Aerobic Fitness and Orthostatic Tolerance: Evidence Against an Association

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Introduction

When humans stand, the force of gravity (one g) promotes pooling of blood in the lower extremities. This reduces the return of venous blood to the heart and produces an *orthostatic challenge* to the cardiovascular system. Higher gravitational forces, in the head-to-foot direction, are commonly experienced by Navy and Air Force personnel and astronauts for relatively brief periods during high-speed maneuvering of sophisticated jet fighters and during launch and reentry of manned space craft.

The reduction in venous return to the heart during gravitational stress results in a lowering of cardiac output through Frank-Starling mechanisms, which can often lead to a decrease in blood pressure. If cardiac output and blood pressure are not adequately maintained, reduced perfusion of the cerebral circulation may lead to a loss of consciousness (syncope). This response in flight could be catastrophic. Thus, the high level of interest by the military and NASA in understanding gravitational stress responses and identifying physiologic situations and pharmocologic manipulations which alter individual tolerance to gravitational stress is well understood.

The two primary mechanisms whereby adequate cardiac output and blood pressure are maintained during orthostatic stress are by reflex activation of the autonomic nervous system and by contraction of skeletal muscles in the lower extremities (the *skeletal muscle pump*). During many types of orthostatic challenge, the skeletal muscles are inactive (i.e., passive head-up tilt, lower body negative pressure [LBNP]) and acceleration stress in pilots and astronauts. To lessen the pooling of blood in the lower body, flight personnel routinely employ compression trousers to *squeeze* pooled blood back to the central circulation.

The second major mechanism that is engaged to compensate for reductions in central blood volume and blood pressure is mediated through the autonomic nervous system. Baroreceptors are located in the carotid and aortic blood vessels in the arterial circulation and are located in the heart and great veins on the low pressure side of the circulation [20, 21]. These receptors respond to blood pressure and blood volume changes and initiate reflex increases in heart rate, cardiac contractility, and peripheral vascular tone.

This presentation will focus on only one side of the debate as to whether high levels of aerobic fitness have a deleterious effect on tolerance to gravitational stress. This issue was raised in the early 1970's as a result of two research publications. The first was work reported by Stegemann *et al.* [31] who studied the carotid sinus baroreflex of humans with an airtight chamber that surrounded the head and neck. The steady-state reflex changes in blood pressure that were recorded 3 minutes after application of the head and neck stimuli, were attenuated in an athletic group compared to a sedentary group of volunteers. A second report in the NASA literature by Luft *et al.* [18] indicated that five endurance-trained runners were less tolerant to LBNP than five nonrunners. These early research findings have stimulated a considerable amount of interest that

has lead to a growing number of research efforts seeking an association between aerobic fitness and orthostatic tolerance in humans. I will briefly review some of the more pertinent published research information which suggests that there is no relationship between aerobic fitness and orthostatic tolerance in humans.

Cross-Sectional Studies

Prior to 1970, the general belief was that orthostatic tolerance was greater in the athletic compared to the sedentary individual. Research findings as early as the 1920's suggested that, in general, athletes made better circulatory adjustments upon standing than did nonathletes [8, 33]. Supporting data were provided several decades later by Schvartz *et al.* [28], who studied the responses of 18 healthy subjects during head-up tilt testing. Syncope occurred in four subjects. Retrospective analyses revealed that those who experienced syncope could perform fewer sit-ups and pushups compared with 14 subjects who tolerated the tilt stress. These investigators concluded that conditioning of the upper body muscles was important for maintaining orthostatic tolerance. A subsequent study by these investigators in the early 1970's, included measurements of peak oxygen uptake to better evaluate fitness levels [29]. Twenty-eight men were stressed by passive standing and the frequency of fainting was noted to be less in the men who had higher aerobic capacities than those who were less fit.

However, the early belief that cardiovascular fitness was associated with improved orthostatic tolerance was questioned as early as 1940, when investigators were unable to find differences in the orthostatic tolerance of athletes and nonathletes [1, 22]. A large number of the recently published cross-sectional studies have failed to identify a significant statistical relationship between endurance capacity and tolerance to orthostatic stress. For example, Klein *et al.* [15] reported on a group of 12 athletes who, due to many years of intense physical training (long distance running, bicycling, or ice skating), had about a 50 percent higher maximum work capacity than 12 healthy students ($\dot{V}O_{2max}$ 65 vs. 44 $mL \cdot kg^{-1} \cdot min^{-1}$). The orthostatic tolerance to both a 20-minute, 90 degree head-up tilt and centrifugal (+Gz) forces were found to be identical between groups. Similar results have been reported in cross-sectional studies on female volunteers undergoing LBNP [14].

