Journal of the American College of Cardiology
© 1999 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 35, No. 1, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(99)00530-6

Contracted Plasma and Blood Volume in Chronic Heart Failure

Matthew S. Feigenbaum, PHD,† Michael A. Welsch, PHD,† Matthew Mitchell, MS,* Kevin Vincent, MS,* Randy W. Braith, PHD,* Carl J. Pepine, MD, MACC*

Gainesville, Florida; Greenville, South Carolina; Baton Rouge, Louisiana

OBJECTIVES The purpose of this study was to determine if long-term pharmacotherapy mediated changes in intravascular plasma and blood volumes in patients with chronic heart failure (CHF).

BACKGROUND Intravascular fluid volume expansion is an acute compensatory adaptation to ventricular dysfunction in patients with CHF. To our knowledge there are no reports on plasma and blood volume measures in clinically stable patients with CHF receiving standard pharmacotherapy. Such information may provide a better understanding of the clinical hallmarks of heart failure.

METHODS Plasma volume (PV) and blood volume (BV) were measured in 12 patients (62.8 ± 8.2 years old, 175.2 ± 6.8 cm, 96.2 ± 18.2 kg, peak oxygen consumption ($\dot{V}O_2$max) 15.2 ± 3.3 ml/kg per min) with CHF secondary to coronary artery disease (left ventricular ejection fraction 31.2 ± 9.7, New York Heart Association functional class 2.5 ± 0.5) and seven healthy subjects (71.7 ± 5.3 years old, 177.1 ± 10.8 cm, 84.4 ± 11.7 kg, $\dot{V}O_2$max 26.0 ± 6.5 ml/kg per min) 3 to 4 h after eating and after supine rest using the Evan's blue dye dilution technique. Venous blood samples were collected before blue dye infusion and analyzed for hematocrit (corrected 4% for trapped plasma and venous to whole body hematocrit ratio) and hemoglobin.

RESULTS Hematocrit was 36.6 ± 3.5% and 37.4 ± 1.1%, and hemoglobin was 15.4 ± 1.9 and 16.2 ± 1.4 g/dl for patients with CHF and control subjects, respectively. Absolute PV was 3489.3 ± 655.0 and 3728.7 ± 813.2 ml, and absolute BV was 5,496.8 ± 1,025.4 and 5,942.4 ± 1,182.2 ml in patients with CHF and control subjects, respectively. Relative PV was 34.1 ± 12.9 versus 44.5 ± 9.0 ml/kg ($p \leq 0.05$), and relative BV was 58.5 ± 12.3 versus 70.8 ± 12.6 ml/kg ($p \leq 0.05$) in patients with CHF and control subjects, respectively.

CONCLUSIONS Our data indicate significantly lower intravascular volumes in patients with CHF than in control subjects, indicating a deconditioned state or excessive diuresis, or both. The contracted PV and BV may contribute to exercise intolerance, shortness of breath and chronic fatigue, secondary to reduced cardiac output or regional blood flow, or both. (J Am Coll Cardiol 2000;35:51–5) © 1999 by the American College of Cardiology

Previous investigators have established that the sympathetic and neurohormonal adaptations associated with chronic heart failure (CHF) influence fluid regulation and vascular reactivity and permeability (1,2). Intravascular fluid volume expansion is one consequence of the hypersecretion of pressor and antidiuretic hormones (i.e., norepinephrine, vasopressin, angiotensin II, aldosterone) in an attempt to maintain perfusion pressure coincident with depressed ventricular function. In contrast, excessive sodium and water retention often results in extravascular edema in the lungs and skeletal muscle, contributing to shortness of breath, exercise intolerance and chronic fatigue (1,3,4). Management of patients with early signs of heart failure traditionally include 1) restriction of physical activity; 2) restriction of sodium intake; and 3) administration of diuretic agents, angiotensin-converting enzyme (ACE) inhibitors and cardiac glycosides. After initiation of such treatment many patients experience resolution of their symptoms at rest. Most patients, however, continue to experience activity-related symptoms, in part due to reduced cardiac output, excessive vasoconstriction, vascular remodeling and skeletal muscle atrophy (3–5). We are unaware of studies that report on plasma volume (PV) and blood volume (BV) measures in clinically stable patients with CHF receiving standard pharmacotherapy. Such information may provide further insight regarding the management of patients with CHF. Accord-

