</td>
<td>4.1±0.12</td>
<td>3.7±0.11</td>
<td></td>
</tr>
<tr>
<td>(l/min)</td>
<td>ET</td>
<td>6.0±0.16</td>
<td>5.5±0.15</td>
<td>4.8±0.14</td>
<td>4.2±0.14</td>
<td>3.7±0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HR</td>
<td>UT</td>
<td>66±4</td>
<td>66±4</td>
<td>66±4</td>
<td>69±4</td>
<td>63±4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(bpm)</td>
<td>ET</td>
<td>57±4</td>
<td>57±4</td>
<td>57±4</td>
<td>60±5</td>
<td>67±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SV</td>
<td>UT</td>
<td>87±6</td>
<td>80±6</td>
<td>73±5</td>
<td>54±5</td>
<td>47±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(mls)</td>
<td>ET</td>
<td>109±8</td>
<td>99±7</td>
<td>87±6</td>
<td>65±6</td>
<td>55±6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP</td>
<td>UT</td>
<td>121±4</td>
<td>121±4</td>
<td>119±5</td>
<td>114±3</td>
<td>107±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>ET</td>
<td>119±3</td>
<td>118±3</td>
<td>116±3</td>
<td>108±2</td>
<td>101±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP</td>
<td>UT</td>
<td>77±2</td>
<td>77±2</td>
<td>77±2</td>
<td>78±3</td>
<td>79±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>ET</td>
<td>74±2</td>
<td>74±2</td>
<td>73±3</td>
<td>72±3</td>
<td>70±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MBP</td>
<td>UT</td>
<td>92±3</td>
<td>92±3</td>
<td>91±3</td>
<td>90±2</td>
<td>88±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>ET</td>
<td>89±3</td>
<td>89±3</td>
<td>88±3</td>
<td>84±3</td>
<td>80±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FBF</td>
<td>UT</td>
<td>2.2±0.2</td>
<td>1.8±0.2</td>
<td>1.7±0.3</td>
<td>1.6±0.2</td>
<td>1.3±0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(ml/dl/min)</td>
<td>ET</td>
<td>2.7±0.3</td>
<td>2.2±0.3</td>
<td>1.8±0.2</td>
<td>1.7±0.3</td>
<td>1.4±0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FVR</td>
<td>UT</td>
<td>41.8±4</td>
<td>54.3±7</td>
<td>60.2±7</td>
<td>59.3±5</td>
<td>72.9±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(Units)</td>
<td>ET</td>
<td>35.0±5</td>
<td>46.3±10</td>
<td>52.3±10</td>
<td>51.5±7</td>
<td>57.8±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PVR</td>
<td>UT</td>
<td>16.3±0.6</td>
<td>17.9±0.6</td>
<td>19.3±0.6</td>
<td>22.0±0.5</td>
<td>23.8±0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(Units)</td>
<td>ET</td>
<td>15.0±0.7</td>
<td>16.4±0.8</td>
<td>18.4±0.8</td>
<td>20.2±0.2</td>
<td>22.3±0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( \Delta ) IgV</td>
<td>UT</td>
<td>0.0</td>
<td>5.9±0.6</td>
<td>18.6±3.8</td>
<td>53.9±7.4</td>
<td>77.9±11.5</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>(mls)</td>
<td>ET</td>
<td>0.0</td>
<td>10.9±1.7</td>
<td>30.6±5.1</td>
<td>64.7±8.2</td>
<td>89.1±12.2</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Data represented as mean ± SEM. Variable abbreviations used as defined in text. p-values indicate significance pre- to post-training.
However, despite the tachycardia to -45 torr LBNP being significantly less post-training compared to pre-training, the post-training decrease in the ratio of ΔHR/ΔSBP of 1.0 ± 0.5 beats/min/mmHg was not significantly different (p=0.11).

Factors Related to Decreases in LBNP Tolerance: In an attempt to determine the physiologic factors related to the significant decrease in LBNP tolerance we carried out a multiple stepwise linear regression (237) using the decrease (change) in cumulative stress index from pre- to post-training as the dependent variable. Six independent variables reflecting pre- to post-training changes in response to 0 to -45 torr LBNP were selected from a correlation matrix of 22 measured and calculated changes based upon their statistical lack of collinearity in the multiple regression, yet were physiologically important in predicting the decrease in LBNP tolerance. However, when statistically significant correlations between changes in LBNP tolerance were observed, physiological importance and statistical lack of collinearity were used in selecting the maximum number of independent variables (N=6). These included the pre- to post-training differences in response to -45 torr LBNP of (a) HR; (b) SV; (c) SBP; (d) DBP; (e) slope of PVR from -15 to -45 torr LBNP; and the (f) pre- to post-training change in TBV. The regression line of PVR measured at -15, -35 and -45 torr reflected a linear increase in peripheral vascular resistance, primarily
related to high pressure baroreceptor reflex activation by the narrowing pulse pressure and the decreasing systolic blood pressure. Table IV, summarizes the results of the multiple stepwise linear regression and identifies the three primary factors which significantly increased the predictive power of the model.

**TABLE IV: ORTHOSTATIC TOLERANCE: PREDICTIVE MODEL**

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>( r^2 [\text{Var.}] )</th>
<th>( r^2 [\Sigma \text{model}] )</th>
<th>( F )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Slope PVR</td>
<td>0.85 (&lt;0.01)</td>
<td>0.85 (&lt;0.01)</td>
<td>22.62</td>
</tr>
<tr>
<td>2. ( \Delta ) TBV</td>
<td>0.12 (&lt;0.05)</td>
<td>0.97 (&lt;0.01)</td>
<td>10.47</td>
</tr>
<tr>
<td>3. ( \Delta ) SBP</td>
<td>0.03 (&lt;0.02)</td>
<td>0.99 (&lt;0.001)</td>
<td>91.08</td>
</tr>
</tbody>
</table>

Variables defined in the test. Numbers in parenthesis indicate \( p \) values.