A somewhat different research approach was undertaken by Sather and colleagues [26], who determined the tolerance of 18 men, ages 29 to 51 years, to progressive LBNP that was continued until the onset of presyncopal signs (sudden hypotension or bradycardia) or symptoms (dizziness, nausea, discomfort). Subjects were then classified into high-tolerance (n=10) or low-tolerance (n=8) groups. Retrospective analyses indicated that there were no significant differences between the two groups when age, height, weight, percent body fat, total blood volume, and $\dot{V}O_{2max}$ were compared.

Similar results have been reported for 45 healthy women who underwent graded LBNP to 50 mmHg [11]. These women had peak aerobic capacities ranging from 23 to 55 $mL \cdot kg^{-1} \cdot min^{-1}$. There were six women who developed signs and symptoms of impending syncope during LBNP, but retrospective analyses indicted that their average $\dot{V}O_{2max}$ values did not differ from those of the 39 LBNP tolerant females. These authors concluded that orthostatic tolerance was not related to aerobic capacity.

In summary, these series of cross-sectional studies on both men and women employed orthostatic stresses with a presyncopal endpoint. These investigators were unable to draw a statistical relationship between orthostatic tolerance indices and aerobic capacity as measured by $\dot{V}O_{2max}$.

Convertino, Sather, *et al.* [6] applied multiple regression statistics to their previously reported data, which had been collected from 18 subjects, to derive a prediction model for LBNP tolerance. Numerous physical and physiological variables, including age, height, weight, $\dot{V}O_{2max}$, body fat, blood volume, arterial pulse volume, thigh fluid accumulation index, thigh compliance index, heart rate, stroke volume, cardiac output, mean arterial pressure, and peripheral resistance were included in their analyses. $\dot{V}O_{2max}$ did not correlate highly or significantly with the peak level of LBNP achieved prior to onset of presyncopal symptoms. The best predictive model for LBNP tolerance was achieved by including thigh fluid accumulation index, blood volume, and thigh compliance index in the regression model. The accumulation of fluid in the thigh was a major contributor (82 percent) to the prediction model. Based upon this model, the more accumulation of fluid in the thigh, the greater the predicted tolerance to LBNP. Blood volume provided a negative contribution to the prediction equation such that individuals with larger estimated blood volumes were less tolerant to the LBNP stress. Paradoxically, it is a well-known fact that blood volume is increased in endurance-trained athletes [23].

A recent study by Ludwig and colleagues [17] employed a different statistical modeling procedure in a retrospective analysis of 25 women and 22 men who had undergone centrifuge studies $\dot{V}O_{2max}$ ranged from 18 to 50 $mL \cdot kg^{-1} \cdot min^{-1}$. Two biostatistical modeling procedures (proportional hazard and logistic discriminant function) were used to estimate the risk of *gray-out* during centrifugation. Study variables included gender, age, weight, height, percent body fat, base-line heart rate, blood pressure, $\dot{V}O_{2max}$, and plasma volume. Only age, gender, height, and plasma volume significantly contributed to the risk equation. Tall young women with large plasma volumes were at increased risk for orthostatic intolerance. Tolerance to gravitational stress was statistically independent of aerobic fitness ($\dot{V}O_{2max}$).

Longitudinal Studies

Several longitudinal studies have been carried out in which orthostatic tolerance has been carefully assessed before and after an exercise training program. Cooper *et al.* [7] determined the orthostatic tolerance of 11 subjects to +Gz forces produced by centrifugation. These subjects were randomized to two groups: six exercisers and five controls. The exercising group engaged in a daily progressive running program for 3 months, while the controls were asked to avoid vigorous exercise. At the conclusion of the 3 months, the exercising group had increased their endurance capacity by 13 percent. Despite this, there were no significant differences noted between the two groups in their ability to tolerate gravitational stresses.