From the *Center for Exercise Science and Division of Cardiovascular Medicine, College of Health and Human Performance and College of Medicine, University of Florida, Gainesville, Florida; †Department of Health and Exercise Science, Furman University, Greenville, South Carolina; and ‡Department of Kinesiology, Louisiana State University, Baton Rouge, Louisiana. This study was supported in part by a grant from Sigma Tau, Gaithersburg, Maryland.

Manuscript received March 23, 1999; revised manuscript received July 29, 1999, accepted October 5, 1999.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ANCOVA	= analysis of covariance
BV	= blood volume
CHF	= chronic heart failure
PV	= plasma volume
RPE	= rating of perceived exertion
$\dot{V}O_2max$	= maximum oxygen consumption

ingly, this study was designed to investigate the long-term effect of standard pharmacotherapy on PV and BV in patients with CHF.

METHODS

Subjects. Twelve men with a history of CHF (average duration 5 ± 3 years) secondary to coronary artery disease and left ventricular systolic dysfunction (ejection fraction 31.2 ± 9.7%) were studied. They were clinically stable (New York Heart Association functional class 2.5 ± 0.5) and free of other major illnesses. Patients were taking diuretic agents (n = 12), ACE inhibitors (n = 12), digitalis glycosides (n = 8), beta-blockers (n = 8), nitrates (n = 9) and anticoagulant agents (n = 9).

Seven healthy subjects matched for age (by decade) and body composition (body mass index) were recruited and served as the control group. They were sedentary and had no evidence of cardiac or pulmonary disease, as determined by clinical examination and graded exercise testing, and none were receiving prescription medication. The protocol was approved by the Institutional Review Board for the protection of human subjects at the University of Florida, and all subjects provided written, informed consent for participation in the study.

Plasma volume measurement. In an attempt to standardize conditions and collect clinically representative data, patients were requested to adhere to their physician's instructions for prescription medications and to maintain their current body weight by not altering their normal daily dietary and activity patterns for four days before measurement of PV. Anthropometric (sum of seven skinfolds) and blood pressure measurements were recorded at the orientation session. Four days after the orientation session, patients reported to the Center for Exercise Science at the University of Florida (10:00 to 12:00 AM) ~3 h after ingesting a light breakfast and their prescribed medications. Subjects completed diet and activity recalls and underwent a physical examination, supine 12-lead electrocardiography and blood pressure measurement by auscultation. Mean arterial pressure was calculated as diastolic pressure + 1/3(systolic pressure − diastolic pressure). Anthropometric measurements were unchanged over the five days before PV measurement.