**Blockade Data: Effect of Training and LBNP:**

Figures 9 to 14 show the mean data ± SEM for the various cardiovascular parameters measured during LBNP under conditions of control, \( \beta_1 \)-adrenergic receptor blockade (metoprolol), muscarinic receptor blockade (atropine), and double blockade (metoprolol + atropine). In Figure 9 the \( \dot{Q}_c \) was significantly decreased from control to -45 torr LBNP under all blockade conditions \( (p<0.001) \). A significant interaction existed between training and metoprolol blockade, and training and atropine blockade \( (p<0.001) \).
FIG. 9. Cardiac output responses during LBNP through stages of control: (unblocked), $\beta_B$: metoprolol blockade, MB: atropine blockade, and DB double cardiac autonomic blockade $\dagger$ significant difference pre- to post-training.
During the unblocked state, \( \dot{Q}_e \) was elevated at rest after training and decreased to a similar endpoint by -45 torr LBNP, indicating a greater decrease in \( \dot{Q}_e \) post-training \((p<0.05)\). With \( \beta_1 \)-blockade no differences were noted between the training groups. Under muscarinic blockade, however, \( \dot{Q}_e \) fell less at -45 torr LBNP than the control conditions \((p<0.0019)\). This suggests that \( \dot{Q}_e \) was maintained to a greater extent with atropine blockade after endurance training. Double blockade resulted in no significant differences in percentage change in \( \dot{Q}_e \) from baseline to -45 torr pre- versus post-training. This again suggests that \( \dot{Q}_e \) was better maintained with double cardiac blockade versus the control state at -45 torr LBNP.

The data for the stroke volume (SV) is shown in Figure 10. Stroke volume decreased significantly from control to -45 torr LBNP in all subjects under all blockade conditions \((p<0.0001)\). Significant interactions existed for SV between training and atropine: training, LBNP, and atropine, and LBNP and atropine \((p<0.001)\). These interactions probably reflect the relationship between training and heart rate bradycardia. At rest SV was significantly greater post-training in the unblocked state. With metoprolol blockade a significantly greater increase in SV was noted across LBNP. Atropine blockade, however, resulted in a less of a decrease in SV post-training across LBNP \((p<0.001)\). No significant
FIG. 10. Stroke volume responses during lower body negative pressure during various blockade conditions. Symbols are as described in Figure 9.
FIG. 11. Heart rate responses during lower body negative pressure during various blockade conditions. Symbols are as described in Figure 9.
differences were seen in SV under complete cardiac autonomic blockade (p=0.25).

In all blockade conditions heart rate (HR) was significantly increased from control to -45 torr LBNP (p<0.001), See Figure 11. Significant interactions for HR existed only between training and atropine blockade (p<0.001) and may be related to the expected training increase in parasympathetic tone. At rest, HR was significantly decreased with training in the unblocked state. With atropine blockade the change in HR was now greater post-versus pre-training by -45 torr LBNP (p<0.001), suggesting an increased tachycardiac response post-training when the vagal efferent effects on the heart were blocked. With metoprolol blockade no significant changes were noted with training (p<.9556). There was also a significant decrease in HR change at -45 torr LBNP with double cardiac blockade post-training (p<0.04). However, HR was also not significantly altered from 0 to -25 torr LBNP under any of the various blockade conditions and was significantly different from -35 and -45 torr LBNP. Table V outline the various resting heart rates under the blockade conditions.

Mean arterial pressure (MAP) (Figure 12) was significantly decreased in all blockade conditions pre- and post-training at -45 torr LBNP versus stage 0 LBNP (p<0.001). No significant interactions existed between MAP and any of the blockade conditions. Under control conditions
TABLE V: RESTING HEART RATE WITH CARDIAC AUTONOMIC BLOCKADE

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Metoprolol</th>
<th>Atropine</th>
<th>Double</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>66.4 ± 3.6</td>
<td>56.1 ± 3.0</td>
<td>99.9 ± 2.5</td>
<td>85.4 ± 3.1</td>
</tr>
<tr>
<td>Post</td>
<td>56.9 ± 3.7</td>
<td>48.9 ± 3.9</td>
<td>101.4 ± 3.3</td>
<td>83.7 ± 2.9</td>
</tr>
</tbody>
</table>

Heart rate was significantly lower unblocked post training, and with metoprolol blockade (p<0.05).

MAP fell to a greater degree at -45 torr LBNP post-training (p<0.05). With atropine blockade no significant difference was found pre-to post-training from control to -45 torr LBNP (p=0.2558).

The difference between MAP pre-training was not significantly different while the MAP decreased less post-training under atropine blockade suggesting better arterial pressure regulation with atropine blockade post-training. No significant differences were noted with metoprolol or double blockade post-training (p=0.5977 and 0.2422, respectively).

Furthermore, MAP was not significantly altered during LBNP under the various blockade conditions until LBNP was more negative than -35 torr (p<0.05).

Total peripheral resistance (TPR) (Figure 13) increased in all blockade conditions from control to -45 torr LBNP (p<0.001). No significant interactions existed between TPR and the blockade conditions except for training level (ie. pre-to the post-trained state) and atropine blockade. With atropine blockade the change in TPR from control to -45 torr
FIG. 12. Mean arterial pressure responses during lower body negative pressure during various blockade conditions. Symbols are as described in figure 9.
FIG. 13. Total peripheral resistance responses during lower body negative pressure during various blockade conditions. Symbols are as described in figure 9.
FIG. 14. Forearm vascular resistance responses during lower body negative pressure during various blockade conditions. Symbols are as described in figure 9.
LBNP was significantly augmented in the ET state (p<0.001). Metoprolol blockade did not significantly affect TPR (p=.1314). Training, however, did have a significant effect on TPR (p<0.001).

Forearm vascular resistance (FVR) was not significantly increased during blockade conditions from 0 to -45 torr LBNP (p>0.05), see Figure 14. No significant interactions existed for FVR between the various conditions. Training resulted in a significant decrease in FVR across all blockade conditions (p<0.001). In the unblocked state FVR was decreased at -45 torr in the ET versus UT state (p<0.05). Atropine blockade resulted in a significant increase in FVR in UT and ET subjects (p<0.05), suggesting that parasympathetic tone was attenuating the vascular response to LBNP.

Cardiopulmonary Baroreflex Responsiveness: Central Venous Pressure:

During LBNP, venous pooling reduced cardiac filling, leading to reductions in Q̇̇ and MAP. The extent of cardiac filling was determined by measuring central venous pressure during LBNP. Figure 15 illustrates that central venous pressure (CVP) fell progressively during LBNP (p<.0001). The mean CVP at rest of the UT subjects, increased from 8.34 ±0.95 mmHg to 9.87 ±1.05 mmHg (ET) and this trend remained throughout all levels of LBNP (p<0.0119). The gain of the baroreflex response, estimated from the slope of the linear relationship between FVR and CVP (132,210) was significantly
attenuated following training in the 0 to -15 torr LBNP range (-4.6 ±2.2 UT to -1.9 ±1.0 U/mmHg ET), and in the 0 to -45 torr LBNP range (-2.7 ±0.9 to -1.7 ±0.8 U/mmHg) (p<0.02).