In a recently published longitudinal study [16], eight young male students underwent a 10-week aerobic exercise training protocol which consisted of alternating sessions on a treadmill and cycle ergometer. This program resulted in a 21 percent increase in $\dot{V}O_{2max}$ (45.7 to 55.2 $mL \cdot kg^{-1} \cdot min^{-1}$). Subjects underwent a presyncopal-limited LBNP test before and after training which consisted of progressive, 10 mmHg increases in LBNP until one of the following criteria was met: (1) a systolic blood pressure <70 mmHg or (2) a decrease of systolic blood pressure of >25 mmHg, diastolic blood pressure of >15 mmHg or heart rate of >15 b/min in two consecutive 1-minute readings. The increases in calf circumference and heart rate and the decreases in forearm blood flow and systolic pressure produced by LBNP were not different after training. Three indices of LBNP tolerance were derived: (1) duration of exposure to LBNP, (2) magnitude of negative

pressure at onset of presyncope and, (3) cumulative stress, determined by summing the products of the duration and pressure magnitude of each LBNP level. None of these indices of tolerance were altered following the 10-week training program. These authors concluded that there was no discernible adverse effect of improved aerobic capacity on orthostatic tolerance over a 10-week training period.

There have been several other longitudinal studies on orthostatic tolerance in which exercise training programs have been employed for as short as 8 days and for as long as 6 months [5, 9, 12, 27]. None of these studies have demonstrated an adverse effect of exercise training on orthostatic tolerance. Only a few of these longitudinal studies included running as the sole type of exercise training. Various combinations of running, bicycling, and weight training have generally been employed.

There is an increasing amount of reported data that suggests that weight training may improve orthostatic tolerance. This may be related to the ability of weight training to increase the muscle mass of the lower extremities that could reduce venous compliance and thereby diminish caudal blood pooling during orthostatic stress [4]. Strength training is also known to increase plasma volume and to preserve baroreceptor reflex function [13].

To summarize these series of studies, it seems clear that in a random population there is no relationship between $\dot{V}O_{2max}$ and orthostatic tolerance. Secondly, longitudinal aerobic training programs from as little as 8 days to 6 months do not adversely influence orthostatic tolerance, despite significant increases in $\dot{V}O_{2max}$. And finally, strength training may improve orthostatic tolerance. However, there are a number of limitations of these previously reported studies that I have overlooked to reach these general conclusions. For example, in many of the reported studies, the level of orthostatic stress was quantitated by measurements of calf blood pooling. This has been done with a strain gauge or an impedance system placed on a lower extremity. These measurements are in fact quite removed from the pressure sensing receptors within the thorax that initiate autonomic reflex responses. It would seem that to best match stresses between groups, a reliable measure of central hemodynamics such as central venous pressure or left ventricular end-diastolic volume should be employed. Moreover, the fluid and electrolyte balance of research volunteers has not been well controlled (if controlled at all). It is conceivable that the endurance-trained athlete comes to the testing lab in a state of hydration that differs from that of sedentary volunteers. Thirdly, the type of exercise employed to achieve aerobic fitness has not been well controlled in the published cross-sectional and longitudinal studies. The degree of blood pooling in the legs may be significantly influenced by the amount of muscle mass that surround and restricts expansion of the venous bed [4]. The aerobically fit individual who participates in bicycling, rope jumping, and weight lifting exercise may have a larger muscle mass in their lower extremities relative to the leg muscles of the endurance-trained runner. Finally, the measurement of aerobic capacity by $\dot{V}O_{2max}$ may have inherent limitations. Up to 75 percent of $\dot{V}O_{2max}$ is determined genetically while only 15 to 25 percent may be influenced by exercise training.

In the next section of this discussion, I will focus my comments on the autonomic nervous system and its role in orthostatic tolerance. Certainly the major mediators of acute cardiovascular adjustments to gravitational stress are the arterial and low-pressure cardiopulmonary baroreceptor reflexes [20, 21]. The arterial baroreceptor reflex modulates both cardiac output and peripheral resistance to maintain blood pressure [20]. An adequate reflex response to gravitational-induced preload reduction is essential for orthostatic tolerance. We have recently examined the cardiac limb of the carotid sinus baroreflex in high-fit and sedentary subjects [2]. This was done with an airtight neck chamber that fit about the anterior two-thirds of the neck. Brief controlled pressure

pulses were administered to the chamber to reduce the transmural pressure at the carotid sinus baroreceptor, and immediate heart rate responses were assessed. Steady state responses are difficult to interpret because as the neck stimulus is maintained blood pressure increases occur. This diminishes the transmural pressure change at the carotid sinus and also alters aortic baroreceptor stretch, such that the net effect in the steady state situation is due to a combination of opposing influences. We, and others [2, 25], have been unable to demonstrate a significant difference in the immediate reflex cardio-acceleration that occurs during carotid sinus hypotension in aerobically fit individuals, when compared to sedentary volunteers.

