Does Training-Induced Orthostatic Hypotension Result from Reduced Carotid Baroreflex Responsiveness?

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Introduction

As manned space travel has steadily increased in duration and sophistication the answer to a simple, relevant question remains elusive. Does endurance exercise training (high intensity rhythmic activity, performed regularly for extended periods of time) alter the disposition to, or severity of, postflight orthostatic hypotension? Research results continue to provide different views; however, data are difficult to compare because of the following factors that vary between investigations:

- the type of orthostatic stress imposed (+Gz, lower body negative pressure [LBNP], head-up tilt);
- pretest perturbations used (exercise, heat exposure, head-down tilting, bed rest, water immersion, hypohydration, pharmacologically-induced diuresis;
- the length of the training program used in longitudinal investigations (days versus weeks versus months);
- the criteria used to define fitness; and
- the criteria used to define orthostatic tolerance.

Generally, research results indicate that individuals engaged in aerobic exercise activities for a period of years have been reported to have reduced orthostatic tolerance compared to untrained control subjects [9, 13, 15, 19, 22], while the results of shorter term longitudinal studies remain equivocal [5, 12]. Such conclusions suggest that chronic athletic training programs reduce orthostatic tolerance, whereas relatively brief (days to weeks) training programs do not affect orthostatic tolerance to any significant degree (increase or decrease).

Our laboratory has established a primary objective to identify the alterations in blood pressure control that contribute to training-induced orthostatic hypotension (TIOH). Although any aspect of blood pressure regulation is suspect, current research has been focused on the baroreceptor system. Reductions in carotid baroreflex responsiveness have been documented in exercise-trained rabbits [6], reportedly due to an inhibitory influence from cardiac afferent (presumably vagal) nerve fibers that is abolished with intrapericardiac denervation [7]. The purpose of this investigation was to attempt to determine if similar relationships existed in men with varied levels of fitness (using maximal aerobic power, $\dot{V}O_{2max}$, as the marker of fitness).

Methods and Procedures

Subjects

Volunteers were recruited from the Dallas-Fort Worth metropolitan area and local universities. Each prospective subject was informed of the nature and purpose of each procedure and was asked to provide written informed consent for the procedure. All procedures conformed to the Declaration of Helsinki and were approved by the Institutional Review Board at the Texas College

of Osteopathic Medicine. Screening procedures included a physical examination, resting 12-lead electrocardiogram, graded-exercise test to volitional fatigue for determination of metabolic responses to exercise, $\dot{V}O_{2max}$, and a resting echocardiogram. Subjects were classified according to $\dot{V}O_{2max}$ into one of three groups: low fit ($\dot{V}O_{2max}$ <40 mL•kg^{-1}•min^{-1}); mid fit ($\dot{V}O_{2max}$=50±2 mL•kg^{-1}•min^{-1}), and high fit ($\dot{V}O_{2max}$ >65 mL•kg^{-1}•min^{-1}). The groups of subjects reported diverse exercise histories. In the low-fit group, no subject engaged in regular exercise and all reported that their present jobs did not require any great amount of physical activity. To the contrary, all subjects in the high-fit group were trained athletes (competing in bicycle races) and trained 4 to 7 days per week for 1 to 3 hours each day, and traveled at least 150 miles (and as much as 450 miles) during a week of training. The mid-fit group encompassed elements of the low-fit and mid-fit group. Six of the eight subjects were recreational athletes, of these subjects all engaged in mixed modes of training (primarily running and weight lifting) approximately two to three times per week. The other two subjects did not engage in recreational sports, but maintained lifestyles that required some aerobic activity during the day.

Lower Body Negative Pressure (LBNP)

Venous return was reduced using graded LBNP distal to the subjects' iliac crests. Subjects were exposed to levels of LBNP at -5, -10,-15, -20, -35 and -50 torr, with each stage lasting 10 minutes. Heart rate and blood pressure were monitored continuously from the electrocardiogram and a radial artery, respectively. The final 5 minutes of the stage were reserved for assessments of carotid baroreflex responsiveness. Electromyographic activity of abdominal and quadriceps muscle groups was monitored continuously to ensure that each subject remained relaxed during the LBNP protocol, and the protocol was terminated if a subject demonstrated signs of lipothymia (derivation Greek: leipein - to fail, thymos - mind).