Plasma volume was determined using a modified Evans blue dye (T-1824, New World Trading Corp., DeBary, Florida) dilution technique (6). A catheter, kept open with dilute heparinized saline, was inserted into the antecubital vein of the right arm, and a butterfly infusion catheter was inserted into a forearm vein of the left arm. After 20 min of supine rest a 5-ml venous sample was drawn into a heparinized vacutainer to provide plasma that was used in the generation of the blue dye standard. A 2.5-ml quantity of a 0.5% aqueous T-1824 solution was injected over 2 min into the butterfly catheter, and syringe and butterfly catheter weights were measured before and immediately after infusion of the blue dye. Plasma samples were drawn at 10, 20 and 30 min after injection of blue dye, and the data were extrapolated to 0 time in calculating the PV. The dye from the plasma sample was extracted onto a wood-cellulose powder (Solka Floc SW 40A, Sigma Chemical, St. Louis, Missouri) chromatographic column after it had been separated from albumin by the action of a detergent (Teepol 610 in 2% Na_2HPO_4, Sigma Chemical, St. Louis, Missouri). Interfering substances such as pigments, proteins and chylomicrons were washed from the column with 2% Na_2HPO_4. The dye was eluted from the column with a 1:1 acetone–water mixture. The addition of KH_2PO_4 buffered the pH of the eluate to 7.0; absorbance of the eluate was read at 615 nm. Plasma volume was determined from plasma concentrations of T-1824 using standard indicator dilution formulas: $PV = (V \times D)(St \times v)/1.03(T)$, where V = volume (ml) of T-1824 dye injected (22.6 mg/5 ml); D = dilution of standard (1:250); St = absorbance of the standard; v = volume of the sample extracted (1.0 ml); T = absorbance of the plasma sample; and 1.03 = correction factor for dye uptake by tissues. Triplicate microhematocrit determinations were made using a microhematocrit centrifuge and a Micro-Capillary Tube Reader (Fisher Scientific, Pittsburgh, Pennsylvania). Raw microhematocrit values were corrected (×0.91) for trapped plasma and whole body microhematocrit (7). Blood volume was calculated as PV(1 − corrected hematocrit). Red cell volume was calculated as BV(corrected hematocrit)/100. Absolute PV and BV (ml) were corrected for body weight to reflect relative PV and BV (ml/kg).

Exercise testing. Symptom-limited graded exercise was performed using a modified (2-min stages) Naughton protocol. Heart rate and a 12-lead electrocardiogram were monitored continuously (Model Q2000, Quinton Instruments, Seattle, Washington). Systolic and diastolic blood pressures were measured by auscultation. Exertion was scored at the end of each minute using Borg's perceived exertion scale (RPE), perceived difficulty of breathing (dyspnea) on a 0 to 4 scale and any chest discomfort (angina) on a 0 to 4 scale. Respiratory gases were collected and analyzed for oxygen and carbon dioxide content with a metabolic system (Model CPX/MAX, MedGraphics Cardiopulmonary Gas Exchange System, St. Paul, Minnesota) calibrated with certified pure medical-grade gases. Maximum oxygen

Table 1. Physical Characteristics of the Chronic Heart Failure and Control Groups

Variable	CHF Group (n = 12)	Control Group (n = 7)
Age (yrs)	62.8 ± 8.2	71.7 ± 5.3*
Height (cm)	175.2 ± 6.8	177.1 ± 10.8
Weight (kg)	96.2 ± 18.2	84.4 ± 11.7
Body mass index (kg/m^2)	31.3 ± 5.8	27.1 ± 4.6
Body fat (%)	27.9 ± 6.1	25.8 ± 5.4
Heart rate (beats/min)	76.9 ± 11.9	73.1 ± 7.4
Systolic BP (mm Hg)	115.1 ± 14.2	126.9 ± 6.7
Diastolic BP (mm Hg)	73.5 ± 8.6	76.0 ± 6.7
MAP (mm Hg)	87.2 ± 9.6	92.8 ± 5.1

*$p \leq 0.05$ chronic heart failure (CHF) group vs. control group. Data are presented as the mean value ± SD.
BP = blood pressure; MAP = mean arterial pressure.

consumption ($\dot{V}O_2$max) was defined as the highest $\dot{V}O_2$ achieved at the end of exercise. When necessary, the American College of Sports Medicine guidelines for test termination were used (8).

Statistical analysis. Descriptive characteristics and PV and BV measures were compared between groups using analysis of variance. Analysis of covariance (ANCOVA) with repeated measures was used to analyze all response variables during graded exercise. When a significant group by time interaction was observed, intragroup comparisons and intergroup comparisons were performed using ANCOVA with contrast analysis for obtaining appropriate post hoc custom hypothesis tests. The relation between BV and exercise capacity was correlated using Pearson's r coefficient. All statistical analyses were performed using the SPSS statistical program (SPSS Inc., Chicago, Illinois). Data are expressed as the mean value ± SD. An alpha level of $p \leq 0.05$ was required for statistical significance.

