Elevated central venous pressure:
a consequence of exercise training-induced hypervolemia?

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CONVERTINO, VICTOR A., GARY W. MACK, AND ETHAN R. NADEL. Elevated central venous pressure: a consequence of exercise training-induced hypervolemia? Am. J. Physiol. 258(0):R000-R000, 1990.-- Resting plasma volumes, and arterial and central venous pressures (CVP) were measured in 16 men before and after exercise training to determine if training-induced hypervolemia could be explained by a change in total vascular capacitance. In addition, resting levels of plasma vasopressin (AVP), atrial natriuretic peptide (ANP), aldosterone (ALD) and norepinephrine (NE) were measured before and after training. The same measurements of vascular volume, pressures and plasma hormones were measured in 8 subjects who did not undergo exercise and acted as controls. The exercise training program consisted of 10 weeks of controlled cycle exercise for 30 min/d, 4 d/wk at 75-80% of maximal oxygen uptake (VO_2max). A training effect was verified by a 20% increase in VO_2max, a resting bradycardia, and a 370-ml (9%) increase in blood volume. Mean arterial blood pressure was unaltered by exercise training, but resting CVP increased ($P < 0.05$) from 9.5 ± 0.5 mmHg before training to 11.3 ± 0.6 mmHg after training. The percent change in blood volume from before to after training was linearly related to the percent change in CVP ($r = 0.903$, $P < 0.05$). As a consequence of elevations in both blood volume and CVP, the volume-to-pressure ratio was essentially unchanged following exercise training. Plasma AVP, ANP, ALD and NE were unaltered. Our results indicate that elevated CVP is a consequence of training-induced hypervolemia without alteration in total effective venous capacitance. This may represent a

resetting of the pressure-volume stimulus-response relation for regulation of blood volume.

Key Words: venous pressure; arterial pressure; blood volume; venous capacitance; venous compliance; atrial natriuretic peptide; vasopressin; aldosterone; norepinephrine

INTRODUCTION

The increase in blood volume which accompanies exercise training is well documented [4,5,6,8,17,19]. However, the mechanism which allows volume within the vascular space to expand is unclear. One possibility is that total "effective" vascular capacitance, defined as the ratio of volume to pressure in the vascular space [9,16], may increase when blood volume is expanded without elevating central venous pressure (CVP). This would act to maintain a constant stimulus to right atrial receptors involved with the control of fluid-regulating hormones. The other possible scenerio is a chronically-elevated CVP in the face of greater blood volume perhaps by reducing the gain of the stimulus-response relation of volume regulating reflex mechanisms. To determine which of these possible explanations of exercise-training-induced hypervolemia might prevail, both volume and pressure of the vascular system must be measured. We are unaware of any study in which resting CVP has been measured before and after exercise training in man. Therefore, we measured mean arterial and central venous blood pressures before and after a period of endurance exercise training designed to increase blood volume. We hypothesized that exercise training would cause an increase in total vascular capacitance which would act to maintain constant CVP in the face of increased blood volume. Our results did not support our hypothesis and indicated that an increase in CVP without alteration in total vascular capacitance may represent a resetting of the pressure-volume stimulus-response relation for regulation of blood volume.

METHODS

Twenty-four healthy nonsmoking normotensive men, with a mean ($\pm$SE) age of 36 $\pm$ 1 yrs , a mean height of 177 $\pm$ 1 cm, and a mean weight of 80.5 $\pm$ 3.0 kg, gave written consent to participate in this study, which was approved by the Kennedy Space Center Human Research Review Board. Selection of subjects was based on a screening evaluation that consisted of a detailed medical history, physical examination, complete blood count, a battery of blood chemistry analyses, urinalysis, a resting and treadmill electrocardiogram, and pulmonary function tests. All subjects were relatively inactive at the time of the study as indicated by a mean maximal oxygen uptake (VO_2max) of 40.8 $\pm$ 0.9 ml/kg/min and never had participated in any formal endurance training program. Following selection, subjects were randomly assigned to either an exercise group (N = 16) that underwent 10 weeks of endurance exercise training, or a control group (N = 8) that maintained normal sedentary activities. The groups were matched for age, height, weight and VO_2max.

The exercise training program consisted of 10 weeks of cycle ergometer exercise in the upright posture for 30 min/day, 4 days/week at a work intensity calculated to be within the range of 70-80% of pre-training VO_2max. Training intensities were adjusted upward throughout the 10-week training period to maintain a constant training stimulus, which we estimated from

measurements of exercise heart rate. This technique has been demonstrated as a successful method of expanding blood volume [5].

