Research Summary for:

NASA Grant NAG9-297
"Fitness, Autonomic Regulation and Orthostatic Tolerance"
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Work on this grant has consisted of two major studies of cardiovascular regulation in athletes along with several smaller supporting studies. This summary will give a brief overview of two major studies, and then conclude with an analysis of what the findings from these studies mean practically, and how they can be applied to current problems with post-flight orthostatic intolerance.

BACKGROUND

Orthostatic intolerance has been a consistent finding after spaceflight. The factors modulating the severity of this intolerance, however, have not been clear. Also, the adaptation leading to postflight orthostatic intolerance has been called "cardiovascular deconditioning", implying that exercise might help to prevent orthostasis. But the relationship between aerobic fitness and orthostatic intolerance is controversial. For example, the U.S. Air Force encourages its fighter pilots to avoid excessive aerobic training, out of a concern that it might reduce G tolerance. On the other hand, aerobic exercise is being studied as a possible countermeasure for the orthostatic intolerance seen after spaceflight.

To deal with this controversy, this project had two main goals. One was to determine whether aerobically trained individuals do indeed have greater orthostatic intolerance, and if so, what are the mechanisms. The second was to determine the differences between those individuals with orthostatic intolerance and those without, to see if any mechanisms for the intolerance could be elucidated. Dr. Benjamin Levine at UT-Southwestern was the leader of the team performing the studies done for this project.

STUDY 1: CROSS-SECTIONAL STUDY OF ORTHOSTATIC INTOLERANCE IN HIGHLY AEROBICALLY TRAINED INDIVIDUALS

(see enclosed paper Levine et al. "Physical Fitness and Cardiovascular Regulation: Mechanisms of Orthostatic Intolerance" for complete data.)

The first study was a cross-sectional study of individuals with varying degrees of fitness. Three groups were identified, a high fit group (Max. VO2=60 ml/min/kg), a mid-fit group (Max. VO2=48.9 ml/min/kg) and a low-fit group (Max. VO2=35.7). The large range of fitness levels allowed for correlations to be drawn between fitness and various cardiovascular variables--including orthostatic intolerance. Graded lower body negative pressure (LBNP) was used to measure orthostatic tolerance, and as a test of cardiovascular regulation. Cardiac output, stroke volume, heart rate, blood pressure, arm flow, plasma volume and maximal leg

conductance were measured during supine rest. The changes in cardiac output, stroke volume, heart rate, blood pressure, and arm flow were measured during LBNP.

Baroreceptor function was measured two ways. A neck collar made of silastic was placed around the neck to stimulate the carotid baroreceptors. A short R-wave triggered protocol during held expiration was used to measure "open-loop" baroreceptor function, and a prolonged (2 minute) protocol using random sequence of negative and positive pressures was used to measure "closed-loop" gain. The "open-loop" procedure and equipment used for the baroreflex testing was the same as the one used after Shuttle flights as part of DSO #467.

The study produced several interesting results. The highly fit individuals did have lower orthostatic tolerance, when compared to the mid and low fit subjects together (LBNPxtime=1175 mmHg-min high-fit, 2003 mid-fit, 1883 low-fit). But, orthostatic tolerance (as measured by LBNP) did not correlate with VO2. A multivariate function predicting tolerance was developed, and it included terms both related and unrelated to physical fitness. This indicates that orthostatic tolerance is a complex function of many different variables, and that no linear relationship between fitness and orthostatic tolerance exists. It is also clear, however, that orthostatic tolerance is not better in the fit individuals, which calls into question using regular aerobic training to counter orthostatic intolerance.

The baroreceptor data was also intriguing. Typically, the baroreceptor curves use R-R interval as the dependent variable. Differences in R-R interval can be expected since the fit individuals will have lower heart rates. This change in baseline heart rate does not necessarily reflect a change in baroreflex responsiveness. The important consideration, when investigating orthostatic intolerance, is what would the change in blood pressure be for a given change in heart rate. Since a fit individual also has a greater stroke volume than an unfit one, the same heart rate change will lead to a much greater change in cardiac output in the fit person. To compensate for this, the baroreceptor curves were plotted in a novel way, using the effective change in blood pressure (the triple product of heart rate, stroke volume and total peripheral resistance) as the dependent variable. No differences in baroreceptor function between groups were seen, but "closed-loop" gain of the carotid baroreceptor did correlate with orthostatic intolerance.

