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Exercise Training in Patients With Severe Congestive Heart Failure: Enhancing Peak Aerobic Capacity While Minimizing the Increase in Ventricular Wall Stress

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Objectives. **The aims of the study were to 1) assess the effects of 12 weeks of exercise training at low work loads (i.e., corresponding to ≤50% of peak oxygen consumption [Vo_2]) on peak Vo_2 and hyperemic calf blood flow in patients with severe congestive heart failure; and 2) evaluate left ventricular diastolic pressure and wall stress during exercise performed at work loads corresponding to ≤50% and 70% to 80% of peak Vo_2.**

Background. **Whether the benefits of exercise training can be achieved at work loads that result in lower left ventricular diastolic wall stress than those associated with conventional work loads is unknown in patients with severe congestive heart failure.**

Methods. **Sixteen patients with severe congestive heart failure trained at low work loads for 1 h/day, four times a week, for 12 weeks. Peak Vo_2 and calf and forearm reactive hyperemia were measured before and during training. Nine of the 16 patients underwent right heart catheterization and echocardiography during bicycle exercise at low and conventional work loads (i.e., 50% and 70% to 80% of peak Vo_2, respectively).**

Results. **The increase in left ventricular diastolic wall stress was substantially lower during exercise at low work loads than during exercise at conventional work loads, (i.e., [mean ± SEM] 23.3 ± 7.4 vs. 69.6 ± 8.1 dynes/cm^2 ($p < 0.001$). After 6 and 12 weeks of training, peak Vo_2 increased from 11.5 ± 0.4 to 14.0 ± 0.5 and 15.0 ± 0.5 ml/kg per min, respectively ($p < 0.0001$ vs. baseline for both). Peak reactive hyperemia significantly increased in the calf but not in the forearm. The increases in peak Vo_2 and calf peak reactive hyperemia correlated closely ($r = 0.61$, $p < 0.02$).**

Conclusions. **In patients with severe congestive heart failure, peak Vo_2 is enhanced by exercise training at work loads that result in smaller increases in left ventricular diastolic wall stress than those observed at conventional work loads.**

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Long-term exercise training at conventional work loads (i.e., corresponding to 70% of peak aerobic capacity [Vo_2]) increases peak Vo_2 in patients with congestive heart failure (1–4). The increase in peak Vo_2 results from an augmented cardiac output at peak exercise, an enhanced vasodilatory response of the skeletal muscle beds and a reversal of skeletal muscle metabolic abnormalities (5). Because peak heart rate and left ventricular contractility are unchanged by long-term exercise, an increase in stroke volume resulting from left ventricular dilation appears to be responsible for the training-induced increase in cardiac output (6). Because long-term exercise at conventional work loads may result in further left ventricular dilation by exposing the ventricle to periods of elevated wall stress, the safety of training patients with left ventricular dysfunction at conventional work loads has been questioned (7–9).

Long-term exercise at work loads below the conventional 70% of peak Vo_2 (i.e., low work load exercise) has recently been shown (10) to improve peak Vo_2 in patients with congestive heart failure. Regression of the peripheral abnormalities that limit the increase in Vo_2 during symptom-limited graded exercise appears to mediate the increase in peak Vo_2 induced by low work load training in patients with congestive heart failure (10). Whether low work load exercise training can reverse peripheral abnormalities without exposing the heart to periods of markedly elevated left ventricular wall stress is currently unknown.

Accordingly, left ventricular filling pressure and diastolic wall stress were measured during exercise at low and conventional work loads in patients with severe congestive heart failure. Low work loads corresponded to <50% of peak Vo_2, whereas conventional work loads corresponded to >70% of peak Vo_2. Subsequently, patients underwent training at low work loads for 12 weeks, with sequential measurements of peak Vo_2, dilatory capacity of the skeletal muscle vasculature and left ventricular volume.

