PATHOPHYSIOLOGY AND NATURAL HISTORY

CONGESTIVE HEART FAILURE

Isometric exercise in patients with chronic advanced heart failure: hemodynamic and neurohumoral evaluation

URI ELKAYAM, M.D., ARIE ROTH, M.D., LAURA WEBER, R.N., WILLA HSUEH, M.D., MICHELE NANNA, M.D., LINDALEE FREIDENBERGER, R.N., P. ANTHONY N. CHANDRARATNA, M.D., AND SHAHBUDIN H. RAHIMTOOLA, M.B., F.R.C.P.

ABSTRACT We evaluated the hemodynamic effects of isometric exercise in 53 patients with congestive heart failure (CHF) and compared them with those found in 10 normal subjects. In both groups, isometric exercise increased heart rate and blood pressure. Systemic resistance increased in patients with CHF (1862 ± 520 vs 2126 ± 642 dyne-sec-cm⁻²; p < .001) but not in normal subjects (1359 ± 268 vs 1380 ± 252 dyne-sec-cm⁻²). Cardiac index and stroke volume index increased mildly but not significantly in the normal subjects (2.8 ± 0.5 vs 3.1 ± 0.7 liters/min/m² and 46 ± 8 vs 47 ± 7 ml/m²) and showed a significant fall in the patients with CHF (2.1 ± 0.6 to 1.9 ± 0.6 liters/min/m², p < .01 and 23 ± 7 vs 20 ± 7 ml/m², p < .01). Mean pulmonary arterial wedge pressure increased in patients with CHF from 26 ± 7 to 30 ± 8 mm Hg (p < .001). Although no significant change was found in mean value for stroke work index (21 ± 9 vs 20 ± 9 g-m/m²), the individual changes were variable, with marked decrease (>15%) in 17 of the patients. This hemodynamic deterioration could not be predicted from resting hemodynamics, left ventricular ejection fraction, or functional classification. Isometric exercise resulted in no significant change in circulatory catecholamine levels or plasma renin concentration in our 10 normal subjects. In the patients with CHF renin (measured in 12 patients) and epinephrine (measured in 16 patients) also did not change during isometric exercise, but norepinephrine levels (measured in 16 patients) increased significantly. No correlation was found between changes in hormonal levels and any of the hemodynamic changes during static exercise. We conclude that in patients with chronic CHF, isometric exercise can lead to a significant increase in left ventricular outflow resistance and filling pressure and to a fall in cardiac performance. In the presence of CHF, this form of exercise results in a consistent elevation in norepinephrine levels, but there is no correlation between changes in its plasma level and in hemodynamic values. There is considerable individual variation in the hemodynamic response, with a significant deterioration in cardiac performance in some patients, which cannot be separated by resting hemodynamic values, left ventricular ejection fraction, or clinical status.

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THE EFFECTS of isometric exercise on the cardiovascular system and their neurohumoral mechanisms have been extensively investigated in animals and in normal individuals. In contrast, few data are available on the consequences of isometric exercise in patients with chronic congestive heart failure (CHF), in whom both hemodynamic and neurohumoral status is significantly altered. In this study we evaluated the hemodynamic effects of isometric exercise and the response of plasma catecholamines and renin concentration in patients with severe advanced CHF.

Methods

Patients with CHF. Hemodynamic effects of isometric exercise were evaluated in 53 patients who were admitted to the University of Southern California/Los Angeles County Medical Center for inadequate control of chronic CHF. There were 39 men and 14 women, ranging in age from 20 to 80 years (mean ± SD 51 ± 6 years). The cause of CHF was coronary artery disease in 14 patients and congestive cardiomyopathy in 39 patients. Thirty-two of the patients were classified on admission into the NYHA functional class III and 21 were class IV. The diagnosis of left ventricular systolic dysfunction was confirmed by cardiac catheterization in 26 patients, by radionuclide ventriculography in 22 patients, and by echocardiography in five

From the Department of Medicine, Sections of Cardiology and Endocrinology, LAC/USC Medical Center, University of Southern California School of Medicine, Los Angeles.
Address for correspondence: Uri Elkayam, M.D., USC School of Medicine, Section of Cardiology, 2025 Zonal Ave., Los Angeles, CA 90033.
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patients. Left ventricular ejection fraction was measured either by contrast or radionuclide ventriculography in 48 patients and ranged from 0.08 to 0.41 (mean 0.20 ± 0.07). None of the patients had evidence of a primary valvular disease, congenital disease, or active myocardial ischemia at the time of the study.