The arterial baroreflex regulation of vascular resistance has not been adequately compared in fit and unfit humans. When high levels of LBNP are applied to reduce systemic blood pressure and unload arterial baroreceptors, reflex increases in forearm vascular tone can be assessed by plethysmography. In one study, which compared endurance-trained swimmers and nonswimmers, no significant differences in reflex forearm vasoconstrictor responses were noted [10]. However, when endurance-trained football players were studied, reflex increases in forearm vascular resistance were reported to be greater than those recorded from sedentary controls [32]. In contrast, when LBNP was applied to individuals before and after a 12-week cycle exercise program, baroreflex-mediated forearm vascular resistance increases were reported to have decreased [34]. Finally, Raven *et al.* [24] reported that increases in peripheral vascular resistance provoked by LBNP were less in high-fit compared with average-fit individuals.

The low-pressure baroreceptors are located at the junction of the vena cava and the right and left atria, the pulmonary veins, and within the walls of the heart. These are stretch receptors that respond to small changes in intrathoracic blood volume and initiate reflex alterations in splanchnic and muscle vascular resistance to maintain arterial pressure [21]. The integrity of these receptors in the endurance-trained athlete is not clearly known. However, there is reason to believe that neural afferent traffic from these receptors may be altered in the endurance-trained state. For example, it is well known that high levels of aerobic fitness are associated with elevations of plasma and blood volume [23]. This may lead to chronic stimulation of the low-pressure baroreceptors and may alter their discharge pattern. Moreover, ventricular mass is increased in endurance-trained athletes and this may also alter the afferent profile from baroreceptors located within the ventricle. In fact, it has been demonstrated that when the low-pressure baroreceptors of athletes are stimulated by head-out water immersion, there is an attenuated diuresis and natriuresis compared with that noted from immersed nonathletes [3]. This may be due to a blunted cardio-renal reflex or reduced cardiopulmonary baroreceptor-mediated regulation of the renin angiotensin-aldosterone system. These receptors can also be unloaded by application of low levels of LBNP to specifically reduce cardiac filling pressures without lowering systemic blood pressure. There have been several published reports in which the reflex vasoconstrictor responses of trained and untrained individuals have been compared [19, 32, 34]. However, the study populations and research techniques differ and the reported findings are at odds such that no firm conclusions can be reached at this time.

I will not have the time nor space to pursue the possible role of vasoactive hormones in the response to orthostatic challenge in trained and untrained individuals. Changes in these vasoactive hormones occur gradually during orthostatic stress and may play a role during prolonged exposures to higher gravitational forces. However, they may not have an important role in the acute orthostatic responses (first 5 to 10 minutes) in humans.

To summarize the current data on autonomic control of the cardiovascular system, it appears that arterial baroreceptor reflex regulation of cardiac function is not impaired in the endurance-trained athlete. However, it is less clear whether the reflex regulation of peripheral resistance, which may

play an important role in orthostatic tolerance, is altered in the endurance-trained athlete. Future research on this subject should be designed to control for: (l) the type of exercise that is employed to obtain the aerobically fit state, (2) the age of the research volunteers, and (3) should include specific assessment of central hemodynamics during gravitational stress. Moreover, the state of hydration of research volunteers should be carefully controlled and quantitated prior to initiating orthostatic stress testing.

In summary, the ability to withstand orthostatic stress is a function of the reflex responses of the autonomic nervous system and the degree of pooling of blood in the lower extremities and splanchnic region. The data that I have reviewed in this publication strongly suggest that orthostatic tolerance is not linearly related to aerobic capacity. Moreover, baroreflex regulation of cardiac function does not appear to be adversely influenced by high levels of aerobic capacity.

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