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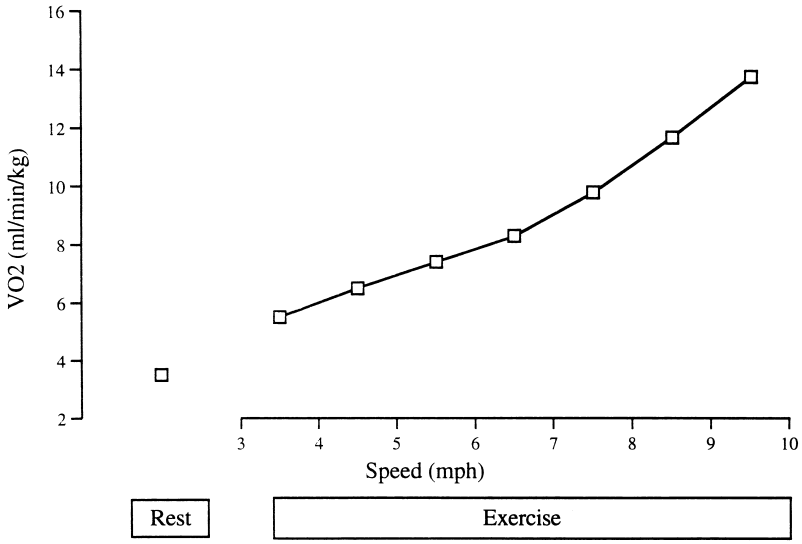

Figure 1. Calibration of energy expenditure (VO2) as a function of speed on the Tunturi E803 semirecumbent stationary bicycle. Ten normal subjects and 10 patients with congestive heart failure bicycled at increasing speeds while V_{O_2} was monitored. The SEM of V_{O_2} was <0.3 ml/min per kg at each speed (not represented).

Methods

Study patients. Nine men and seven women with severe congestive heart failure underwent physical training (mean [±SEM] age 61 ± 2 years, range 45 to 78). Eleven of the 16 patients, (6 men, 5 women; mean age 60 ± 3 years, range 45 to 78) consented to undergo right heart catheterization to evaluate left ventricular diastolic pressure and wall stress during exertional low and conventional work loads. All patients had an ejection fraction ≤30% and a mean left ventricular ejection fraction of 21 ± 2%, as determined by radionuclide angiography. Congestive heart failure was due to ischemic cardiomyopathy in seven patients and nonischemic cardiomyopathy in nine. All patients had stable symptoms of congestive heart failure for ≥3 months. According to New York Heart Association criteria, six patients had symptoms compatible with functional class II, seven with functional class III and three with functional class IV. Mean peak V_{O_2} determined by expired gas analysis during symptom-limited maximal exercise on an upright bicycle ergometer was 11.5 ± 0.4 ml/min per kg. Therapy for congestive heart failure included furosemide and angiotensin-converting enzyme inhibition in all patients, digoxin in 12 and long-acting nitrates in 7. No patient had a significant change in medical regimen during the study period, and none received treatment with a beta-adrenergic blocking agent. Patients with a recent myocardial infarction, exercise-induced angina, atrial fibrillation, uncontrolled diabetes, peripheral vascular disease, significant pulmonary disease or neurologic or musculoskeletal abnormalities limiting exercise capacity were excluded. The study was approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine. All patients gave written informed consent before enrollment.

Exercise training. *Bicycle calibration.* A Tunturi E803 semirecumbent stationary bicycle was used for hemodynamic studies and training. Oxygen consumption at a given speed was established by calibration studies in 10 normal volunteers (mean age 58 ± 4 years) and 10 patients with congestive heart failure (mean age 62 ± 3 years), with continuous monitoring of V_{O_2} using expired gas analysis. The tension belt resistance was set at the minimal level, and subjects exercised starting a 3.5 mph until V_{O_2} stabilized and then increased speed by 1 mph every 4 min, up to a speed of 9.5 mph (Fig. 1). All work loads were submaximal for all subjects, and no significant difference in V_{O_2} for a given speed was demonstrated between normal subjects and patients with congestive heart failure. The V_{O_2} attained at each speed was used to select work loads during hemodynamic studies and training.

Measurement of expired gas. Expired gas was continuously analyzed with a Medical Graphics CPX System that was calibrated immediately before each test during 1) calibration studies on the semirecumbent bicycle in normal subjects using the previously described protocol; and 2) determination of peak V_{O_2} in patients on an upright bicycle ergometer using a 10-W/min ramp at 60 rpm beginning at 0 W. Measured and derived variables included time, oxygen consumption, production of carbon dioxide, exercise duration, work load, and respiratory exchange ratio. Peak V_{O_2} was defined as the point where oxygen consumption is increased ≤1 ml/kg per min over that attained at the previous work load, and the respiratory exchange ratio was >1.1 (11). Patients underwent determination of peak V_{O_2} 6 and 3 weeks before training and again immediately before the start of training to ensure that their peak aerobic capacity remained constant. Each patient performed at least three maximal graded exercise tests at each time point until two values for peak V_{O_2} within 10% of each other were obtained. The highest value was then utilized for analysis.