RESULTS

Plasma and blood volumes. The descriptive characteristics of the patients with CHF and control subjects are presented in Table 1. The average age of subjects enrolled in the study was 66.1 ± 8.4 years, and the two groups did not differ ($p \geq 0.05$) with respect to body mass index or body composition. Absolute PV was 3,489.3 ± 655.0 and 3,728.7 ± 813.2 ml, and absolute BV was 5,496.8 ± 1,025.4 and 5,942.4 ± 1,182.2 ml in patients with CHF and control subjects, respectively. The BV and PV data, normalized for body weight (ml/kg), are presented in Figure 1. Relative PV and BV were contracted 23.4% and 17.4%, respectively, in the patients with CHF. Neither hemoglobin concentration (15.5 ± 1.9 vs. 16.2 ± 1.4 g/dl) nor hematocrit (36.6 ± 3.5% vs. 37.4 ± 1.1%) differed ($p \geq 0.05$) at rest between patients with CHF and control subjects, respectively. There were no adverse allergic reactions to the Evans blue dye dilution technique.

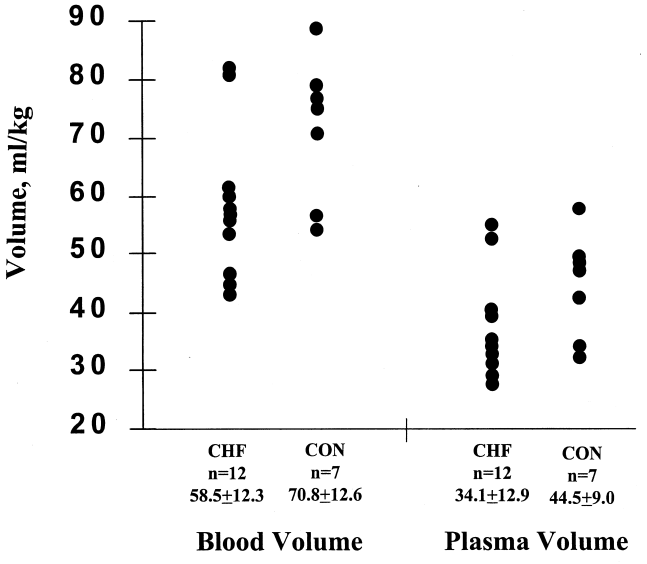

Figure 1. Relative PV and BV in men with CHF. *$p \leq 0.05$ CHF vs. control (CON) group.

Cardiorespiratory responses to early exercise. Peak oxygen uptake achieved by the patients with CHF during the graded exercise test was 58% of that attained by the control group (15.2 ± 3.3 vs. 26.0 ± 6.5 ml/kg per min) ($p \leq 0.05$). Peak heart rate achieved by the patients with CHF was 85% of that attained by the control group (128.8 ± 22.2 vs. 145.6 ± 24.6 beats/min) ($p \geq 0.05$). Peak systolic blood pressure was 181.8 ± 27.5 vs. 201.1 ± 24.9 mm Hg ($p \geq 0.05$), and peak diastolic blood pressure was 89.8 ± 15.0 vs. 89.4 ± 10.2 mm Hg ($p \geq 0.05$) in patients with CHF and control subjects, respectively. Peak mean arterial pressure achieved by the patients with CHF was 94% of that attained by the control group (120.2 ± 18.0 vs. 128.2 ± 16.0 mm Hg) ($p \geq 0.05$). All subjects exercised to exhaustion and reported marked exertional fatigue at peak exercise (patients with CHF: RPE = 18 ± 2; dyspnea = 2.5 ± 1.0; angina = 2.0 ± 1.0; control subjects: RPE = 18 ± 2; dyspnea = 1.1 ± 1.5; angina = 0.0 ± 0.0). There were no adverse events as a result of the exercise test. The relation between total BV and maximal oxygen uptake is presented in Figure 2.