**ESTIMATED FILLING PRESSURE**  
N=7 (+SE)

**FIG. 15.** Change in mean central venous pressure during lower body negative pressure, in untrained (UT) versus the endurance trained (ET) state.

**Response to Steady-State Infusions of Phenylephrine:**

The basic physiologic responses to progressive steady-state infusions of phenylephrine (PE) for each group are illustrated in Figure 16. Mean arterial pressure (MAP) increased progressively with an increasing dose of PE and was significantly increased by 120 ug min⁻¹ (p<0.05). The ET individuals showed a plateau of MAP after 90 ug min⁻¹ while blood pressure of the UT individuals was still increasing.
The resting MAP was similar between groups despite a greater total blood volume in the ET individuals.

FIG. 16. Pre- post-training responses to steady-state infusion of phenylephrine.
During all stages except 120 ug min⁻¹ absolute HR was lower in the ET group, but the difference between groups was not significant. The change in HR at each stage of infusion was less in the ET group (p<0.05, Figure 16). Resting FBF was increased in ET state (Figure 16), but constricted down to a similar level as in the UT state at 120 ug/min. Similarly, the FVR was decreased at rest in the ET state, p<0.05, (Figure 16) however, the ET constricted to the same degree at 120 ug min⁻¹ as seen in the UT state.

In examining the differences in HR baseline (Figure 17), the ET state resulted in a plateau of the bradycardic response to 60 ug min⁻¹, while the UT HR response continued to decrease in response to increasing MAP. When the slope of the blood pressure curve was examined (ΔHR/ΔMAP) for all infusions from baseline, the results are described in Figure 18. Group D represents data from the present investigation. Note that the slope decreased from 0.884 ±0.10 to 0.446 ± 0.10 (p<0.05), demonstrating a reduction in baroreceptor responsiveness to a hypertensive stimuli. However, when the same data were expressed as RRI no statistically significant differences among the slopes were noted (p>0.05). These data might suggest that the lower slope observed using HR in the numerator of the relationship between ΔHR/ΔMAP resulted from training induced bradycardia rather than changes in baroreflex responsiveness per se.
FIG. 17. The difference in heart rate (HR) from baseline (BL) is plotted versus the differences in mean arterial pressure (MAP). Untrained (UT) condition is represented by solid line and circles. The endurance trained (ET) subjects are represented by the dotted line. ET individuals plateaued their bradycardic responses to increased concentration of phenylephrine HCL at 60 ug·min<sup>-1</sup>. The UT individuals continued to exert a bradycardic response with increases in MAP.

FIG. 18. This is a composite graph of data. A and B represent canine data responses to changes in heart rate per changes in mean arterial pressure (slope), before (UT) and after (ET) 10 weeks of treadmill training (90a). A represents the response to nitroprusside infusions. Both A and B show attenuation of the slope. Figure C represents data from a 6 week human training study (205) and D represents the data from the present study. Both C and D show attenuation of their slopes with training.
CHAPTER V

DISCUSSION

The major null hypothesis tested in this investigation, was that orthostatic tolerance would not be different following endurance exercise training. The findings resulted in a rejection of this hypothesis. In light of this conclusion, this chapter includes a discussion of the other important results of this investigation and explains the findings within the framework of fundamental concepts of physiology and related observations and discussions from the literature. The chapter will be broken down into four subsections including: (i) a discussion of descriptive baseline data including anthropometric data; (ii) responses to an orthostatic stress (including tolerance); (iii) responses to a hypertensive stress, and; (iv) a summary and discussion of directions for future research.

**Baseline Data**

**Anthropometric Measurements**

An advantage of a longitudinal designed study such as reported is that subjects act as their own controls. It has been shown that cardiovascular responses to orthostatic stress are less in older (36,63,153) and shorter individuals
This requires that cross-sectional studies match their subject groups for age and height. In the present study this was not a requirement. The fact that the age variance was less than 10 years between subjects suggests that age was unlikely to affect the responses to an orthostatic stress (63).

In the present investigation eight months of aerobic training produced a significant decrease in body weight, but not lean body mass or percentage body fat. No dietary controls were placed on the subjects and may have accounted for the lack of effect on body fat, however, a trend for a decrease in body fat was seen.

Aerobic Capacity

It has previously been shown that maximal oxygen uptake ($\dot{VO}_{2\text{max}}$) was a reliable indicator of aerobic fitness (141), and was reproducible when defined criteria of maximal effort was achieved (213). Since it has been suggested that a relationship might exist between aerobic fitness and orthostatic tolerance, it was important to have an accurate way of assessing aerobic fitness prior to and after eight months of aerobic training.

Subjects were screened and accepted into the study based on their initial $\dot{VO}_{2\text{max}}$, since it has been shown that the lower the initial $\dot{VO}_{2\text{max}}$ below 45 ml/kg/min the greater the relative and absolute increase with training (179). The initial $\dot{VO}_{2\text{max}}$ of 45 ml/kg/min of the present investigation
accomplished this selection criterion. The length of training stimulus was also an important design criteria of this investigation. It has previously been shown in five longitudinal studies, that 2-3 months of physical conditioning increased $\dot{V}O_{2max}$ from 44 to 51 ml/kg/min (11, 41), or an average of 16%. Unfortunately, training studies of 10 to 12 weeks duration failed to produce significant physiologic adaptations in cardiac pump function (175). However, when the training stimulus has been prolonged, sedentary subjects have been shown to increase their $\dot{V}O_{2max}$ up to 44% from 45 to 65 ml/kg/min (71), and cardiac pump function was markedly increased (175). The increase in $\dot{V}O_{2max}$ found in the present investigation were in agreement with these findings as $\dot{V}O_{2max}$ increased from 45.2 ±6.12 to 57.5 ±7.9 ml/kg/min. This average 27.2% increase in $\dot{V}O_{2max}$ was significant when expressed either as an absolute value or per kg body weight. Maximal heart rate was also significantly decreased with training and has been shown to be an adaptation of training (175).