Limb peak hyperemic blood flow determination. Mercury in Silastic strain gauge plethysmography with venous occlusion was used to measure forearm and calf blood flow in ml/min per 100 ml of limb volume (12,13). The gauges (Parks Medical) were calibrated at a tension of 10 g and placed on the forearm

at 10 cm from the olecranon process and on the calf at its maximal diameter. Gauges were connected to a plethysmograph (Parks Medical), and signals were recorded through a MacLab transducer (AD Instruments) onto a Powerbook 170 (Apple). The upper limb was supinated, and the forearm was elevated 10 cm above the olecranon process, which was 10 cm above the right atrial level. The lower limb was angulated to ~30° at the hip, with the level of the calf ~30 cm above the right atrial level. Before any forearm flow measurements, hand circulation was occluded for at least 1 min using a wrist cuff inflated to 240 mm Hg, and reactive hyperemic flows were measured after release of 5 min of arterial occlusion at 5 and 15 s and then every 15 s thereafter for 1 min. The highest measurement was considered the peak reactive hyperemic flow.

Training protocol. Patients underwent measurement of peak Vo_2, forearm and calf peak reactive hyperemic flow and rest left ventricular volume at baseline and after 12 weeks of exercise training at low work loads. Patients exercised on the semirecumbent bicycle four times a week at minimal belt resistance and a speed corresponding to a work load ≤50% of baseline peak Vo_2. Initial sessions were 15 min in duration, but patients increased to 60-min sessions by the fourth week. Speed and heart rate were monitored continuously during each session. Peak Vo_2 was evaluated at the midpoint of the training period, and exercise speed was adjusted to maintain a work load corresponding to ≤50% of peak Vo_2.

Left ventricular wall stress. *Hemodynamic measurements.* All studies were performed in the morning after an overnight fast, in a room of constant temperature. Cardiovascular medications were held on the morning of the study. After local anesthesia, a 7F Swan Ganz catheter was inserted in the right internal jugular vein and advanced into the pulmonary artery with continuous pressure monitoring, and placement was confirmed by chest X-ray film. Patients then rested for 120 min. Baseline hemodynamic measurements, including mean arterial pressure, heart rate, pulmonary capillary wedge pressure, cardiac output by thermodilution (average of three measurements) and mixed venous oxygen saturation, were continuously monitored with a pulse oximeter, and peak Vo_2 was derived. Patients then exercised at low levels (≤50% of baseline peak Vo_2, mean 48%) and conventional levels (70% to 80% of peak Vo_2, mean 74%) in random order, followed by recording of the same hemodynamic variables measured at baseline. After return of hemodynamic values to baseline, patients rested for an additional 60 min, for a total duration of 75 ± 4 min. Hemodynamic data were obtained from 11 of the 16 patients.

Echocardiography. Echocardiograms were obtained using a Hewlett-Packard Sonos 1000 machine coupled to a 2.5-MHz transducer. Images were recorded in multiple projections on 0.5-in. videotape. Rest echocardiography was performed in all 16 patients before and after 12 weeks of training. In addition, satisfactory echocardiographic studies were obtained in 9 of the 11 patients who underwent hemodynamic evaluation. Hemodynamic and echocardiographic measurements were obtained at baseline and during exercise at each work load, after patients reached a steady state. Left ventricular end-diastolic volumes were calculated from the apical four-chamber view by a Dextra D-300 off-line analysis computer using the single-plane area method (14,15). Left ventricular diastolic circumferential wall stress was calculated using the formula derived by Mirsky (16) for a prolate spheroid and modified for two-dimensional echocardiography by Douglas et al. (17). Using the notation of Douglas et al. (17), the total left ventricular area (A_t) and its cavity area (A_c) were measured at the papillary muscle level in the short-axis view at end-diastole (15). Mean wall thickness was defined as $(A_t/\pi)^{1/2} - (A_c/\pi)^{1/2}$ and left ventricular internal diameter as $2(A_c/\pi)^{1/2}$. The length (L) of the left ventricle was measured as the distance from the midpoint of the mitral annulus to the apical endocardium in the apical four-chamber view. Using these substitutions, left ventricular diastolic wall stress (LVDWS) defined by equation 17 in reference 15 becomes