All patients were in a clinically and hemodynamically stable condition at the time of the study. Hemodynamic stability was ensured by repeated measurements 30 min apart to obtain two consecutive measurements with 10% or less variation in heart rate, blood pressure, cardiac output, and mean pulmonary arterial wedge pressure. Digitalis and diuretic therapy were continued in their prestudy doses and given at least 4 hr before the initiation of the study. Further administration of diuretic agents was not allowed until the termination of the hemodynamic study. Orally administered vasodilator agents, including isosorbide dinitrate, hydralazine, and nifedipine, were discontinued at least 16 hr before the initiation of the study.

**Hemodynamic measurements and computations.** Right-sided cardiac catheterization was performed with a balloon-tipped, triple-lumen Swan-Ganz catheter at least 24 hr before the initiation of the study. Pressure in the right atrium and pulmonary artery and left ventricular filling pressure, determined indirectly from the mean pulmonary arterial wedge pressure, were recorded on Electronics for Medicine VR-12 or AR-6 recorders. Mean pressures were obtained with the use of electronic integration. Heart rate was determined from the electrocardiographic recording, and arterial blood pressure was measured by the standard cuff method. Cardiac output was determined by thermodilution as previously described. Calculations of mean arterial blood pressure, cardiac index, stroke volume index, stroke work index, systemic vascular resistance, and pulmonary vascular resistance were performed by standard formulas.

In 16 patients plasma levels of catecholamines was measured before and during exercise. In 12 of these patients plasma renin concentration was also determined. Blood for hormonal determinations was drawn from the right atrium through the Swan-Ganz catheter.

**Control group.** Hemodynamic and hormonal studies were also carried out in 10 normal male volunteers (mean age 33 ± 4 years). None of these subjects had a history, symptoms, or signs of heart disease or any other disease. All subjects were studied in the morning after eating a light breakfast without drinking caffeinated beverages or smoking cigarettes. All measurements were done in the same examining room with subjects in the supine position. Cardiac output was measured noninvasively by Doppler technique (Ultracom Lawrence Medical Systems, Inc.) in triplicate. This method for cardiac output determination has been previously validated in our laboratory, demonstrating high correlation (r = .97, p < .001) with thermodilution cardiac output in patients and excellent interobserver and intraobserver variability in normal subjects (r = .98, p < .001; r = .97, p < .001, respectively). In addition, the Doppler technique used in this study has been shown to be reliable in detecting changes in cardiac output and has correlated well (r = .88, p < .001) with the thermodilution technique. Measurements of blood pressure and heart rate were obtained in methods identical to those used for the CHF patients. Because right atrial pressure was not obtained in the normal subjects, total systemic resistance was calculated as follows: total systemic resistance = 80 (mean blood pressure/cardiac output). Venous blood for hormonal determination was drawn through a heparin-lock needle that was placed in the nonexercising forearm at least 15 min before the beginning of the study.

**Plasma hormones.** Plasma catecholamines were determined at baseline and 1 to 2 min after the beginning of isometric exercise in 16 patients and in all 10 normal subjects. The determination of both epinephrine and norepinephrine was performed with an isotope radioenzymatic technique. Plasma renin concentration was measured at baseline and during exercise in 12 patients and in all 10 normal subjects by a radioimmunoassay of angiotensin I after addition of excess sheep angiotensinogen.

**Isometric exercise.** Isometric exercise was performed with a commercially available, calibrated hand dynamometer. After the patients and the normal subjects had been instructed and had practiced the handgrip exercise, they were asked to compress the dynamometer once to maximum extent possible with the dominant arm and then to maintain 30% of their previously determined maximal compression pressures while maintaining normal ventilation and avoiding the Valsalva maneuver. In both the control subjects and patients, hemodynamic measurements were started 1 min after initiation of handgrip and were followed by determination of cardiac output. The duration of handgrip exercise ranged between 5 to 7 min in both groups.

**Statistical analysis.** The data were analyzed by paired and nonpaired t tests and by correlation and regression analysis. All group values were expressed as mean ± SD.