DISCUSSION

Assessment of PV and BV in 12 patients with CHF and 7 control subjects revealed significantly lower intravascular volumes for the patients with CHF. Our data indicate that, when normalized for body weight, PV and BV were contracted 23.4% and 17.4%, respectively, in the patients with CHF as compared with the healthy control subjects. This finding is in contrast to a popular hypothesis that hypervolemia persists in patients with CHF despite long-term medical management, including diuretic and ACE inhibitor pharmacotherapy.

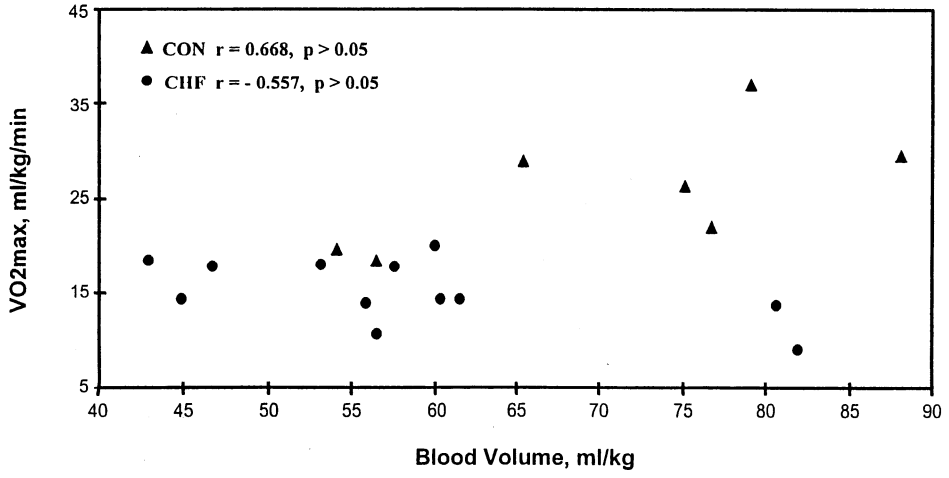

Figure 2. Relation between total BV and maximal oxygen uptake ($\dot{V}O_2max$) in men with CHF. *$p \leq 0.05$ CHF vs. control (CON) group.

Blood volume in health and disease. Although several researchers have reported on BV adaptations in healthy adults, this study is the first to report PV and BV data for patients with CHF receiving long-term pharmacotherapy (9–14). The relative BVs of the sedentary control subjects in the present study were similar to those reported previously by some investigators (~75 ml/kg) (10,11), larger than others (~62 ml/kg) (12,13) and yet smaller than others (85 ml/kg) (14). The discrepancies in the BV data found in the published data may be accounted for by methodologic differences, ergogenic aids, medications, age-related physiologic changes or the subject's training status, or a combination of these. One common problem in these studies is the technical difficulty associated with measuring BV. Although the use of chromium-tagged red blood cells is considered a better method because the red blood cells are believed to stay in the vasculature longer than plasma proteins, the Evan's blue dye dilution technique is well accepted (6,15). The Evan's blue dye dilution technique is most appropriate when measurements are not affected by postural or exercise-induced intravascular pressure changes, which may result in increased leakage of dye from the vascular compartment.

Blood volume and exercise capacity in CHF. Several factors could contribute to the differences in PV and BV in the present study, including deconditioning, hyperactivation of pressor and natriuretic/diuretic neurohormones and/or excessive drug-induced diuresis in the patients with CHF. In a review of the adaptations of BV to endurance training, Convertino (9) indicated that a relation ($r = 0.780$, $p < 0.05$) exists between total BV and maximal oxygen uptake in men. The data from the control group in the present study also indicate a moderate relation between exercise capacity and BV in healthy subjects (Fig. 2). By contrast, there was a moderate inverse relation between exercise capacity and BV in the CHF patients with CHF. It is possible that the hypervolemic condition in the patients with CHF contributes to the exercise intolerance secondary to the pulmonary and/or peripheral congestion. Future studies are needed to determine if more aggressive pharmacologic management of BV in patients with CHF may improve exercise tolerance and clinical status.