$$\text{LVDWS} = \{1{,}333(P)(A_c^{1/2})/(A_t^{1/2} - A_c^{1/2})\} \times \{1 - [4(A_c^{3/2})/\pi L^2(A_c^{1/2} + A_t^{1/2})]\}$$

in dynes/cm^2, where P is pulmonary capillary wedge pressure. An average of three to five measurements was obtained for all determinations.

Statistical analysis. Results are expressed as mean value ± SEM. The Vo_2 before and after training was analyzed by repeated measures analysis of variance, followed by Scheffé post hoc testing. Hemodynamic variables during exercise at low and high work loads were compared using a two-factor within-subjects analysis of variance model. Each patient was observed at rest, during exercise at low work loads, at rest again and during exercise at high work loads, for a total of four observations. Calf and forearm blood flows at rest and peak reactive hyperemia were analyzed by a paired *t* test. Linear regression analysis was performed to relate increases in peak Vo_2 and calf peak reactive hyperemic flow. Statistical significance was accepted at the 95% confidence level ($p < 0.05$).

Results

Hemodynamic responses to exercise at low and conventional work loads. Heart rate, mean systemic arterial pressure, pulmonary capillary wedge pressure and cardiac index are detailed at rest and during exercise at low and conventional work loads in Table 1, whereas left ventricular end-diastolic volume and left ventricular diastolic wall stress are detailed in Table 2. During low and conventional work load exercise, pulmonary capillary wedge pressure significantly increased from rest values, whereas left ventricular diastolic volume did not change. Left ventricular diastolic wall stress significantly increased during low and conventional work load exercise from that measured at rest. The increases in pulmonary capillary wedge pressure and left ventricular diastolic wall stress were substantially less during exercise at low work loads than those observed at conventional work loads (Fig. 2).

Table 1. Hemodynamic Response to Exercise at Low and Conventional Work Loads in 11 Study Patients

Work Load	HR (beats/min)	MAP (mm Hg)	PCWP (mm Hg)	CI (liters/min per m^2)	Vo_2 (ml/min per kg)
Baseline 1	92 ± 4	89 ± 5	16 ± 2	2.1 ± 0.1	3.2 ± 0.3
Low	104 ± 4*	96 ± 5*	22 ± 3*	2.7 ± 0.2*	5.4 ± 0.3*
Baseline 2	90 ± 3	92 ± 4	16 ± 2	2.0 ± 0.1	3.1 ± 0.3
Conventional	121 ± 4†‡	104 ± 5†‡	36 ± 2†‡	3.5 ± 0.2†‡	8.3 ± 0.5†‡

*$p < 0.05$ versus baseline 1. †$p < 0.001$ versus baseline. ‡$p < 0.001$ versus low work load. Data presented are mean value ± SEM. CI = cardiac index; Conventional = exercise at work load corresponding to 70% to 80% of peak oxygen consumption (Vo_2); HR = heart rate; Low = exercise at work load corresponding to ≤50% peak Vo_2; MAP = mean systemic arterial pressure; PCWP = pulmonary capillary wedge pressure.

Effects of long-term exercise at low work load. *Peak oxygen consumption.* Peak Vo_2 did not vary during the 6 weeks that preceded training. Peak Vo_2 increased from 11.5 ± 0.4 to 14.0 ± 0.5 ml/kg per min after 6 weeks of training ($p < 0.001$ vs. baseline) and to 15.0 ± 0.5 ml/kg per min after 12 weeks of training ($p < 0.001$ vs. baseline and $p < 0.005$ vs. value at 6 weeks) (Fig. 3).

Peak reactive hyperemia. Peak reactive hyperemia was significantly increased in the calf by training (i.e., from 19 ± 2 to 32 ± 3 ml/min per 100 ml ($p < 0.001$), whereas it was unchanged in the forearm (i.e., 33 ± 3 vs. 33 ± 2 ml/min per 100 ml, p = NS). The increases in calf peak reactive hyperemia and peak Vo_2 were linearly related ($r = 0.61$, $p < 0.02$) (Fig. 4).