**Results**

**CHF patients.**

**Hemodynamic effect of isometric exercise.** Figures 1 and 2 demonstrate mean hemodynamic values at rest and during isometric exercise in all 53 patients. Isometric exercise was associated with an increase in heart rate in 36 of the patients. Group values showed a mild but significant increase in heart rate from 94 ± 15 to 99 ± 16 beats/min (p < .001). Mean blood pressure increased in most patients (n = 46), with a change in mean value from 93 ± 12 to 101 ± 14 mm Hg (p < .001). Cardiac index decreased in 36 patients and showed a fall from 2.1 ± 0.6 to 1.9 ± 0.6 liters/min/m² (p < .01), and stroke volume index fell from 23 ± 7 to 20 ± 7 ml/m² (p < .01). Mean right atrial pressure increased in the majority of the patients (n = 41) during exercise and changed from 11 ± 6 to 14 ± 7 mm Hg (p < .001), and mean pulmonary arterial wedge pressure increased from 26 ± 7 to 30 ± 8 mm Hg (p < .001). Mean pulmonary arterial wedge pressure increased in 44 patients. Baseline pulmonary arterial wedge pressure was greater than 30 mm Hg in 21 patients and exceeded 40 mm Hg in only one of them. During isometric exercise this parameter measured 30 mm Hg or greater in 33 patients and was 40 mm Hg or greater in 10 of them (figure 3). Isometric exercise also resulted in a rise in systemic vascular resistance in 36 patients (from 1862 ± 520 to 2126 ± 642 dyne-sec-cm⁻⁵; p < .001). No change, however, was noted in group values for pulmonary vascular resistance (267 ± 139 vs 281 ± 138 dyne-sec-cm⁻⁵) and left ventricular stroke work index (21 ± 9 vs 20 ± 9 g-m/m²).

Although mean values for stroke work index did not change significantly during exercise, individual analysis has shown variable changes. We divided our patients into groups A and B according to the response of
their stroke work index to isometric exercise. To identify clinically important changes, we included in group A 17 patients with a greater than 15% fall in stroke work index (-17% to -56%). Group B included the other 35 patients, who showed either no change, a small decrease (-4% to -11%), or an increase (3% to 50%) in stroke work index. Figures 4 and 5 demonstrate the hemodynamic measurements at baseline and during isometric exercise in these two groups of patients. No significant difference was found in baseline hemodynamic values and ejection fraction (0.21 ± 0.08 vs 0.19 ± 0.07) between the two groups. Nine group A patients were classified in the NYHA class III and eight were in class IV. The incidence of functional class IV in group A did not differ significantly from that found in group B (12 class III patients and 24 class IV patients; p = .232). Hemodynamic values as measured during the performance of isometric exercise, however, were significantly different in these two groups. Cardiac index and stroke volume index were lower in group A than in group B (1.7 ± 0.4 vs 2.1 ± 0.7 liters/min/m², p < .005; 17 ± 4 vs 21 ± 7 ml/m², p < .01). Mean pulmonary arterial wedge pressure was 34 ± 7 mm Hg in group A and 28 ± 8 mm Hg in
group B (p < .001). Exercise stroke work index, as expected by definition of our analysis, was significantly lower in group A. (14 ± 5 vs 23 ± 9 g·m/m²; p < .001). No statistically significant differences were found between exercise values of heart rate (104 ± 14 vs 97 ± 16 beats/min), mean blood pressure (99 ± 16 vs 102 ± 13 mm Hg), mean right atrial pressures (15 ± 8 vs 13 ± 7 mm Hg), and systemic vascular resistance (2268 ± 535 vs 2059 ± 683 dyne·sec·cm⁻²).

Neurohumoral effects of isometric exercise. Figure 6 demonstrates the effect of isometric exercise on group values of both catecholamines and renin. A mild increase was seen in the levels of all three measured hormones; however, only the change in norepinephrine level was statistically significant (from 721 ± 520 to 842 ± 634 pg/ml; p < .02). Regression analysis between hormonal changes and changes in the various hemodynamic

FIGURE 3. Relationships between mean pulmonary arterial wedge pressure (PAW) at rest and during isometric exercise. Baseline PAW was greater than 30 mm Hg in 21 patients and greater than 40 mm Hg in only one of them (pressures ≥40 mm Hg are shown by the open circles); during isometric exercise PAW was 30 mm Hg or greater in 33 patients and 40 mm Hg or greater in 10 of them.