**Blood Volumes**

Circulating blood volume has been shown to have an influence on the cardiovascular responses to an orthostatic stress, with the suggestion that the smaller the blood volume the greater the susceptibility to fainting (50, 190). Evidence acquired over the past several years supports this contention that endurance trained individuals have a larger
blood volume (48,49,151). This training hypervolemia should provide some measure of orthostatic protection versus their relatively hypovolemic counterparts. The contribution of blood volume changes and their interaction with cardiovascular reflex integration for blood pressure control will be dealt with in a separate section. In the present study, the training program produced a significant increase in blood volume on an absolute or relative basis. The majority of the increase in blood volume was secondary to an increase in plasma volume, as has been shown previously to be the case (49,171).

Resting Cardiovascular Measurements

The eight months of endurance training despite the increase in blood volume did not significantly affect systolic blood pressure (SBP), diastolic blood pressure (DBP), or pulse pressure (PP). There was, however, a significant decrease in mean arterial pressure of 2 mmHg. Tipton (219) has recently shown that the majority of longitudinal studies "indicate that training would be associated with a lower SBP and lower DBP". Although SBP and DBP were not significantly altered post-training, both blood pressures were tending to a decrease, such that MAP was significantly decreased. This decrease in MAP may be secondary to a significant increase in resting cardiac output ($\dot{Q}_c$) and a tendency for the resting total peripheral resistance to be lower post-training.
The larger resting Q post-training was reflective of a reduced resting heart rate (66.4 ±3.6 to 56.9 ±3.7) and an elevated stroke volume (87.3 ±6.2 to 108.9 ±8.5). However, no measures of cardiac function per se were determined in the present investigation. In a recent investigation, Pawelczyk (155) has shown that contractility at rest was not altered in three groups of men matched for age and height and of varying fitness ranges. However, they did report greater end-diastolic volumes of the heart for the high fit individuals (158). Therefore, the greater SV at rest in the present study was assumed to be due to the increased total blood volume and the Frank-Starling mechanism of the heart.

Lower Body Negative Pressure Tolerance and Cardiovascular Responses:

The findings of the present investigation suggest that physiologic adaptations associated with prolonged endurance exercise training, which produced a large increase in \( \dot{V}O_{2\text{max}} \) and total blood volume (TBV) and altered the hemodynamic response to LBNP, resulted in a reduction in LBNP tolerance. These findings were in direct contrast to the results of previous longitudinal investigations utilizing shorter duration training programs, resulting in only moderate increases in \( \dot{V}O_{2\text{max}} \) and TBV (47,50,124). However, the findings of a change in the degree of the hemodynamic response to LBNP of the present study confirm previous cross-sectional comparisons of untrained (\( \dot{V}O_{2\text{max}} <43 \))
ml/kg/min) versus highly trained (\(\dot{V}O_{2\text{max}} \geq 60\) ml/mg/min subjects (165,195,196) and suggests that there may be a critical amount of physiologic adaptation necessary to occur, which is reflected by large increases in \(\dot{V}O_{2\text{max}}\) and TBV, before LBNP intolerance becomes manifest. The concept that genetic determinants of \(\dot{V}O_{2\text{max}}\) (59) may be associated with blunted arterial baroreflex responses to orthostatic stress (47,124), can be discounted because (a) the range of the subjects pre-training \(\dot{V}O_{2\text{max}}\) was 35 ml/kg/min to 54 ml/kg/min; (b) the post training subjects \(\dot{V}O_{2\text{max}}\) ranged from 43.6 ml/kg/min to 66.3 ml/kg/min; (c) each subject increased their \(\dot{V}O_{2\text{max}}\) as a result of training; (d) each subject had a reduction in their post-training orthostatic tolerance to LBNP; and (e) each subject had an attenuated ΔHR/ΔSBP response to -45 torr LBNP. However, the definitive investigation in which LBNP tolerance and physiologic adaptations to progressively increasing durations of endurance exercise training has not been performed. It does appear, however, that marked increases in TBV and \(\dot{V}O_{2\text{max}}\), as found in the present investigation, are prerequisites for training related decreases in LBNP tolerance and altered hemodynamic responses to LBNP.

In a complex and detailed cross-sectionally designed investigation into the physiologic factors associated with aerobic fitness and tolerance to LBNP stress, Levine et al. (114) compared high fit chronic endurance exercisers (\(\dot{V}O_{2\text{max}}\)
>60 ml/kg/min), mid fit moderate exercisers ($V_{O_{2\max}}$ 45 to 55 ml/kg/min) and low fit sedentary ($V_{O_{2\max}}$ <40 ml/kg/min) subjects. Stepwise linear regression analysis indicated that maximal calf vasodilator capacity and closed-loop carotid arterial baroreflex gain obtained at rest were primary factors in predicting LBNP tolerance. However, a secondary factor of large decreases in stroke volume during LBNP was associated with the high fit subjects having larger resting stroke volumes and decreased LBNP tolerance. Subsequently, Levine et al. (115,116) have reported that high fit subjects have greater myocardial compliance than average or low fit subjects and therefore, have greater decreases in cardiac filling volumes for a given amount of LBNP stress. This altered Frank-Starling relationship results in a more marked drop in stroke volume during LBNP and appears associated with the high fit subjects reduced LBNP tolerance (114-116).

In the present investigation, the major physiologic prediction of a decrease in LBNP tolerance was the decreased slope of the peripheral vascular resistance (PVR) responses to LBNP from -15 torr to -45 torr LBNP. These findings indicate that the prolonged endurance exercise training program induced a reduction in the vasoconstrictor response to LBNP. The reduced vasoconstrictor response below -15 torr LBNP may be more reflective of high pressure baroreceptor reflex attenuation, as supported by the
findings of Raven et al. (165) and Smith et al. (195) in humans and by Tipton et al. (220) and Bedford et al. (14,15) in the rat model and Dicarlo et al. (57) in the rabbit model. However, Mack et al. (132) have clearly found a reduced forearm vascular reflex response to the lower levels (0 to -20 torr) of LBNP implicating an attenuated cardiopulmonary baroreflex. The findings of reduced reflex vasoconstriction suggests (a) possible resetting of the cardiopulmonary baroreceptor’s operational point; (b) changes in central integration of the afferent information and subsequent reduced efferent output; or (c) possible alterations in $\alpha$-receptor sensitivity or responsiveness.