Central Venous Pressure

Hydrostatically-dependent peripheral venous pressure was determined on a separate day using an abbreviated version of the LBNP protocol outlined above using the *dependent arm* method of Gauer and Sieker [10]. Central venous pressure was estimated directly by zeroing the transducer to the subjects' mid-sternal line. In all experiments a prominent venous pressure wave form was observed, and venous pressure could be rapidly increased by performing a Valsalva's maneuver or passively elevating the subjects' legs.

Arterial Blood Pressure

Systolic, diastolic, mean, and pulse pressures were measured directly from a radial artery using a 1.1 mm OD, 3.2 cm Teflon catheter inserted by a collaborating anesthesiologist. Lidocaine (1 percent) was injected subcutaneously prior to catheterization to minimize discomfort. Blood pressure was transduced using a Hewlett-Packard system (Model 1280C transducer and Model 78205 amplifier) and was monitored in real time by computer. The signal to noise ratio of this system allowed us to resolve changes in pressure greater than 0.32 torr.

Carotid Baroreceptor Responsiveness

Carotid baroreflex control of heart rate and blood pressure was assessed using the rapid neck pressure and neck suction protocol outlined by Sprenkle *et al.* [20] using a malleable neck collar [8]. At least five trains with correlation coefficients between neck chamber pressure and R-R interval in excess of 0.80 were obtained during each stage of LBNP for later averaging and analysis. The neck pressure/suction system was controlled using custom software developed for a laboratory minicomputer (Digital Equipment Corporation MINC-23, Maynard, MA, with performance enhancements by Adcomp, Inc., Amesbury, MA). Beat-to-beat changes in blood pressure and heart rate were determined from computerized analysis of the radial artery pressure wave form and the ECG.

Data Analyses

Carotid baroreflex stimulus-response curves using either R-R interval or mean arterial pressure as the dependent variable were fit to a four-parameter logistic function described by Kent *et al.* [11] using the equation:

R-R interval or mean arterial pressure $A_1 \cdot \{1+e[A_2(\text{estimated carotid sinus pressure}-A_3)]\}-1+A_4$

where:
A_1 = the range of the response (maximum-minimum)
A_2 = a gain coefficient that is a function of carotid sinus pressure
A_3 = the carotid sinus pressure required to elicit equal pressor and depressor responses
A_4 = the minimum response of mean arterial pressure or R-R interval

Using this model, the operating, threshold, and saturation pressures for a baroreflex response can be determined. Carotid sinus pressure was estimated for each heart beat in the stimulus train as the difference of radial mean pressure and neck chamber pressure, assuming that neck chamber pressures were fully transmitted to the carotid sinuses. The gain (i.e., slope) of the carotid-cardiac and carotid-blood pressure baroreflexes was determined from the first derivative of the logistic function. Maximum gain was calculated as the gain at the neck pressure equal to parameter A_3, the centering point of the function. This point corresponds to the steepest slope of the stimulus-response curve. Mean arterial pressure or R-R interval data for the group during carotid baroreflex stimulation at each stage of LBNP were fitted to the function using nonlinear least squares regression (Statistical Analysis System, Cary, NC). Coefficients of determination (r^2) of the fitted lines ranged from 99.80 to 99.99 percent. The interaction of cardiopulmonary and carotid baroreceptors was then described by the relationship carotid baroreflex gain and central venous pressure, as central venous pressure was reduced using LBNP [14].

Results

Subjects

Characteristics of the subject groups are presented in Table 1. The groups were well matched for age, height, lean body mass, and resting blood pressure, but differed on several variables related to aerobic conditioning.