Pre- and post-training measurements included VO_2max, and resting levels of total blood volume, mean arterial blood pressure and central venous pressure. In addition, resting levels of plasma arginine vasopressin, atrial natriuretic peptide, aldosterone, and norepinephrine were measured because of their association with blood volume homeostasis. All measurements were conducted at the same time of day and in the same sequence pre- and post-training. All subjects abstained from autonomic stimulants and did not exercise for 24 hours prior to each testing session.

VO_2max was determined using a graded protocol on a Quinton electronically-braked cycle ergometer. Mechanical power output was incremented by 67 W every 3 min until volitional exhaustion, and oxygen uptake (VO_2) was determined every 30 sec from measurements of expired O_2 fraction, expired CO_2 fraction, and minute ventilation (Beckman Metabolic Cart). Following the continuous graded test, subjects were allowed to rest for 5-10 min and then instructed to exercise at a power requirement 34 W greater than that attained at the end of the graded exercise test. This testing procedure was continued until VO_2max could be identified by a plateau in VO_2, i.e., no increase in VO_2 despite an increase in power requirement.

Plasma volume was determined using a modified Evans blue dye dilution technique [15]. After each subject was stabilized in the supine position for 30 min, an intravenous injection of 11.5 mg of dye diluted with isotonic saline solution (2.5 ml) was administered. The dye from a 10-min post-injection blood sample, recovered from the plasma with a wood-cellulose powder (Solka-Floc SW-40A) chromatographic column, was compared with a standard dye solution at 615 nm with a spectrophotometer. Total blood volume was calculated from the plasma volume and peripheral venous hematocrit measurements. Using these procedures in our laboratory, test-retest correlation coefficient for blood volume was 0.969 (N = 12) and the day-to-day variation was 82 ml (1.5%, N = 17) over 4 days, 75 ml (1.5%, N = 19) over 8 days, and 56 ml (1.1%, N = 23) over 15 days [15]. Blood volume was measured in all of the exercise subjects but only in four of the control subjects due to a limited supply of Evans blue dye.

Resting systolic (SBP) and diastolic (DBP) arterial blood pressures were measured non-invasively from the left arm with an automated system which included a microphone-containing cuff of an automatically-inflating sphygmomanometer. Mean arterial pressure (MAP) was calculated by dividing the sum of SBP and twice DBP by three. Central venous pressure (CVP) was determined by the method of Gauer and Sieker [13,18] using the measurement of peripheral venous pressure (PVP). This method requires the subject to lie in the right lateral decubitus position with the right arm dependent. Using this procedure in our laboratory, we

have demonstrated that changes in PVP recorded from a catheter in an antecubital vein of the dependent limb accurately reflects changes in CVP [18]. Resting PVP was monitored continuously for 2 min with a Statham model PD23 ID pressure transducer and recorded on a two-channel chart recorder. With the subject in the lateral decubitus position, the transducer was positioned at the level of the mid-sternum and was calibrated with a water-filled manometer such that a full scale deflection (100 divisions) corresponded to 15 mmHg. Care was taken to use a specially-designed ruler and level to ensure accurate, repeatable location of the transducer for subsequent CVP determinations. Two orientation sessions prior to pre-training evaluations were used to familiarize the subjects with all testing procedures and ensure that they were comfortable and relaxed during the actual experiments. We used the data collected from 6 control subjects during pre- and post-testing sessions to examine the test-retest reliability of the resting CVP determination. The intraclass correlation coefficient (r) for the test-retest reliability of resting CVP was 0.86 (P < 0.05) and there was a day-to-day variation over 10 weeks of 0.36 ± 1.29 mmHg (3.2%).

Antecubital venous blood samples were taken without stasis during the postinjection Evans blue dye sampling. Radioimmunoassay procedures were used to analyze plasma for arginine vasopressin (AVP, Instar Nuclear Corp.), atrial natriuretic peptide (ANP, Peninsula Laboratories, Inc.), and aldosterone (ALD, Diagnostic Products Coat-a-count Method). Plasma concentrations of

norepinephrine (NE) were measured by high performance liquid chromatography.