Cardiopulmonary Baroreflex Responsiveness:

Central Venous Pressure: During LBNP, venous pooling reduces cardiac filling, leading to reductions in $Q_c$ and arterial pressure. In the present investigation, the extent of cardiac filling was determined by measuring central venous pressure (CVP) during LBNP. Central venous pressure fell progressively during LBNP ($p<0.0001$). The data of the present investigation demonstrate that the cardiopulmonary baroreflex responsiveness was attenuated by endurance exercise training. These findings are in agreement with Mack et al. (132), but are in disagreement with Takeshita et al. (210). The difference between the present results and those of Takeshita et al. (210) may be explained by examining the subject populations utilized in the two studies. In the
Takeshita study, the athletes were former football players, and were not characterized based on $\dot{V}O_{2\text{max}}$ or blood volume thereby preventing direct comparisons with our study. Smith and Raven (199) have shown that blood pressure control during LBNP differed among athletes depending on their training regimen (ie. distance runners vs. weight lifters). The cardiovascular responses of the football players appears similar to those of the weight lifters in the Raven and Smith study (199). It is perhaps not contradictory that Takeshita et al. (210) found an augmentation in the cardiopulmonary control of FVR. In summary, prolonged endurance training causes an attenuation of the gain of the cardiopulmonary reflex, and appears related to volume expansion induced by training.

Levine et al. (114) found that maximal calf conductance was a strong independent predictor of LBNP tolerance and Snell et al. (200) has previously demonstrated a strong positive correlation between $\dot{V}O_{2\text{max}}$ and maximal calf conductance. Whether the greater metabolic vasodilator capacity of endurance trained individuals, found by Snell et al. (200), and Levine et al. (114) is related to the finding of the present investigation of a training induced reduction in vasoconstriction to LBNP induced hypotension is questionable. However, from results of the previous investigations and the present findings, one could speculate that a change in the neurohumoral control of the resistance
vessels may be a resultant of prolonged endurance exercise training.

The second major physiologic factor which significantly strengthens the predictive model of decreases in LBNP tolerance was the observed increase in total blood volume (TBV). Large increases in the average TBV (+15.8%) of the eight subjects occurred as a result of the prolonged endurance exercise training program. The increased TBV occurred without statistically significant changes in resting SBP, DBP, pulse pressures (PP) or calculated arterial compliance (PP/SV), yet there was a minor and statistically significant decrease in resting MAP of -2 mmHg. These findings suggest that an increase in the resting venous volume occurred as a result of the endurance exercise training.

Levine et al. (114-116) in their cross-sectional investigations have reported greater decreases in left ventricular filling pressures and CVP of high fit subjects compared to low fit subjects during LBNP. They concluded that endurance exercise training resulted in altered ventricular pressure - volume relationships which resulted in greater decreases in stroke volume per unit decrease in cardiac filling pressure. In the present investigation, the data indicate that the average decrease in SV of -31 ml between 0 torr and -45 torr LBNP prior to training was significantly less than the 54 ml decrease observed
following training (Table III). Surprisingly, and unlike the predictive model of Levine et al. (114) the difference in SV changes during LBNP pre- to post-training of the present investigation was not a primary factor in the predictive model of decreases in LBNP tolerance. In many of the short term endurance exercise training studies (days or weeks) the increase in blood volume has been demonstrated to improve orthostatic tolerance (47). However, measures of central venous compliance or left ventricular pressure-volume relationships were not made. We suggest, therefore, that when the exercise training program is of a long enough duration to alter physiologic variables, such as; (a) central venous compliance and ventricular pressure-volume relationships; (b) chronic training induced large increases in blood volume and \( \dot{V}O_{2\text{max}} \) (155,165,195,196); and (c) a reduced vasoconstrictor response to LBNP, only then will a reduction in LBNP tolerance become manifest.

In the present investigation, a significantly greater rate of pooling (\( \Delta LgV/\Delta LBNP \)) during lower level LBNP (0 to -15 torr) following training was found. The rate of LgV pooling at the higher levels of LBNP (-15 to -45 torr) were not different prior to and following training, although the total amount of LgV change during LBNP was greater post-training compared to pre-training (Table III). In a more recent investigation using direct measurements of CVP (166) it has been found that highly trained subjects (\( \dot{V}O_{2\text{max}} \)
>60ml/kg/min) had a greater drop in CVP during 0 to -20 torr LBNP than unfit subjects (\( \dot{V}O_{2max} < 45ml/kg/min \)). However, the change in CVP from -20 to -50 torr LBNP was not different between the two groups. These findings suggest that highly trained subjects appear to rapidly pool blood into the lower limbs or into the great veins of the iliac region (35). This suggestion of an increased pooling during low levels of LBNP was consistent with the proposed increased central venous compliance reported by Levine et al. (114,115) and the report of increased lower limb compliance of Luft et al. (129). However, the findings of the present investigation were in direct contrast to our previous work (165, 195,196) in which we were unable to demonstrate a difference in lower limb compliance of high and low fit subjects. These findings do, however, confirm Convertino et al.'s (51) model for predicting peak LBNP tolerance, which identified changes in LgV, leg compliance and TBV as being significant primary factors of predicting the peak LBNP attained. Even though changes in LgV and SV were greater during 0 to -45 torr LBNP post-training in the present investigation they were not related as significant predictors of change in LBNP tolerance 'per se'. Clearly, the model is multifactorial and when the findings of the present study are combined with the findings of the previous work (51,114-116) the primary factors related to the training induced orthostatic intolerance appear to be an accentuated central hypovolemia
and a reduced function of the cardiovascular reflexes which are engaged to protect MAP from decreasing during central hypovolemia. These factors have been clearly described by Blomqvist (22) as being the major mechanisms of clinical orthostatic hypotension.

Although the reduced slope of PVR from -15 torr to -45 torr LBNP and the pre-to post-training increase in TBV account for 97% of the variance of prediction (P<0.006) of the post-training decrease in LBNP tolerance, the difference in the decrease in SBP from 0 torr to -45 torr LBNP contributes further significance (P<0.011) to the prediction of the stepwise linear regression model (r² = 0.9993), P<0.0011. Physiologically this average 1.0 mmHg difference of the individual SBP response appears physiologically insignificant. However, the average of individual change in HR from 0 to -45 torr LBNP was 4.7 beats/min less post-training compared to pre-training and resulted in a trend towards a non-significant decrease in ΔHR/ΔSBP ratio. These data do not confirm our previous reports (165,195,196) of a training induced reduction in ΔHR/ΔSBP ratio and by inference an attenuation of the baroreceptor reflex. However, the data presented in Table III do identify a significant endurance exercise training effect on the hemodynamic responses to LBNP. For example, the post-training decrease in Q̇ and SV from 0 to -45 torr LBNP was greater, yet the HR increase was less. Both PVR and FVR
increased less while MAP, SBP and DBP decreased more following training. Interestingly, the average DBP response prior to training increased 2 mmHg from 0 to -45 torr LBNP, whereas, the average DBP during LBNP to -45 torr decreased 4 mmHg following training. This difference in the DBP response to LBNP confirms cross-sectional findings of Pawelczyk et al. (155) in which he found increases of DBP in low fit (\(\dot{V}O_{2max} < 40\text{ml/kg/min}\)) subjects during LBNP to -50 torr, while high fit (>60\text{ml/kg/min}) subjects had a decrease in DBP. This apparent fitness related difference in DBP response may be indicative of a training induced alteration of \(\alpha\)-receptor function, cardiopulmonary and arterial baroreceptor control of vasomotion, and a possible altered neural control of blood pressure during an orthostatic challenge.