Mechanisms of BV contraction in CHF. In patients with CHF, activation of pressor and fluid-regulating neurohormones causes renal sodium and water retention despite an increase in extracellular fluid and total BV. The resulting hypervolemia is well documented as a compensatory adaptation to acute heart failure and often precedes any perceptible increases in venous pressure or edema (12,15). In untreated patients with CHF (average duration of CHF eight months), Anand et al. (12) reported that PV was expanded 34% higher than that in control subjects (57.9 vs. 43.2 ml/kg), BV 22% (75.1 vs. 61.7 ml/kg), extracellular volume 33% and total body water content 16%, with subsequent peripheral edema, ascites and dyspnea in most patients (12). Although this initial increase in BV facilitates cardiocirculatory stability, sustained volume expansion may compromise vascular wall function and integrity owing to endothelial remodeling, sodium and water retention and smooth muscle contraction. Collectively, these mechanisms may decrease vascular capacitance over the long term in patients with CHF (12,16–18). The reduced BV in the patients with CHF, despite nonsignificant differences in hematologic variables or mean arterial pressures between the groups evaluated in the present study, suggests that systemic vascular resistance remains increased.

An important factor in the maintenance of mean arterial pressure is an increase in systemic resistance mediated by an increased activity of the sympathetic nervous system and pressor hormones. Although pressor hormones were not measured in the present study, previous CHF studies conducted in our laboratory indicate that several pressor and fluid-regulating neurohormones (i.e., angiotensin II, aldosterone, vasopressin, atrial natriuretic peptide) remain hy-

persecreted despite long-term pharmacotherapy (19). Thus, it seems probable that chronic systemic vasoconstriction mediated by neurohormonal hyperactivity may reduce the size of the intravascular compartment within the arterial bed. This hypothesis is consistent with Poiseuille's equation regarding the factors that affect local blood flow and distribution (flow = pressure gradient × vessel radius^4/vessel length × viscosity) (20). Recognizing that the most important factor affecting blood flow is the vessel's radius and the resistance to flow changes with the vessel's radius, raised to the fourth power (i.e., flow is reduced 16-fold when the vessel radius is reduced by one-half), small changes in total peripheral resistance can significantly influence the vascular capacitance and consequently intravascular BV. For example, a 4% increase in total peripheral resistance reduces the volume of blood flowing through the systemic vasculature by ~18%.

Pharmacotherapy and BV in CHF. Although treatment with ACE inhibitors and diuretic agents delays deterioration and improves survival in CHF, the long-term effects of these medications on the vasculature or BV are not well understood (3,4,21). Long-term inhibition of aldosterone secretion by ACE inhibitors, the natriuretic and diuretic actions of atrial natriuretic peptides and/or excessive diuresis resulting from long-term pharmacotherapy (i.e., diuretic agents) could induce hypovolemia. The patients with CHF enrolled in the present study had been prescribed diuretic agents and ACE inhibitors for several years (5 ± 3), and the summative effects of long-term pharmacotherapy may have contributed to the contracted PV and BV in these patients. The importance of tailoring pharmacotherapy for patients with CHF should be recognized considering that the potential for drug-induced volume contraction increases with long-term pharmacologic management.

Study limitations. This study included a relatively small number of patients who were carefully selected and receiving expert cardiac care. The assessment of intravascular fluid volumes in this study was made under standard drug therapy, and participants were instructed to continue with their normal daily activity and dietary patterns for four days before the measurement of PV. However, we think that it is more appropriate and useful to assess intravascular fluid volumes while patients are taking their usual therapy, rather than when they are off treatment, because the latter would not depict clinically representative data. Finally, the study would be strengthened with the measurement of extravascular fluid volumes.