Although fitness was not a strong predictor of orthostatic tolerance, the data could be analyzed in a different way. How did the subjects who did experience pre-syncope differ from those who did not? When this analysis was done, one striking finding emerged (Figure 1). The people who did have pre-syncope not only had a greater stroke volume, but had a greater decrease in stroke volume during LBNP. This suggested that the fainters were having a greater

decrease in filling pressure than the non-fainters. Could this be due to a difference in ventricular compliance between the groups?

STUDY #2: VENTRICULAR PRESSURE/VOLUME RELATIONSHIPS IN ATHLETES (see enclosed paper Levine et al. "Left Ventricular Pressure/Volume and Frank/Starling Relations in Endurance Athletes: Implications for Orthostatic Tolerance and Exercise Performance" for complete data.)

The question about compliance led to the second major study on this grant. Perhaps there is another, less studied, mechanism behind the orthostatic intolerance seen in very highly aerobically trained individuals. Differences in myocardial compliance between highly fit and unfit individuals would led to strikingly different Frank-Starling relationships. The highly fit athlete not only has a larger resting stroke volume than the non-athlete, but is also able to increase stroke volume during exercise to a greater extent than the non-athlete. This suggests that the athlete's heart operates on the steep portion of the Starling curve. While this may be an advantage during exercise, allowing for greater increases in stroke volume for a given change in filling pressure, this could also be a major disadvantage during orthostatic stress. Stroke volume would drop to a greater degree with a fall in filling pressure.

To test this hypothesis, two groups of subjects were studied. One consisted of highly trained endurance athletes (Max. VO2=68 ml/min/kg), and the other sedentary subjects (Max. VO2=41 ml/min/kg). Left ventricular end-diastolic pressure was measured with a Swan-Ganz catheter. This pressure was varied using two interventions, lower body negative pressure to -15 and -30 mmHg, and saline infusion at 15ml/kg and 30ml/kg. Cardiac volume was measured with two techniques. Stroke volume was calculated from acetylene rebreathing cardiac outputs and end-diastolic volume was calculated from echocardiography.

The results from this study are shown in Fig. 2. The fit subjects have a much greater change in stroke volume for a given change in pulmonary capillary wedge pressure. The echocardiographic data produced the same result; the athletes had greater decreases in end-diastolic volume with LBNP. The athletes also had significantly less orthostatic tolerance as measured by LBNP. This suggests that basic cardiac structural differences (i.e. a change in myocardial compliance) may be significant contributors to orthostatic tolerance.

CONCLUSIONS AND RELEVANCE

Orthostatic intolerance and aerobic fitness

In both these studies, the fit individuals had diminished orthostatic tolerance compared to unfit controls. This supports the data from many other studies showing a decrease in orthostatic intolerance with aerobic fitness. It is significant, however, that this is not a simple, linear relationship. The interactions between orthostatic tolerance and fitness are complex, many highly fit individuals have excellent tolerance, while many unfit subjects pass out easily.

Nevertheless, several inferences can be made. While proscribing aerobic exercise for astronauts in space or on the ground would be excessive, using regular intense aerobic exercise as a countermeasure for orthostatic intolerance does not make sense. The relationship between fitness and orthostatic tolerance may be U shaped. Very highly fit subjects are on the steep portion of the Frank-Starling relationship, moderately fit subjects have the best tolerance, and very unfit subjects (such as would occur after bedrest or spaceflight), like the highly fit subjects, also have hearts on the steep portion of the Starling curve. In the very unfit subject, plasma volume and stroke volume are so low that very small changes in filling pressure would lead to orthostatic instability. This may explain why the bouts of maximal exercise proposed by Convertino are effective during bedrest in reducing post-bedrest orthostatic intolerance. The bed-rested subjects may experience a transient increase in plasma volume and stroke volume after the exercise thereby moving "up" the Frank-Starling curve.