The average percentage decrease from resting MAP that occurs for similar LBNP induced decreases in \(\dot{Q}\) prior to and following the endurance training program had a slope of 5.51 to 2.78 (pre- to post-training respectively). Clearly there was a marked decrease in MAP at -35 torr and -45 torr LBNP after training, indicating inadequate arterial baroreflex mediated control of blood pressure. We have previously discussed the greater decrease in SV during LBNP post-training and related these finding to a training induced decrease in cardiac filling pressure (114-116) during LBNP. In addition, the greater post-training
decreases in $Q_c$ of the present investigation, were reflective of a reduced tachycardiac response to a given drop in MAP, (slope of % change HR / % change in MAP; decrease from -7.19 to -3.41 with training), indicating an attenuated reflex tachycardiac response to hypotension induced by the central hypovolemia during LBNP.

In conclusion, the data of the present study indicate that physiologic adaptations to a prolonged endurance exercise training program which resulted in large increases in $\dot{V}O_{2max}$ and TBV were associated with adaptations of the blood pressure control system. These adaptations in the blood pressure control system result in attenuated reflex responses to LBNP induced central hypovolemia. This inadequate response was identified as being a reduced vasoconstriction and a reduced tachycardiac response to -45 torr LBNP, which in conjunction with the previously reported more marked decreases in cardiac filling as a result of training-induced alterations in ventricular pressure/volume relationships (116), results in decreased LBNP tolerance. Furthermore, the trend to a decreased diastolic blood pressure during LBNP and the identification of a decreased PVR as being a primary factor associated with the decreased LBNP tolerance suggests a training-induced alteration in the neural control of vasomotion.

**Cardiac Autonomic Blockade:**

In the previous section of the discussion we examined
the possible mechanisms responsible for the decreased orthostatic tolerance of the present study. It was noted that the major predictor for a decrease in orthostatic tolerance was a decrease in the slope of the PVR responses to LBNP between -15 and -45 torr LBNP. These results correlated with a decreased vasoconstrictor response to LBNP. It was also noted that the vasoconstrictor effect was attenuated at LBNP pressure <-15 torr, with the suggestion of an attenuated cardiopulmonary reflex. The findings, however, were unable to provide a mechanism to support the attenuated vasoconstrictor drive. In this section, the regulation of arterial pressure and the effect of cardiac autonomic blockade on arterial pressure regulation during an orthostatic stress will be examined, in hopes of uncovering the mechanism.

Multiple regional vasoconstriction is a normal cardiovascular adaptation to LBNP. It has been noted that a significant increase in peripheral sympathetic nerve traffic accompanies changes in LBNP (207). The net effect of this increased sympathetic outflow is vasoconstriction of the vasculature in skeletal muscle, (176,207), skin (139), and splanchnic circulation (99,176).

We have discussed earlier the fact that MAP was significantly reduced by -45 torr LBNP in the unblocked state post-training versus pre-training. With atropine or double cardiac autonomic blockade (metoprolol and atropine),
however, MAP pressure was regulated post-training similar to the pre-training unblocked state. The MAP was not significantly altered with atropine blockade between the two training states at any level of LBNP. Metoprolol blockade did not affect the relationship between training state, as the ET subjects still exhibited lower MAPs. Since MAP is defined as the product of \( Q \) times TPR, the atropine blockade must have increased one or both of these responses. Smith et al. (196) using a similar blockade protocol during LBNP, but in a cross-sectional design, also found improved arterial pressure regulation during atropine blockade and postulated increased parasympathetic tone as the mechanism responsible for the increased orthostatic intolerance (OIT) of training.

During the unblocked state, the change in \( Q \) from control to -45 torr LBNP was increased post-training. Metoprolol blockade did not effect the relationship, while atropine blockade resulted in a significantly lower drop in \( Q \) post-training versus the pre-trained state. Complete cardiac blockade also resulted in better maintenance of the \( Q \), at -45 torr post-training. The increased \( Q \) seen post atropine blockade could be explained by either an increased inotropic effect or an augmentation in venous return. Nixon et al. (148), has proposed that contractility was unchanged at -40 torr LBNP as determined by the mean velocity of circumferential fiber shortening. Several investigators
have suggested increases in indexes of contractility during carotid sinus hypotension when preload, afterload, and HR were held constant, suggesting that the carotid reflex may mediate cardiac inotropic responses. The contractile effect, if present in the present investigation, should have been blocked by β-adrenergic blockade, and it was thereby supporting the concept that the augmented \( \dot{Q} \) post-training with atropine blockade could be due to an increase in contractility. Alternatively, the augmented \( \dot{Q} \) post-training with atropine blockade could be secondary to a reduced fall in filling pressure. In this study filling pressure was not measured during atropine blockade. The fall in stroke volume post-training with atropine blockade was decreased compared to the pre-training state, suggesting that stroke volume was maintained. This response again could be secondary to an increase in contractile function post-training under atropine blockade.

The improved maintenance of MAP post-training with atropine blockade could not be explained by an increase in TPR, since TPR was not significantly altered from the unblocked state post-training. Interestingly, however, the pre-training state with atropine blockade resulted in a significant augmentation of TPR versus the unblocked pre-train state. This suggests that the untrained subjects had an increased ability to vasoconstrict their periphery versus the ET subjects. The mechanism behind this finding is
unknown. These results are similar to those found by Smith et al. (196), who also noted increases in TPR with atropine blockade in the untrained state.