Left ventricular end-diastolic volume. Left ventricular end-diastolic volume at rest was not affected by long-term exercise at low work loads (229 ± 11 vs. 232 ± 11 ml).

Discussion

The present data clearly demonstrate that in patients with congestive heart failure, exercise training for 12 weeks at a work load corresponding to <50% of peak Vo_2 substantially increases peak Vo_2 and maximal dilatory response in the trained skeletal muscle vasculature, whereas the heart is exposed to only modest increases in wall stress.

Exercise training and congestive heart failure. Before training, our patients were severely symptomatic, as evidenced by a mean baseline peak Vo_2 of 11.5 ± 0.4 ml/min per kg. After 6 and 12 weeks of training, peak Vo_2 increased by 22% and 30%, respectively. The effects of exercise training at a conventional work load have been assessed by several investigators in patients with moderate congestive heart failure (1–4). Coats et al. (3) reported an 18% increase in peak Vo_2 after 8 weeks of conventional training, whereas Sullivan et al. (1) and Hambrecht et al. (4) observed 23% and 31% increases in peak Vo_2, respectively, after 24 weeks of training. Overall, the magnitude of the increase in peak Vo_2 documented in our patients with low work load exercise training is comparable to that attained with training at conventional work loads. Recently, Bellardinelli et al. (10) documented a 17% increase in peak Vo_2 with low intensity training for 8 weeks in patients with moderate congestive heart failure. Our data extend the benefits of training to patients with severe congestive heart failure. Our data also point out the dissimilar effects of exercising at low and conventional work loads on left ventricular diastolic wall stress. Although training at low work loads increases peak Vo_2 to a similar extent as that of training at conventional work loads, the increase in left ventricular diastolic wall stress is significantly less. Finally, our data suggest that low work load training may increase peak Vo_2 by enhancing maximal vasodilation in the trained limb, as evidenced by an increase in calf peak reactive hyperemia.

Table 2. Left Ventricular Response to Exercise at Low and Conventional Work Loads in Nine Study Patients

Work Load	LVED (ml)	LVDWS (dynes/cm^2)
Baseline 1	239 ± 12	51.1 ± 6.2
Low	242 ± 13	74.5 ± 10.1*
Baseline 2	237 ± 13	50.7 ± 7.1
Conventional	234 ± 13	120.7 ± 8.0†‡

*$p < 0.01$ versus baseline 1. †$p < 0.001$ versus baseline 2. ‡$p < 0.001$ versus low work load. Data presented are mean value ± SEM. LVEDV = left ventricular end-diastolic volume; LVDWS = left ventricular diastolic wall stress; other abbreviations as Table 1.

Vascular effects of exercise training. The ability of exercise training to increase vascular flow capacity in the trained limb has been well documented in rats (18). After 6 to 10 weeks of running exercise, the delivery of substrate to the capillary was significantly greater in the trained rats than in the sedentary animals (18). In normal subjects, similar in age to our patients, Martin et al. (19) showed that exercise training enhances leg vasodilatory capacity, as evidenced by an increase in peak reactive hyperemia in the trained limb. Moreover, the same investigators reported a close correlation between the increases in maximal Vo_2 and maximal vasodilatory capacity of the calf after a 12-week program of intensive swimming in middle-aged women and men (20). Similarly, in patients with congestive heart failure, Sullivan et al. (1) showed excellent correlation between the training-induced change in peak leg blood flow and peak Vo_2 in patients with congestive heart failure. Thus, our findings in patients with severe congestive heart failure are in complete agreement with those previously reported in animals and normal subjects without heart failure and in patients with moderate congestive heart failure. Vascu-