Table 1. *Physical characteristics of the subject groups*

	LF (n=8)	MF (n=8)	HF (n=8)	DIF
Age (yrs)	28.4±1.1	24.6±0.8	27.4±0.9	2
Height (cm)	179.1±2.0	179.6±2.3	181.1±1.7	
Weight (kg)	87.7±5.1	78.2±2.6	75.3±2.1	
LBM (kg)	68.0±2.8	68.7±2.1	67.3±1.6	
Resting HR ($beat \cdot min^{-1}$)	68.9±2.9	62.2±1.8	58.2±2.0	1,3
SBP (torr)	139.6±6.9	148.2±4.9	140.9±2.6	
DBP (torr)	70.9±4.1	69.4±2.8	72.6±2.5	
MAP (torr)	92.2±4.9	91.2±3.1	92.1±2.5	
EDD (cm)	4.8±0.1(3)	4.9±0.0(4)	5.4±0.1(6)	1,3
Blood Volume ($mL \cdot kg^{-1}$)	75.1±3.8	97.2±9.2	117.0±5.3	1,2
$\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	38.9±1.5	50.9±1.4	67.0±1.9	1,2,3

1. Significant difference between LF and HF groups, $p<0.05$.
2. Significant difference between LF and MF groups, $p<0.05$.
3. Significant difference between HF and MF groups, $p<0.05$. Values represent mean ±SEM. Numbers in parentheses=n when n≠8. HR=heart rate; SBP=systolic blood pressure; DBP = diastolic blood pressure; MAP=mean arterial pressure; EDD=end-diastolic dimension of the left ventricle; $\dot{V}O_{2max}$=maximal aerobic power.

$\dot{V}O_{2max}$ differed significantly between groups, as dictated by our screening efforts to define three distinct subject groups. Other hallmarks of aerobic conditioning (resting and maximal heart rate, heart size, and blood volume) were different between groups. As a whole, analysis of these variables suggested that the groups presented distinctly different autonomic and morphological characteristics associated with their training status.

Carotid Baroreflex Responsiveness

Results from logistic modeling of the neck pressure/suction data are summarized in Tables 2 and 3. The carotid-cardiac vagal reflex, using R-R interval as the response to a change in carotid transmural pressure, appeared to be enhanced by athletic training, since the A_1 (range) parameter was augmented in the high-fit group. As will be discussed, this conclusion may result from inappropriate representation of the data using R-R interval.

Table 2. *Effect of fitness of carotid baroreflex control of R-R interval*

	LF (n=8)	MF (n=8)	HF (n=8)	DIF
A_1	397±27	463±32	565±54	1
A_2	0.190±0.028	0.200±0.045	0.224±0.034	
A_3	106.4±2.6	104.8±2.6	93.7±2.0	
A_4	712±21	773±20	835±25	1,2,3
Threshold (torr)	93.9±3.3	89.7±3.1	80.5±4.5	
Saturation (torr)	118.9±2.4	119.9±2.7	113.0±4.5	
Operating Point (msec)	818±23	897±24	1027±32	1,2,3
Maximum Gain (msec•torr^{-1})	15.8±2.0	20.5±4.6	22.6±2.6	
Response at Threshold (msec)	797±20	871±20	954±33	
Response at Saturation (msec)	1029±24	1138±20	1280±33	1,2,3
Threshold-Saturation (msec)	232±16	267±18	326±31	1

1. Significant difference between LF and HF groups, $p<0.05$.
2. Significant difference between LF and MF groups, $p<0.05$.
3. Significant difference between HF and MF groups, $p<0.05$. Values represent mean ±SEM. A_1=maximum-minimum; A_2=gain coefficient; A_3=entering point; A_4=minimum response.

Table 3 suggests that a major difference between fitness groups lay in the ability to alter blood pressure when carotid sinus transmural pressure was changed. The range of responses was reduced significantly in the high-fit group compared to the other two groups. It is possible that this alteration may partially account for the TIOH reported in other investigations.