Forearm vascular resistance (FVR) post-training demonstrated a plateau after -15 torr LBNP in the unblocked state. With atropine blockade FVR showed a linear relationship to LBNP in the ET and UT state. These data are similar to Smith et al. (196), who demonstrated increases in FVR with atropine blockade in UT and ET subjects with a cross-sectional design. Blockade of the β1-adrenergic receptors with metoprolol did not affect the vasoconstrictor responses to LBNP. These results suggest that removal of parasympathetic control unmasked a greater potential for vasoconstriction in the untrained and endurance trained state. A possible alternative explanation could be one of a cholinergic vasodilatory response being blocked by atropine. This reflex has been shown to exist in muscle vasculature of dogs (212) and cats (169). At rest, however, with atropine blockade FVR was decreased. If a vasodilator system was functional then atropine blockade should result in an increase in resting FVR.

Evidence of increased cholinergic tone to the myocardium can be inferred from the heart rate data. It has previously been documented that endurance exercise training is accompanied by a decrease in resting heart rate (72,122,125). Sigvardson et al. (193) examined the role of
the sympathetic nervous system in training induced bradycardia. In his experiments, treadmill trained control rats were compared with chemical sympathectomized trained rats. The control rats had a significant reduction in resting HR (RHR) whereas the sympathectomized rats exhibited no training bradycardia. They also investigated intrinsic HR (IHR) utilizing bilateral vagotomy, pithing and chemical sympathectomy, and found a training induced reduction in IHR. Ordway et al. (150), trained dogs on a treadmill for six weeks after dividing his dogs into a sham operated group and a cardiac denervated group. The sham operated group had a significant reduction in RHR from 64 to 51 beats per minute. The submaximal HR was also reduced. The cardiac denervated group had no significant change in RHR (95 to 96 bpm). There was also no change in submaximal heart rate. They concluded that the training bradycardia was reflective of changes in autonomic nervous system input to the heart since IHR was not altered. In previous work Tipton (217), has demonstrated that chronically trained rats with training induced bradycardia had less chronotropic response to atropine versus the untrained rats. Tipton postulated that trained rats may have more non-neuronal acetylcholine to compete against the atropine in a competitive basis for the cardiac muscarinic receptors. Tipton et al. (217) looked at IHR of rodents using an isolated heart technique on the effect of training. They found no difference in the
spontaneous heart rate with training. Astrand (11) has suggested that training induced bradycardia was a result of increased vagal cholinergic drive and central nervous system inhibitory mechanisms.

In 1981 Williams et al. (233), examined the effects of isoproterenol on marathon runners versus age matched controls. They found no change in sino-atrial node (SA) sensitivity. They also looked at $\beta$-adrenergic receptor sites on the lymphocytes pre-and post-six weeks of aerobic training and found no difference in the number of sites or the affinity. They concluded that training bradycardia was due to a change in the autonomic nervous system input to the SA node and not to a decreased sensitivity of the node itself.

The results from the present study corroborate some of these previous findings and not others. When the heart was under complete muscarinic blockade (MB), (Table V), a measure of cardiac adrenergic tone existed. Under these conditions no significant differences were found in RHR, suggesting that no alteration in cardiac resting adrenergic tone had taken place. With full cardiac $\beta_1$-adrenergic blockade a measure of muscarinic tone existed to the myocardium. A significant decrease in HR post-training with complete $\beta_1$-adrenergic blockade was suggestive of an increased cholinergic input to the heart with training. With double cardiac blockade the HR response was again not
significantly different between the trained versus untrained states, suggesting that no change in IHR had taken place. In conclusion, eight months of endurance exercise training evoked a resting bradycardia that was the result of an increase in vagal tone to the myocardium, and not decreased IHR, or decreased adrenergic tone.

In summary, the decrease in MAP was significantly augmented post-training in the unblocked state at -45 torr LBNP. With the introduction of atropine blockade, the decrease in MAP at -45 torr LBNP was more like that of the pre-trained state. The mechanism behind this attenuated decrease in MAP post-training during muscarinic blockade appears to be related to an increased $Q_c$ and increased forearm vascular resistance. These data suggest that the endurance trained athlete has the capacity to maintain MAP when subjected to an orthostatic stress, but that augmented parasympathetic tone inhibits his natural anti-orthostatic reflexes. The net effect being that the athlete becomes more susceptible to orthostatic intolerance.

Responses to Phenylephrine Infusions:

One of the aims of the present study using a longitudinal design was to determine if endurance exercise training would effect the baroreflex response to a hypertensive challenge with phenylephrine HCL (PE).

Stegemann et al. (204) 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 smaller mean arterial pressure and heart rate responses to a given change in estimated transmural pressure. Although the apparatus was a crude ancestor to the neck suction devices of today, the results were obtained with minimal assumptions other than the accuracy of the estimation of carotid sinus pressure. Bedford and Tipton (14,15) performed similar experiments on isolated carotid sinuses of endurance trained and sedentary rats. They evaluated the systemic pressure response to changes in carotid perfusion pressure and found that training reduced the compensatory changes to both hypertensive and hypotensive perfusion. They interpreted this to be a decrease in the responsiveness of the baroreceptor. Gwritz et al. (90a) in a later study, found that trained dogs had an attenuated baroreflex responsiveness to phenylephrine and nitroprusside injections (Figure 18).

The responsiveness of the high pressure baroreceptors can be estimated by the relationship between heart rate and arterial blood pressure as shown earlier in this discussion. The attenuation of this reflex (ie. $\Delta HR/\Delta MAP$) in the present
study with phenylephrine infusion was similar to that shown previously in a 6 week training program, (205) and in endurance trained dogs (90a). A question in the literature, however, has arisen regarding the use of HR employed in the numerator of the slope of the stimulus response relationship rather than RRI. Pawelczyk et al. (158) has recently shown that when the gain of the baroreflex (carotid-cardiac) was plotted as change in HR/change in MAP, high fit individuals report attenuated reflexes. If, however, RRI was substituted for HR and the analysis repeated, no significant differences were found between the ET and UT groups. Rowell (175) has used the term "the fallacious scheme" for utilizing RRI, rather than HR. The answer to the question might be that the choice of numerator depends on how the reflexes are being measured. It has been suggested that when the carotid sinus is affected on a beat-to-beat basis (as with neck suction / pressure), then RRI is the numerator of choice (87). If, however, arterial pressure is altered at discrete increments of time, HR rather than RRI would be the variable of choice. In the present investigation the use of HR as the numerator therefore seems appropriate, and supports the contention that high pressure baroreceptor responsiveness was attenuated with training under hypertensive stimuli.