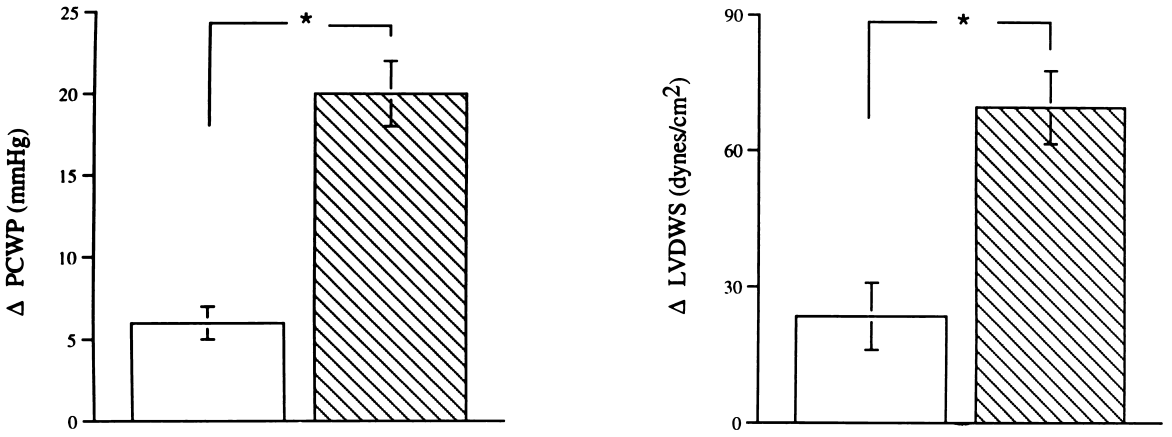

Figure 2. Changes in pulmonary capillary wedge pressure (PCWP) in 11 patients and left ventricular diastolic wall stress (LVDWS) in 9 patients during exercise at low work loads **(open bars)** and conventional work loads **(hatched bars)**. *$p < 0.001$.

lar flow capacity, as demonstrated by calf peak reactive hyperemia, was substantially increased by 12 weeks of low work load exercise training in our patients, and the increases in peak reactive hyperemia significantly correlated with the increases in peak Vo_2. Because the skeletal muscles of untrained patients with severe congestive heart failure already maximally extract oxygen at peak exercise, increasing vascular flow capacity appears to be the only mechanism available to enhance oxygen delivery to the skeletal muscles in these patients (21,22). In contrast, the skeletal muscles of untrained normal subjects and patients with stable coronary artery disease do not maximally extract oxygen at peak exercise. Thus, besides increasing skeletal muscle blood flow, enhancing oxygen extraction is an additional mechanism by which exercise training enhances oxygen delivery in normal subjects and patients with stable coronary artery disease (23). The present data do not permit commentary on the effects of exercise training on the capillary exchange capacity. However, as previously indicated, the capillary exchange capacity of untrained patients with congestive heart failure appears to be near maximum at peak exercise.

Exercise training and left ventricular enlargement. Physical training at work loads corresponding to 70% to 80% of peak Vo_2 leads to left ventricular enlargement in young and middle-aged normal subjects (24–27). In patients with stable coronary artery disease, Ehsani et al. (28) reported a 9% increase in left ventricular end-diastolic dimension after 12 months of training, whereas left ventricular end-diastolic dimensions remained constant over the same period in comparable patients who did not exercise. In most studies involving patients with stable coronary artery disease, left ventricular enlargement is not present after 3 months of training and only becomes apparent after 6 to 12 months of training (24–28).

Detrimental effects of exercise training at conventional work loads have been demonstrated in rats with a large myocardial infarction (29). Not only was global left ventricular dilation aggravated by conventional work load exercise train-

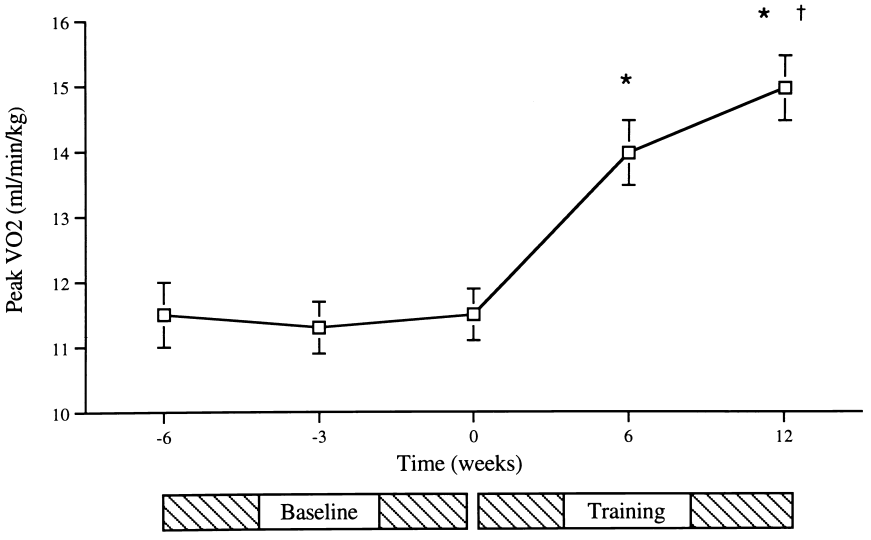

Figure 3. Peak Vo_2 measured 6 and 3 weeks and immediately before training and after 6 and 12 weeks of low work load exercise training. *$p < 0.001$ versus baseline. †$p < 0.005$ versus 6 weeks.