Table 3. *Effect of Fitness of Carotid Baroreflex Control of Blood Pressure*

	LF (n=8)	MF (n=8)	HF (n=8)	DIF
A_1	20.8±1.9	24.8±1.9	16.2±1.7	1,3
A_2	0.081±0.011	0.078±0.007	0.093±0.010	
A_3	95.9±5.0	110.9±3.7	88.8±3.1	2,3
A_4	106.6±2.5	102.4±1.7	100.3±1.7	1
Threshold (torr)	72.3±7.3	85.6±4.5	69.9±3.7	2,3
Saturation (torr)	119.6±3.7	136.1±5.6	107.8±3.6	2
Operating Point (torr)	96.5±2.6	95.8±1.7	91.4±1.8	
Maximum Gain	0.365±0.054	0.420±0.034	0.340±0.036	
Response at Threshold (torr)	102.2±2.4	97.1±1.8	96.9±1.6	
Response at Saturation (torr)	90.2±2.3	82.8±2.6	87.6±1.7	2
Threshold-Saturation (torr)	12.0±1.1	14.3±1.1	9.4±1.0	1,3

1. Significant difference between LF and HF groups, $p<0.05$.
2. Significant difference between LF and MF groups, $p<0.05$.
3. Significant difference between HF and MF groups, $p<0.05$. Values represent mean ±SEM. A_1=maximum-minimum; A_2=gain coefficient; A_3=centering point; A_4=minimum response.

Cardiopulmonary Receptor Modulation of Carotid Baroreflex Responsiveness

We hypothesized that reductions in cardiac filling pressure using LBNP would remove the inhibition of carotid baroreflex responsiveness normally exhibited by cardiopulmonary baroreceptors, leading to augmented carotid baroreflex gain.

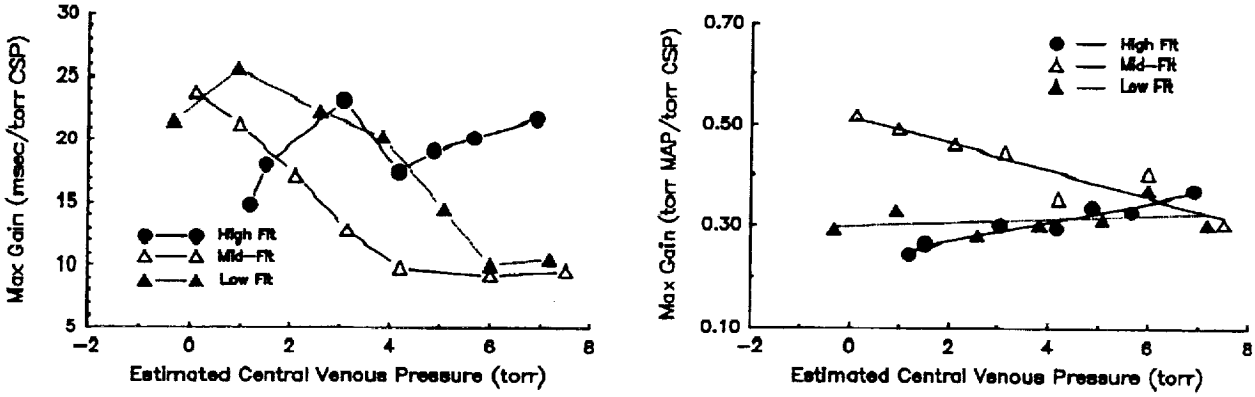

Figure 1. *Gain of the carotid-cardiac (1A) and the carotid-blood pressure (1 B), stimulus-curves when central venous pressure (CVP) was reduced using lower-body negative pressure (LBNP). In A, gain was inversely related to CVP in the LF and MF groups, Gain did not increase when CVP was reduced in the HF group. In B, gain decreased in the HF group when CVP was reduced, whereas it was unchanged in the LF group and increased in the MF group. The data suggest that an inhibitory influence from cardiopulmonary receptors on carotid baroreflex responsiveness is not removed by reducing central blood volume in the HF group. CSP=carotid sinus pressure; MAP=mean arterial pressure; LF=low fit; MF=mid-fit; HF=high fit.*

Figure 1 demonstrates that this relationship existed for the carotid-cardiac baroreflex in the low-fit and mid-fit groups, and for the carotid-blood pressure baroreflex in the mid-fit group only. Reflex gain consistently failed to increase, or actually decreased in the high-fit group during LBNP. Therefore, we were unable to eliminate cardiopulmonary receptor inhibition in the high-fit group by reducing central blood volume.