The mechanism behind the attenuation of baroreflex function during a steady-state infusion of PE is not known. As shown in Figure 16, FBF exhibited a greater absolute
decrease at 120 ug min\(^{-1}\) of PE in the ET versus the UT state. As expected, the FVR was decreased at rest with ET, but increased to a similar level as the UT state by 120 ug min\(^{-1}\). The MAP, however, did not achieve as high an absolute value by 120 ug min\(^{-1}\) with training. Since PE is a non-selective \(\alpha\)-adrenergic agonist it will cause both a venoconstriction and arteriolar vasoconstriction. The similar end points for FBF and FVR between the training states would suggest that the PE had a similar maximal vasoconstrictor effect on the peripheral veins. Since MAP was not increased in the ET state above that of the UT state with infusions of PE, it was possible that a component of the decreased heart rate response was secondary to an attenuated input to the baroreceptor itself. Further insight to this can be gained with a critical evaluation of Figure 17. The MAP change from baseline in the ET state was significantly reduced between 90 and 120 ug min\(^{-1}\), and may have resulted in a decreased stimulus to the baroreceptor. Consequently, no change in HR was seen for the same infusion interval. This, however, does not explain the finding that from 60-90 ug min\(^{-1}\) infusions of PE, the MAP in the ET individuals increased by a similar magnitude versus the UT state, yet very little further bradycardia was noted. Since, the MAP pressure change from baseline occurred in smaller increments in the ET state and did not achieve as high an absolute value, it was possible \(\alpha\)-adrenergic receptor sensitivity was altered with training.
A further explanation could be that the heart rate response to increasing MAP was attenuated after 60 ug min$^{-1}$ in the ET state because the reflex bradycardic response was at its physiologic limit. Two of the subjects following training had the PE infusion stopped at a lower dose because of the occurrence of a junctional rhythm. It appears, therefore, that part of the attenuation of the high pressure cardiac baroreflex may be secondary to limitations in the ability of the heart to slow to a further degree or that the reflex has achieved saturation.

In conclusion, we have previously shown that endurance exercise results in a decreased vasoconstrictor ability during an orthostatic stress. Using PE (hypertensive stimulus) we have documented an attenuation of the baroreceptor-cardiac reflex. Some of our data, however, suggest that part of the decreased bradycardic response to a hypertensive stimulus with ET may exist at the level of the heart where bradycardic reserve function approached the saturation point. The relationship between these findings and orthostatic intolerance following training are not known, however, a decreased responsiveness of the high pressure baroreceptors to alterations in blood pressure appears to become manifest with endurance exercise training. Further studies are required to increase our understanding of this mechanism.

Theoretical Model of Tolerance:
To explain the divergent results of previous investigations and the findings presented in this paper we propose that orthostatic tolerance has a bimodal distribution of susceptibility to orthostatic hypotension within the general population. Figure 19 illustrates this conceptual model for syncopal tendency plotted against some measure of fitness. The model suggests that an inverse bell shape represents individuals susceptible to orthostatic intolerance (OIT), with individuals at the extremes of fitness being more prone to OIT.

**THEORETICAL MODEL**

**SYNCOPE - FITNESS**

![Graph showing the inverse bell shape model of fitness and syncope.](#)

**FIG. 19.** A proposed model of fitness and syncope.

In Figure 20 we have plotted the data for the pre-trained subjects. Note that outliers exist on either side of the curve that tend to have an increased susceptibility to OIT.
FIG. 20. Theoretical model for syncope, with subject pre-training data (N=7).

The subject on the far left of the graph was our least fit subject, and had the lowest blood volume. His mechanism of OIT may have been a hypovolemic hyperadrenergic state as defined by Blomqvist (22). Following the training program his blood volume expanded but he was still less tolerant than his pre-training state. The reason for his exacerbated OIT may be, that although he was functionally volume expanded he was still relatively hypovolemic based on his predicted blood volume. Training may have resulted in an alteration of venous compliance and attenuated baroreflexes making him more prone to OIT and subsequently functionally hypoadrenergic during LBNP. We have noted that the vasoconstrictor ability of ET individuals was less than that
of their UT counterparts. The subject on the far right was our most fit subject (based on \( \dot{V}O_{2\text{max}} \)) and had the highest pre-training blood volume yet, was equally as intolerant as our least fit subject. The mechanism behind his OIT may be related to a hypoadrenergic response (22) with a further contributory influence of the cardiopulmonary baroreceptors inhibiting the high pressure baroreceptors, as reported recently by Pawelczyk and Raven (156).

In general, most subjects fall in the middle of the hypothetical model and the mechanisms of exercise training induced orthostatic intolerance appears to be related to a combination of a more marked LBNP induced central hypovolemia and an attenuated sympathetic vasoconstrictor response.

Summary and Directions for Future Research:

In summary, the major findings of the present investigation were that: i) Eight months of endurance exercise training reduced orthostatic tolerance as determined by LBNP to presyncope; ii) Stepwise linear regression identified that the major factors to significantly predict the decreased orthostatic tolerance pre- to post-training were a reduced response of PVR to LBNP from -15 to -45 torr, the change in total blood volume, and the greater post-training reduction in SBP to LBNP from 0 to -45 torr; iii) Endurance exercise trained athletes did not exhibit any changes in DBP during LBNP suggesting a
hypoadrenergic response to LBNP; iv) Endurance exercise training altered the gain of various baroreceptor populations, i.e. the gain of the HPBR to infusions of PE was attenuated, and the attenuated bradycardic response appeared related to a limitation of cardiac interval to continue to prolong without the development of dysrhythmias. In addition the gain of the cardiopulmonary reflex was also attenuated post-training and was related to the increase in blood volume associated with training; and v) The ET individuals had an increased parasympathetic activity at rest as defined by examining the heart rate under the various blockade conditions. This elevated parasympathetic tone appeared associated with depressing the normal cardiovascular adjustments that occurred during LBNP. These data suggest that physiologic adaptations associated with the increased \( \dot{V}_{O_{2\text{max}}} \) and TBV resulting from a prolonged endurance exercise training program can alter the reflex control of vasomotion and cardiac output during LBNP and reduce the LBNP tolerance.

These data implicate alterations in autonomic regulation induced by training as important features of blood pressure regulation. A logical next step would be to analyze atropine and metoprolol blockade kinetics to determine end organ changes in vagal tone. We are currently working on this aspect. In an animal model the biochemistry of muscarinic receptors could be examined, secondary to the
effects of exercise training. The future looks good for those with a molecular interest.
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