Significant effects of training (pre- vs post-training) were determined by analysis of variance for repeated measures, with significance established at the 0.05 level. We pooled the data from the second orientation test and the pre-training test to characterize the resting venous pressure before training. We were able to obtain a complete set of data on resting venous pressure before and after training on 21 of the original 24 subjects. Thus, statistical analysis of venous pressure was performed on only 21 subjects (14 exercise and 7 control subjects).

RESULTS

Ten weeks of exercise training increased VO_2max by 20%, caused a resting bradycardia, and induced a 9% increase (P < 0.05) in total blood volume from 63.6 ± 2.1 to 69.3 ± 2.8 ml/kg in the exercise group (Table 1). The hypervolemia represented a 370-ml increase in total blood volume. Mean arterial blood pressure was unaltered by exercise training, but resting CVP increased (P < 0.05) from 9.5 ± 0.5 mmHg before training to 11.3 ± 0.6 mmHg after training. As a consequence of increases in both blood volume and CVP, the volume-to-pressure ratio was essentially unchanged (P > 0.05) following exercise training (Table 1). The percent change in blood volume from before to after training was linearly related to the percent change in CVP (Fig. 1, r = 0.903,

P < 0.05).

VO_2max and resting levels of total blood volume, heart rate, MAP, and CVP were not changed significantly over the 10-week period of normal activity for the control group (Table 1).

Resting plasma concentrations of AVP, ANP, ALD and NE were unchanged after 10 weeks of training in both trained and control subjects (Table 1).

DISCUSSION

We measured blood volume, MAP, CVP, and hormones associated with fluid homeostasis before and after a 10-week exercise training program which increased aerobic capacity by 20% to test the hypothesis that hypervolemia induced by exercise training results from an increase in total vascular capacitance without changing CVP. The main finding of this study was that the 370-ml expansion of blood volume following 10 weeks of exercise training by our subjects was associated with a 19% (1.8 mmHg) increase in resting CVP. The magnitude of the blood volume expansion in our subjects was similar to that reported in previous studies [4,5,6,19]. Although the measurement of blood volume represents that volume distributed throughout the total vascular space, it seems reasonable that the increased volume was probably distributed on the venous side of the vascular space since the veins represent a more compliant reservoir for blood compared to

the arteries [22], and mean arterial pressure was not altered by the blood volume expansion while CVP increased. If our assumption is valid, the unchanged volume-pressure ratio can be interpreted as an unaltered total venous capacitance following this type and duration of exercise training.

The repeatability in resting blood volumes and CVP in control subjects is an important finding for two reasons. First, it demonstrates the constancy of blood volume and CVP in normal healthy human subjects when measured under standardized experimental conditions. Second, it indicates that the increases in blood volume and CVP observed in the subjects who underwent exercise training were the result of physical training rather than some factor associated with consistent methodological error. Our data may be the first to demonstrate in healthy humans that an elevation in resting CVP is part of the cardiovascular adaptation associated with exercise training-induced hypervolemia.

Acute expansion of central blood volume and elevation of CVP have been associated with the suppression of AVP [14,20] and the secretion of ANP [25], although the role of these stimuli on the low pressure side of the circulation for control of AVP secretion has been recently challenged [7,21]. These hormonal responses induce diuresis and natriuresis that act to restore both volume and pressure to baseline levels. The chronic elevation in resting CVP coincident with blood volume expansion induced in our

subjects by exercise training may suggest an attenuation of the stimulus-hormone response relation, thus allowing elevation of pressure without inhibiting volume retention and expansion. This relationship was supported by our observation that there were no alterations in resting levels of plasma AVP and ANP despite elevated blood volume and CVP in our subjects after training.

The notion that endurance exercise training attenuates the hormone response to a given central blood volume/CVP stimulus is not without precedent. Freund et al. [12] showed that trained subjects exhibited a blunted AVP depression and diuresis following water drinking compared to their untrained counterparts, although there were no differences between the groups in ANP response. Greater water conservation, i.e., reduced diuresis, and less AVP inhibition in endurance-trained athletes compared to sedentary subjects during water immersion [1,3,24] provides further support that the sensitivity of the pressure-volume relation of cardiopulmonary receptors is attenuated by increased aerobic capacity. Further, exercise training in our subjects reduced baroreflex control of forearm vascular resistance [17], suggesting a reduction of the stimulus-response relation of mechanoreceptors that are sensitive to changes in central blood volume and CVP.. However, our data may be the first to demonstrate that endurance exercise training can chronically elevate resting CVP without altering hormones associated with fluid homeostasis, thus providing a mechanism for expanding vascular volume without changing total venous capacitance.