Discussion

We conducted this investigation to determine whether carotid baroreflex control of heart rate and blood pressure was different in men with varied levels of fitness (defined as $\dot{V}O_{2max}$). Furthermore, we hoped to determine whether any observed differences could be attributed to an inhibitory influence from cardiopulmonary mechanoreceptors. Changes in this regulatory system may potentially play a role in the changes in blood pressure regulation that are associated with space-flight cardiovascular deconditioning. Therefore, this discussion is divided into three sections: (1) carotid baroreflex control of cardiac chronotropism; (2) carotid baroreflex control of vascular resistance; and (3) the influence of cardiopulmonary receptors on carotid baroreflex responsiveness.

Carotid Baroreflex Control of Cardiac Chronotropism

Increases in carotid sinus distending pressure are well known to increase acetylcholine release at the sino-atrial node, hyperpolarizing pacemaker cells, and slowing the rate of phase four depolarization by reducing the permeability of *leak* membrane channels. The net result of this effect is to reduce the sino-atrial node firing rate, or increase the time required to the next depolarization. Based on this electrophysiologic point of view, some investigators have argued that the carotid-cardiac baroreflex is most properly described using the time interval between adjacent P waves of the ECG (or the analogous R-R interval) as a measure of the response to a baroreceptor stimulus.

Two points emphasize the problems with what Rowell termed, "this fallacious scheme" [16]: (1) The R-R interval scheme would indicate improved baroreflex responsiveness whenever heart rate was reduced [16]. Figure 2 illustrates that the relationship between R-R interval and heart rate is not linear; therefore, large changes in R-R interval are required to change heart rate by some increment if the initial heart rate is low. (2) The contribution of the carotid-cardiac baroreflex to maintaining blood pressure is more usefully described using heart rate rather than R-R interval, since heart rate is directly proportional to cardiac output and hence blood pressure.

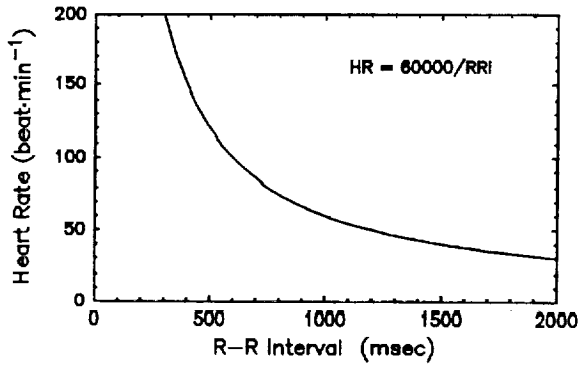

Figure 2. *Relationship between heart rate (HR) and R-R interval (RRI). The curve can be described by the relationship HR (beat•min^{-1})=60000/RRI (msec). Note that for a given change in heart rate, the change in R-R interval will be greater if the initial heart rate is low.*

Other investigators have reported that changes in R-R interval during neck suction or neck pressure are greater in endurance athletes [1]. When we expressed these data as changes in heart rate, no differences were apparent between groups other than the reduction in resting heart rate normally attributed to exercise training. Analysis of our data in this fashion revealed identical findings. Figure 3a represents modelled curves of the carotid-cardiac stimulus-response relationship for the three groups, using R-R interval as the dependent variable. The figure suggests, and statistical analysis of the parameters describing the curve (Table 2) corroborates, that the range and gain of the reflex is greater in the high-fit group. Figure 3b represents the same data using heart rate rather than R-R interval as the dependent variable. It is apparent, both visually and statistically, that no difference exists between groups other than the baseline heart rate.