FIGURE 4. Mean hemodynamic values for groups A and B at baseline (C) and during isometric exercise (EX). HR = heart rate; MBP = mean blood pressure; CI = cardiac index; SVI = stroke volume index.

FIGURE 5. Mean hemodynamic values for groups A and B at baseline (C) and during isometric exercise (EX). RA = mean right atrial pressure; PAW = mean pulmonary arterial wedge pressure; SVR = systemic vascular resistance; SWI = left ventricular stroke work index.

FIGURE 6. Group values of norepinephrine and epinephrine (16 patients) and renin (12 patients) at baseline (C) and during isometric exercise (EX).
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parameters revealed no significant correlation. The highest correlation coefficient (r = .435) was found between percent change in norepinephrine and systemic vascular resistance. This correlation, however, was not statistically significant (p = .09).

Control group

Hemodynamic and neurohumoral response to isometric exercise (table 1). The performance of handgrip isometric exercise in our 10 normal volunteers resulted in a significant increase in heart rate (from 62 ± 11 to 66 ± 9 beats/min; p < .05) and mean blood pressure (from 88 ± 7 to 95 ± 11 mm Hg; p < .05). Both cardiac index and stroke volume index increased slightly but not significantly (from 2.8 ± 0.5 to 3.1 ± 0.7 liters/min/m² and from 46 ± 8 to 47 ± 7 ml/m², respectively). Calculated total systemic resistance showed no significant change during exercise (1359 ± 268 vs 1380 ± 252 dyne-sec-cm⁻⁵). The measurement of hormonal values before and during isometric exercise also revealed no significant changes (196 ± 61 vs 182 ± 58 pg/ml for norepinephrine, 51 ± 11 vs 52 ± 16 pg/ml for epinephrine, and 5.5 ± 1.8 vs 6.0 ± 2.9 ng/ml/hr for plasma renin concentration).

Discussion

The hemodynamic response of isometric exercise seen in our normal subjects is in accordance with results of previous studies demonstrating an elevation in heart rate and blood pressure and augmentation of cardiac output, presumably caused by an increase in left ventricular contractility. The relatively small changes in both stroke volume and cardiac output seen in our study were mostly probably related to a lower level and shorter duration of exercise. With an identical protocol, the performance of handgrip isometric exercise in our patients with CHF resulted in a similar increase in heart rate and blood pressure. However, whereas the increase in blood pressure in normal subjects was mostly caused by an increase in cardiac output, a significant increase in systemic vascular resistance was responsible for the change in blood pressure in patients with CHF. This rise in systemic vascular resistance in patients with heart failure was accompanied by depression of cardiac performance demonstrated by marked fall in both stroke volume and left ventricular stroke work occurring simultaneously with either no change or a substantial increase in left ventricular filling pressure in many of the patients.

A significant relationship was found in this study between the changes in systemic vascular resistance and the changes in left ventricular stroke volume (r = .807, p < .001) and cardiac output (r = −.843, p < .001), emphasizing the dependency and the potentially deleterious effect of further increase in left ventricular afterload in patients with advanced CHF. Ross and Braunwald used angiotensin to increase arterial blood pressure and demonstrated the importance of increasing left ventricular afterload as a test of ventricular reserve. The potential use of sustained handgrip as a test of ventricular performance has been demonstrated in patients with various cardiovascular diseases, including hypertension, coronary artery disease, and valvular abnormalities. The reported experience with this technique in patients with chronic severe CHF has been limited to a few patients. Our study demonstrates significant deterioration of stroke work index in a third of our patients during handgrip exercise. This change was accompanied by either no change or an increase in left ventricular filling pressure and suggests a decrease in myocardial inotropic reserve. Although a large number of patients showed marked deterioration in ventricular performance, some demonstrated a normal response to isometric exercise with augmentation of left ventricular performance. Kivowitz et al. reported a correlation between a response to isometric exercise and clinical status as determined by the NYHA functional classification in patients with coronary artery disease and valvular disease. Our results in a large group of patients with CHF in NYHA functional classes III and IV showed that the hemodynamic response to exercise in these patients was not uniform and could not be predicted on the basis of the functional classification. Hemodynamic deterioration as a response to isometric exercise in our patients was also not distinguishable on the basis of their resting hemodynamic measurements or left ven-

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HR = heart rate; MBP = mean blood pressure; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance.
tricular ejection fraction. Whether the response to isometric exercise in this patient population is of prognostic and/or therapeutic importance needs to be further investigated.