With elevated central venous pressure, the pressure gradient to the heart is increased and the venous return is greater at a given right atrial pressure [22]. This relationship may explain why expanding blood volume increases stroke volume during exercise [10,11] and why reduced stroke volume during exercise following detraining was reversed to training levels by acute expansion of blood volume to a level similar to the trained state [4]. Further, hypervolemia induced by exercise training in our subjects was associated with greater stroke volume at a given level of lower body negative pressure [8]. The physiological benefit of chronically-elevated CVP associated with exercise-training-induced hypervolemia may reside in greater pressure gradients to enhance cardiac filling and increase stroke volume in the face of lower heart rates observed in trained individuals during exercise and orthostasis.

Exercise training caused a significant reduction in total calf compliance of our subjects [8]. We measured calf compliance as defined by the ratio of change in calf blood volume per unit change in distending pressure induced by an occlusion cuff. The major fraction of the calf volume changes during venous occlusion can be attributed to filling. of the deep veins [2], suggesting that exercise training probably decreased regional venous compliance. However, the slope of the relationship between the change in blood volume and the change in CVP from pre-to-post training represents an estimate of total vascular compliance

[9,16], and averaged 2.6 ml/mmHg/kg in our subjects which is similar to the value of 2.1-2.3 ml/mmHg/kg reported by Echt et al. [9] and London et al. [16]. Our results demonstrate that exercise training can alter regional vascular compliance without affecting total vascular compliance and capacitance, emphasizing an apparent dissociation between these two characteristics of the veins [23].

In summary, we demonstrated that exercise training elevates resting CVP as a consequence of blood volume expansion without altering total vascular capacitance. Further, exercise training can cause regional changes in vascular compliance independent of vascular capacitance. The maintenance of a chronically expanded blood volume at elevated CVP may represent a resetting of the pressure-volume stimulus-response relation for regulation of blood volume.

ACKNOWLEDGEMENTS

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TABLE 1. Maximal oxygen uptake (VO2max), resting heart rate, total blood volume, and resting levels of mean arterial pressure (MAP), central venous pressure (CVP), volume/CVP ratio, plasma arginine vasopressin (AVP), plasma atrial natriuretic peptide (ANP), aldosterone (ALD), and norepinephrine (NE) before and after exercise training.

VARIABLES	EXERCISE GROUP (N = 16)		CONTROL GROUP (N = 8)	
	BEFORE	AFTER	BEFORE	AFTER
VO2max, liters/min	2.97 ± 0.11	3.55 ± 0.11 *	3.11 ± 0.12	3.11 ± 0.14
Resting Heart Rate, bpm	63 ± 3	57 ± 2 *	58 ± 3	56 ± 3
Blood Volume, liters	5.04 ± 0.15	5.42 ± 0.19 *	5.45 ± 0.16 †	5.55 ± 0.17 †
Resting CVP, mmHg	9.5 ± 0.5	11.3 ± 0.6 *	11.2 ± 1.0	10.8 ± 1.3
Resting MAP, mmHg	92 ± 2	92 ± 2	95 ± 5	93 ± 4
Volume/CVP Ratio, ml/mmHg	544 ± 21	503 ± 28	507 ± 49 †	536 ± 65 †
Resting Plasma AVP, pg/ml	1.4 ± 0.3	1.2 ± 0.1	1.0 ± 0.1	1.1 ± 0.1
Resting Plasma ANP, pg/ml	23.1 ± 2.1	22.8 ± 1.1	29.5 ± 2.3	26.4 ± 1.4
Resting Plasma ALD, pg/ml	6.7 ± 0.8	7.5 ± 0.9	6.1 ± 1.3	5.5 ± 0.8
Resting Plasma NE, pg/ml	260 ± 21	234 ± 23	247 ± 34	271 ± 28

Values are mean ± SE; * $P < 0.05$ compared to before value; † N = 4.

FIGURE LEGENDS

Figure 1. Relationship between percent change in total blood volume and percent change in central venous pressure (CVP) before and after the 10-week exercise training period in exercise (open circles, N = 14) and control (closed circles, N = 4) subjects. The linear regression equation for best fit was $y = 3.76x - 12.2$ and the correlation coefficient was $r = 0.903$ ($P < 0.05$).