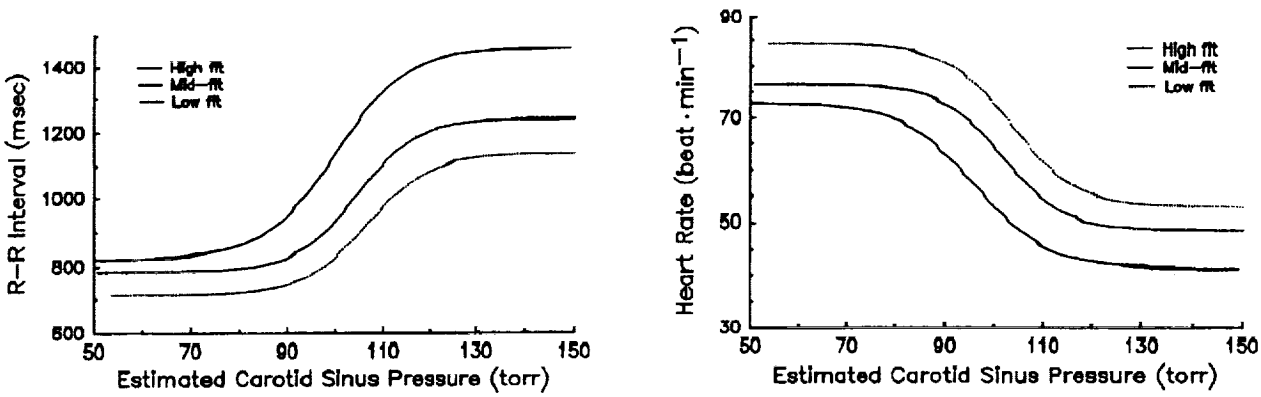

Figure 3. *Carotid-cardiac baroreflex with the response expressed as R-R interval (RRI, 3A) or heart rate (HR, 3B). A was generated using the model parameters in Table 1; B was generated from the data in A and the conversion formula in Figure 1. In A the range and slope of the curves are significantly different between groups, suggesting that the reflex response is enhanced proportionate to fitness level. In B there are no differences between groups in the slopes or ranges of the curves. Using this analysis, one would conclude that the reflex response is not different between curves, except for bradycardia proportionate to fitness level. LF=low fit; MF=mid-fit; HF=high fit.*

To summarize, although the changes in R-R interval due to neck pressure and neck suction were greatest in the high-fit group, the changes in heart rate were not different between groups. We concluded that the carotid-cardiac baroreflex plays no greater or more effective role in helping to maintain the blood pressure of endurance athletes.

Carotid Baroreflex Control of Blood Pressure

An unique aspect of this investigation was our ability to measure the blood pressure responses to rapid changes in carotid sinus distending pressure. It is likely that changes in the regulation of vascular resistance contribute more to alterations in orthostatic tolerance than do changes in the control of heart rate, since vascular resistance can be changed more widely during physiological stresses than can heart rate. For example, during exercise regional vascular resistance can decrease by as much as 20 to 30 fold, while heart rate can be altered only 3 to 4 fold [16].

While a reduction in carotid baroreflex control of arterial resistance has been well documented in endurance exercise trained rats [2, 23], only one published investigation has reported changes in carotid baroreflex control of blood pressure or vascular resistance in trained men [21]. However, the use of long pressure periods (3 minutes) that allows time for other mechanoreceptor reflexes to act and the use of full head enclosure that may affect blood pressure regulating oculomotor reflexes confound the interpretation of these data.

We sought to minimize these effects by examining the responses to *rapid* changes in pressure *applied to the neck only*. Our major finding, that changes in blood pressure to standardized changes in carotid sinus distending pressure, suggests that carotid baroreflex control of vascular resistance is less effective in endurance trained men. This finding is similar to findings reported by Stegemann *et al.* [21], measurements of muscle sympathetic nerve activity during LBNP in endurance trained men [18], and measurements of renal sympathetic nerve activity during experimental hemorrhage in exercise trained rabbits [7].