Left ventricular filling pressure increased during isometric exercise in the majority of our patients (figure 3). Resting mean pulmonary arterial wedge pressure was greater than 30 mm Hg in 21 patients and was greater than 40 mm Hg in only one of them. During exercise this parameter was found to be 30 mm Hg or greater in 33 patients and 40 mm Hg or greater in 10 of them. This rise in left ventricular filling pressure during isometric exercise in patients with CHF can be explained by several mechanisms. Constriction of capacitance vessels caused by increased sympathetic activity has been described during isometric exercise and can result in an increase of both right and left ventricular filling pressures because of increased blood return to the heart. However, no significant correlation was found in the present study between changes in either right or left ventricular filling pressure and changes in catecholamine levels. The significant fall in stroke volume during exercise should also result in an increased left ventricular end-diastolic volume and thus lead to elevation of left ventricular filling pressure. However, analysis of the relationship between changes in stroke volume and mean pulmonary arterial wedge pressure revealed only weak correlation \( r = .3, p < .05 \). An increase in systemic vascular resistance may also lead to the development of worsening of mitral regurgitation and thus to an elevation in left atrial pressures. An alternative mechanism has been suggested by Ludbrook et al., who found a change in left ventricular compliance and displacement of its pressure-volume curve during isometric exercise. These investigators postulated an interaction between right ventricular hemodynamics and left ventricular diastolic pressure-volume function due to constraining effect of the pericardium. The significant correlation between changes in mean right atrial and pulmonary arterial wedge pressures found in our study \( r = .55, p < .001 \) may support this theory. Modification of left ventricular diastolic function during isometric exercise could also be related to myocardial ischemia caused by increased rate-pressure product and thus myocardial oxygen demand or caused by coronary vasoconstriction previously described in experimental animals during static exercise.

Measurements of plasma catecholamines and renin concentration in our normal subjects demonstrated no significant change during isometric exercise in spite of a substantial increase in both heart rate and blood pressure. These findings confirm previous reports showing little change in circulatory catecholamines during short-lasting isometric contractions in normal subjects and reemphasizes the role of vagal withdrawal and the fact that sympathetic nerve stimulation rather than humoral mechanisms are involved in the early circulatory response to isometric exercise. The response of circulatory catecholamines and renin to isometric exercise has not been previously reported in patients with severe CHF. The increase in circulating plasma norepinephrine in our patients with CHF performing an identical exercise protocol to that used for the normal subjects may have been caused by a fall in cardiac output as a result of failure of the myocardium to overcome the rise in peripheral vascular resistance. A previous report has shown an increase with age in the response of norepinephrine to stress in normal subjects. Therefore the difference in norepinephrine response seen between our patients with CHF and our normal subjects could be attributable to the age difference between these two groups. No relationship was found, however, between the age of our patients with CHF and their norepinephrine response to exercise \( r = .234, p = .382 \). The hemodynamic significance of the increase in circulating norepinephrine level in our patients during exercise is not entirely clear from our data. Although the rise in norepinephrine is expected to increase systemic vascular tone further via stimulation of the \( \alpha \)-adrenergic receptors, we found no significant relationship between the magnitude of changes in both systemic vascular resistance and norepinephrine levels. This finding may suggest that the measurement of circulating plasma norepinephrine does not directly reflect stimulation of the sympathetic nerves. In addition, an increase in total vascular resistance may be partially caused by increased intramuscular pressure and compression of the afferent vessels by the exercising muscles. The general relationship between plasma norepinephrine and hemodynamic changes in patients with CHF has been recently challenged by Goldsmith et al., who showed no significant hemodynamic effects after infusion of exogenous norepinephrine. Whether this observation could be extended to the relationship between changes in endogenous norepinephrine and hemodynamic response needs further evaluation.

Resting plasma renin concentration was elevated in most of our patients. However no change was seen in renin concentration during exercise, suggesting that the renin-angiotensin system does not contribute to the hemodynamic changes mediated by this form and level of muscle activity.
In conclusion, our results demonstrate a variable hemodynamic response to isometric exercise in patients with chronic advanced (class III or IV) CHF. This form of exercise can lead to a significant deterioration in left ventricular performance, which cannot be predicted from resting hemodynamics, left ventricular ejection fraction, and clinical status and may be useful in the evaluation of myocardial inotropic reserve.

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