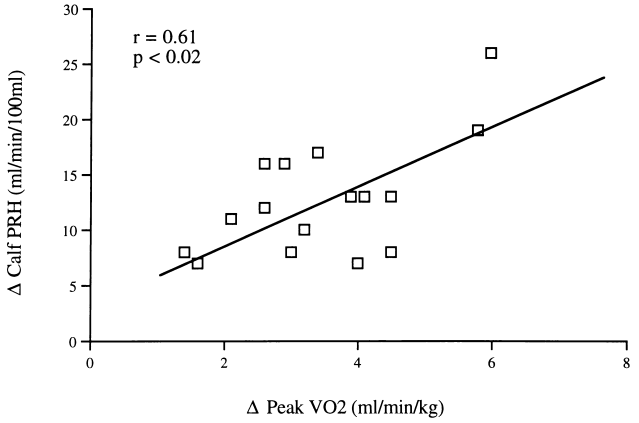

Figure 4. Correlation between increases in peak V_{O_2} and calf peak reactive hyperemia (PRH) after 12 weeks of low work load exercise training.

ing, but mortality in these rats increased as a result of training (29). In patients with a recent myocardial infarction and 18% left ventricular asynergy at baseline, Jugdutt et al. (30) showed that 12 weeks of physical training resulted in further deterioration in left ventricular ejection fraction, expansion index and regional distortion indices. In contrast, Giannuzi et al. (31) reported that progressive left ventricular dilation was similar in patients with a recent myocardial infarction and depressed systolic function who were randomized to a 6-month exercise program or to a control group. In patients with moderate congestive heart failure, Sullivan et al. (1) did not observe left ventricular enlargement after training at a work load corresponding to 75% of peak V_{O_2} for 4 months. However, a duration of 4 months may be too short to assess the effects of exercise training at conventional work loads on left ventricular diastolic volume.

The mechanisms by which physical training tends to promote left ventricular enlargement are not fully understood. The reduction in rest heart rate only accounts for part of the increase in left ventricular end-diastolic volume (28). Periodic exercise at work loads corresponding to >70% of peak V_{O_2} clearly exposes the heart to intermittently elevated left ventricular filling pressures. An increase in left ventricular filling pressure was responsible for the increase in left ventricular diastolic wall stress in our patients because their left ventricular diastolic volumes did not change during exercise at either low or conventional work loads. Repeated increases in left ventricular filling pressure, which have been shown to injure the connective tissue matrix of the myocardium, are likely to ultimately promote left ventricular dilation (32). Although this exposure is episodic, it is similar to the burden that the left ventricle experiences after a large myocardial infarction, where an increase in diastolic wall stress leads to dilation of the noninfarcted region of the ventricle (33,34). Because the periodic increases in left ventricular filling pressure and diastolic wall stress are markedly smaller during exercise training at low work loads than during conventional work loads, the stimulus for progressive left ventricular enlargement is less.

Limitations of the study. Although the present study did not include a nontraining control group, the steady state in peak V_{O_2} serially documented during the 6 weeks that preceded training and the unvarying magnitude of peak reactive hyperemic blood flow in the untrained forearm strongly support the role of training in effecting increases in peak V_{O_2} and calf peak reactive hyperemic blood flow. Although left ventricular diastolic volumes were unchanged in our patients after 12 weeks of exercise training at low work loads, a larger patient cohort and longer training period are needed to assess the impact of training on left ventricular volume.

Summary. Long-term exercise at low work loads (i.e., corresponding to ≤50% of peak aerobic capacity) appears to be a promising approach to physical training in patients with severe congestive heart failure because exercising at low work loads does increase peak aerobic capacity while exposing the left ventricle to lower wall stress than that associated with conventional work loads.

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