Extensive, regular aerobic conditioning in space may be useful for bone or muscle atrophy, and for maintaining endurance, but not for combatting orthostatic intolerance. This does not mean that exercise itself has no role, since static exercise and bouts of maximal aerobic exercise (as mentioned above) have been shown to improve orthostatic tolerance.

Mechanisms of orthostatic intolerance

Often, studies on orthostatic intolerance focus on differences in cardiovascular regulation. Various tests have been used to study the heart rate, cardiac output and peripheral responses to orthostatic stress to see if the response is blunted. For example, the first study in this series used extensive measurements of baroreceptor function to test the hypothesis that baroreceptor responsiveness was impaired in the fit subjects. Despite this, no striking differences in baroreceptor function were noted between groups. This does not mean that the baroreceptors have no role, since closed loop gain did correlate with orthostatic tolerance, but does indicate that any orthostatic intolerance seen in fit individuals cannot immediately be ascribed to baroreceptor differences.

Another possibility to explain differences in orthostatic responses, could be a greater decreases in filling pressures with orthostatic stress. This can be ascribed to basic structural changes in the cardiovascular system (i.e. compliance of the myocardium), rather than a change in neurohumoral regulation. In athletes, this reasoning provides a very useful way of thinking about orthostatic intolerance. The Frank-Starling relationship shows that high stroke volumes during exercise and the large drop in stroke volume with standing are really two sides of the same coin. The shift in the athletes to the steep portion of the Starling curve provides an advantage during exercise and a disadvantage with orthostatic stress.

The athletes produced several structural changes in their cardiovascular systems. They have a greater blood volume at the same central venous pressure as unfit subjects, indicating a much greater venous capacity. Also, their maximal vascular conductance is greater, indicating a greater ability for vasodilation.

Analysis of baroreceptor function

One other result from the set of studies performed on this grant has been a new way to analyze baroreceptor function curves. Typically, R-R interval is plotted as a function of carotid distending pressure to produce a curve describing carotid baroreceptor function. R-R interval is used since it reflects the change in vagal outflow.

This approach has a problem when studying orthostatic intolerance in individuals with different resting values of heart rate, stroke volume and total peripheral resistance. Similar changes in R-R interval in two subjects with greatly differing levels of TPR, for example, would result in widely different changes in blood pressure. This means that to interpret the baroreflex curves, the effective change in blood pressure that would result from a change in R-R interval is important.

One limitation to this approach is the assumption that stroke volume and total peripheral resistance stay relatively constant during a baroreflex testing session. This was checked during a supporting study done as part of this grant. Stroke volume was measured using Doppler echocardiography during the sequence of R wave triggered changes in carotid distending pressure used in the studies. Stroke volume changed less than 5% during the baroreflex test (see enclosed abstract "The Effect of Carotid Baroreceptor Stimulation on Stroke Volume").

Overall, the approach of using the effective change in blood pressure proved useful in normalizing baroreflex curves for greatly different basal values of stroke volume and total peripheral resistance. Obviously, this is a simplified approach that applies an analysis more appropriate for steady flow to a system with pulsatile flow. Nevertheless, it does allow for more meaningful comparisons between groups, and has been used during a study of

changes in baroreceptor function with posture (see enclosed abstract "Effect of posture on the carotid baroreflex").

SUMMARY

The studies performed on this grant have provided new information about fitness and orthostatic intolerance. Orthostatic intolerance is more prevalent in highly trained athletes, but it is not a simple, linear function of VO2 max. The mechanism may have more to do with myocardial compliance, as reflected in the different Frank-Starling relationships (LV end-diastolic pressure vs. LV diastolic volume) between elite athletes and sedentary controls. These points are described in detail in the enclosed paper by Levine, "Regulation of central blood volume and cardiac filling in endurance athletes-utilization of the Frank-Starling mechanism as a determinant of orthostatic tolerance."