However, these data may be interpreted in an alternative fashion. If other baroreceptors (presumably those in the aortic arch) responded rapidly enough to oppose the systemic blood pressure *swing* we induced with rapid neck pressure/neck suction, then the decreased response we elicited in endurance athletes could be due to increased activity of aortic baroreceptors, rather than to reduced activity of carotid baroreceptors.

Recently Sanders *et al.* [17] suggested that aortic baroreceptors play a more dominant role in regulating muscle sympathetic nerve activity, and presumably vascular resistance, than carotid baroreceptors. Due to the anatomical location of aortic baroreceptors (i.e., relatively near the hydrostatic *indifferent* point of the body), aortic baroreceptors would sense little change in blood pressure in the transition from the supine to standing position. To the contrary, the upright posture should reduce carotid sinus blood pressure some 15 to 20 torr by changes in hydrostatic pressure alone; thus, carotid baroreceptors would seem better suited to sense a blood pressure *error signal* resulting from a postural change. Therefore, a suggestion of improved aortic baroreceptor responsiveness may be the hallmark of a baroreceptor system less able to sense changes in posture and less able to prevent orthostatic hypotension.

Influences of Cardiac Receptors on Carotid Baroreflex Responsiveness

An inhibitory influence of cardiac receptors on carotid baroreflex responsiveness has been documented in man and several animal species [3, 7, 24]. DiCarlo and Bishop [7] using rabbits were the first to demonstrate that this influence was augmented with endurance exercise training, since blockade of cardiac receptors with procaine injected into the pericardial sack restored the renal sympathetic nerve response to progressive vena cava occlusion. We hypothesized that progressive reductions in cardiac filling pressure using LBNP might alter cardiac mechanoreceptors such that carotid baroreflex responsiveness was improved.

Figures 1a and 1b suggest that the low-fit and mid-fit groups responded as hypothesized, since the gain of the heart rate or blood pressure baroreflex was inversely related to central venous pressure. However, neither the heart rate nor the blood pressure baroreflexes were improved during LBNP in the high-fit group, suggesting that inhibition was maintained despite reduced cardiac filling, and that the inhibition was not due to an augmented blood volume alone.

The nature of this inhibition remains poorly known. DiCarlo and Bishop could not remove the inhibition with reductions in cardiac filling pressure, lending support to our contention that training-induced expansions in blood volume caused increased inhibition. Perhaps the cardiac hypertrophy of endurance athletes stretched mechanoreceptive areas of the athletes' hearts in a manner not eliminated by volume changes alone. This speculative hypothesis deserves further examination.

Orthostatically-induced Lipothymia

Although the intent of this investigation was not to cause syncope, four subjects (two high-fit and two low-fit) experienced lipothymia. Considering the poor baroreflex control of blood pressure in the high-fit group, it is unlikely that similar physiological mechanisms precipitated lipothymia in the low-fit and high-fit subjects. Blomqvist [4] proposed that orthostatic tolerance could be broadly categorized according to adrenergic responsiveness and blood volume status. Based on this framework, and the data presented previously, we suggest that the high-fit subjects experienced a hypoadrenergic form of orthostatic hypotension, while the low-fit subjects

experienced a hypovolemic form of orthostatic hypotension. (As Table 1 illustrates, the blood volume of the low fit group, on a kilogram body weight basis, was more than one third less than the high-fit group).

The operational implications of these different forms of orthostatic hypotension, and the efficacy of countermeasures to ameliorate each form, are unknown. It is reasonable to hypothesize that a variety of countermeasures are available that affect orthostatic hypotension, but that specific countermeasures would act more preferentially on the hypovolemic or the hypoadrenergic variety. We suggest that orthostatic countermeasures, like exercise, should be prescribed individually. However, this approach will require future investigations to determine the sequelae of events that precipitate lipothymia.

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