Conclusions. The data from the present study suggest that, in addition to the effects of pressor and diuretic/natriuretic neurohormones, standard pharmacotherapy may contract circulating PV and BV in patients with CHF. Future research should focus on the proportional role of each contributing factor to intravascular fluid volume contraction, the role of exercise training on BV expansion and the most appropriate pharmacologic treatment strategy that can be tailored to the individual patient with CHF.

Acknowledgments

The authors acknowledge the late Michael L. Pollock, PhD, for his contributions in the design and implementation of this study.

Reprint requests and correspondence: Dr. Matthew S. Feigenbaum, Department of Health and Exercise Science, Furman University, Greenville, South Carolina 29613. E-mail: Matt.Feigenbaum@Furman.edu.

REFERENCES

1. Drexler HT, Munzel T, Riede U, Just H. Adaptive changes in the periphery and their therapeutic consequences. Am J Cardiol 1991;67:29C–35C.
2. Zelis R, Flam S. Alterations in vasomotor tone in congestive heart failure. Prog Cardiovasc Dis 1982;25:437–59.
3. Francis GS, Benedict C, Johnstone DE, et al., for the SOLVD Investigators. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. Circulation 1990;82:1724–9.
4. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L, for the CONSENSUS Trial Study Group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990;82:1730–6.
5. Remme WJ. Therapeutic strategies and neurohormonal control in heart failure. Eur Heart J 1994;15 Suppl D:129–38.
6. Greenleaf JE, Convertino VA, Mangseth GR. Plasma volume during stress testing in man: osmolality and red cell volume. J Appl Physiol 1979;47:1031–8.
7. Chaplin H, Mollison P, Vetter H. The body/venous hematocrit ratio: its constance over a wide hematocrit range. J Clin Invest 1953;32:1309–16.
8. American College of Sports Medicine. Guidelines for Exercise Testing and Prescription. 5th ed. Philadelphia: Lea & Febiger, 1995:86–109.
9. Convertino VA. Blood volume: its adaptation to endurance training. Med Sci Sports Exerc 1991;23:1338–48.
10. Kjellberg SR, Rudhe U, Sjostrand T. Increase of the amount of hemoglobin and blood volume in connection with physical training. Acta Physiol Scand 1949;19:146–51.
11. Brotherhood J, Brozovic B, Pugh LGCE. Hematological status of middle- and long-distance runners. Clin Sci Mol Med 1975;48:139–45.
12. Anand IS, Ferrari R, Kalra GS, et al. Edema of cardiac origin: studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. Circulation 1989;80:299–305.
13. Carroll JF, Convertino VA, Wood CE, et al. Effect of training on blood volume and plasma hormone concentrations in the elderly. Med Sci Sports Exerc 1995;27:79–84.
14. Dill DB, Braithwaite K, Adams WC, Bernauer EM. Blood volume of middle-distance runners: effect of 2,300m altitude and comparison with non-athletes. Med Sci Sports 1974;6:1–7.
15. Warren JV, Stead EA Jr. Fluid dynamics in chronic congestive failure. Arch Intern Med 1944;73:138–47.
16. Delehanty JM, Liang C. Metabolic control of the circulation: implications for congestive heart failure. Prog Cardiovasc Dis 1995;38:51–66.
17. Drexler H, Hayoz D, Munzel T, et al. Endothelial function in chronic congestive heart failure. Am J Cardiol 1992;69:1596–601.
18. Zelis R, Sinoway LI, Leuenberger U, et al. Time-constant adaptations in heart failure. Eur Heart J 1991;12 Suppl C:2–7.
19. Braith RW, Welsch MA, Feigenbaum MS, et al. Neuroendocrine activation in heart failure is modified by endurance exercise training. J Am Coll Cardiol 1999;34:1170–5.
20. Smith JJ, Kampine JP. Circulatory Physiology. 3rd ed. Baltimore: Williams & Wilkins, 1990:16–24.
21. Sigurdsson A, Swedberg K, Ullman B. Effects of ramipril on the neurohumoral responses to exercise in patients with mild or moderate congestive heart failure. Eur Heart J 1994;15:247–54.