Publications from NASA Grant NAG9-297

Papers:

Levine BD, Buckey JC, Fritsch JM, Yancy CW, Watenpaugh DE, Snell PG, Lane LD, Eckberg DL, Blomqvist CG: Physical fitness and cardiovascular regulation: mechanisms of orthostatic intolerance. J. Appl. Physiol. (in press).

Levine BD: Regulation of central blood volume and cardiac filling in endurance athletes-utilization of the Frank-Starling mechanism as a determinant of orthostatic tolerance. Med. Sci. Sports Exer., 23, (in press).

Levine BD, Lane LD, Buckey JC, Friedman DB, Blomqvist CG: Left ventricular pressure/volume and Frank-Starling relations in endurance athletes: implications for orthostatic tolerance and exercise performance. Circulation (submitted).

Abstracts:

Levine BD, Buckey JC, Fritsch JM, Yancy CW, Watenpaugh DE, Eckberg DL, Blomqvist CG: Physical fitness and orthostatic tolerance: The role of the carotid baroreflex. Clin. Res. 36(3):295A, 1988.

Levine BD, Buckey JC, Fritsch JM, Yancy CW, Watenpaugh DE, Eckberg DL, Blomqvist CG: Physical fitness and cardiovascular regulation: orthostatic intolerance. Circulation, 80(4):II-291, 1989.

Levine BD, Buckey JC, Friedman DB, Lane LD, Watenpaugh DE, Blomqvist CG: Right atrial pressure (RA) vs. pulmonary capillary wedge pressure (PCW) in normal man. Circulation, 80(4):II-250, 1989.

Wright SJ, Levine BD, Blomqvist CG: Effect of posture on the carotid baroreflex. Circulation, 82(4):III-515, 1990.

Levine BD, Lane LD, Buckey JC, Friedman DB, Blomqvist CG: Ventricular pressure/volume relations in endurance athletes: non-autonomic determinants of orthostatic tolerance. Circulation, 82(4):III-694, 1990.

Levine BD, Pawelczyk JA, Buckey JC, Parra BA, Raven PB, Blomqvist CG: The effect of carotid baroreceptor stimulation on stroke volume. Clin. Res., 38(2):333A, 1990.

Figure 1

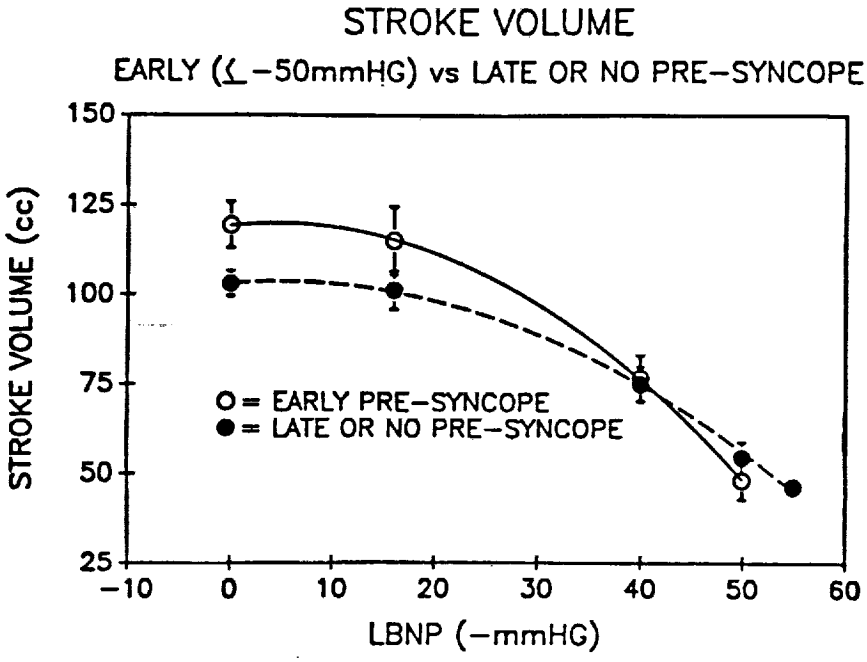

Figure 2