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Physical Training Improves Skeletal Muscle Metabolism in Patients With Chronic Heart Failure

STAMATIS ADAMOPOULOS, MD,*† ANDREW J. S. COATS, DM, FRACP,*†
FRANÇOIS BRUNOTTE, MD,‡ LEONARD ARNOLDA, MB, PHD,‡ THEO MEYER, MB, DPHIL,*
CAMPBELL H. THOMPSON, MB, FRACP,‡ JEFF F. DUNN, DPHIL,‡
JOHN STRATTON, MD, FACC,‡ GRAHAM J. KEMP, BM, BCH,‡
GEORGE K. RADDA, DPHIL, FRS,‡ BHEESHMA RAJAGOPALAN, DPHIL, FRCP‡
Oxford and London, England, United Kingdom

Objectives. This study investigated the effects of physical training on skeletal muscle metabolism in patients with chronic heart failure.

Background. Skeletal muscle metabolic abnormalities in patients with chronic heart failure have been associated with exercise intolerance. Muscle deconditioning is a possible mechanism for the intrinsic skeletal muscle metabolic changes seen in chronic heart failure.

Methods. We used phosphorus-31 nuclear magnetic resonance spectroscopy to study muscle metabolism during exercise in 12 patients with stable ischemic chronic heart failure undergoing 8 weeks of home-based bicycle exercise training in a randomized crossover controlled trial. Changes in muscle pH and concentrations of phosphocreatine and adenosine diphosphate (ADP) were measured in phosphorus-31 spectra of calf muscle obtained at rest, throughout incremental work load plantar flexion until exhaustion and during recovery from exercise. Results were compared with those in 15 age-matched control subjects who performed a single study only.

Results. Before training, phosphocreatine depletion, muscle acidification and the increase in ADP during the 1st 4 min of plantar flexion exercise were all increased ($p < 0.04$) compared with values in control subjects. Training produced an increase ($p < 0.002$) in incremental plantar flexion exercise tolerance. After training, phosphocreatine depletion and the increase in ADP during exercise were reduced significantly ($p < 0.003$) at all matched submaximal work loads and at peak exercise, although there was no significant change in the response of muscle pH to exercise. After training, changes in ADP were not significantly different from those in control subjects, although phosphocreatine depletion was still greater ($p < 0.05$) in trained patients than in control subjects. The phosphocreatine recovery half-time was significantly ($p < 0.05$) shorter after training, although there was no significant change in the half-time of adenosine diphosphate recovery. In untrained subjects, the initial rate of phosphocreatine resynthesis after exercise (a measure of the rate of oxidative adenosine triphosphate [ATP] synthesis) and the inferred maximal rate of mitochondrial ATP synthesis were reduced compared with rates in control subjects ($p < 0.003$) and both were significantly increased ($p < 0.05$) by training, so that they were not significantly different from values in control subjects.

Conclusions. The reduction in phosphocreatine depletion and in the increase in ADP during exercise, and the enhanced rate of phosphocreatine resynthesis in recovery (which is independent of muscle mass) indicate that a substantial correction of the impaired oxidative capacity of skeletal muscle in chronic heart failure can be achieved by exercise training.

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Exercise intolerance is a major limiting symptom in heart failure and has been attributed to skeletal muscle hypoperfusion during exercise as a result of both diminished cardiac output and impaired vasodilator reserve (1–3).

Interventions that improve hemodynamics and left ventricular function do not alter exercise capacity immediately. The failure of exercise capacity or skeletal muscle oxygen utilization to increase immediately when peripheral blood flow is increased (4,5) suggests that intrinsic abnormalities of skeletal muscle also play a role in the pathophysiology of exertional fatigue in chronic heart failure. In contrast, long-term vasodilator therapy can produce significant increases in exercise performance (6), suggesting that any such intrinsic muscle abnormality can eventually be reversed.

Studies (7,8) using phosphorus-31 (^{31}P) nuclear magnetic resonance (NMR) spectroscopy have demonstrated early and excessive acidification and phosphocreatine depletion in skeletal muscle in patients with chronic heart failure. These

From the *Cardiac Department, John Radcliffe Hospital, Oxford; †Cardiac Department National Heart and Lung Institute, London; and ‡MRC Biochemical & Clinical Magnetic Resonance Unit, John Radcliffe Hospital, Oxford, England, United Kingdom. This study was supported by the British Heart Foundation, London, Medical Research Council London, and Eli Lilly Pharmaceutical Company, Basingstoke, England.

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Address for correspondence: Stamatis Adamopoulos, MD, Cardiac Department, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, England, United Kingdom.

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NMR spectroscopic changes could not be explained by alterations in blood flow (8,9), suggesting an intrinsic abnormality in skeletal muscle metabolism. Other investigators (10,11) have shown major alterations in skeletal muscle histology and biochemistry in patients with long-term chronic heart failure, including fiber atrophy, transformation of type I to type II fibers and a decrease in oxidative enzyme capacity.

There are many similarities between the abnormalities associated with chronic heart failure and those seen in physical deconditioning (12). In both conditions, there is exercise intolerance, sympathetic hyperactivity, wasted skeletal muscles, decreased fiber size and depleted skeletal muscle oxidative enzymes (13,14). Physical training programs improve exercise performance, ventilation, autonomic function and symptomatic status in patients with chronic heart failure (15–17). We previously reported (18) on the beneficial effects of physical training in reversing the skeletal muscle metabolic changes in experimental heart failure in rats, and a recent study (19) reported beneficial effects from single-arm training. However, there has been no controlled trial on the effect of endurance training on leg muscle metabolism in patients with chronic heart failure.

In this study we used ^{31}P NMR spectroscopy to investigate the effects of physical training on skeletal muscle metabolic abnormalities in patients with chronic heart failure in a randomized controlled crossover trial, comparing home-based exercise training with activity restriction. We also investigated whether the skeletal muscle metabolism in patients with chronic heart failure after training is similar to that in age-matched normal control subjects.

Methods

Study patients. Twelve subjects gave informed consent for this trial, which was approved by the local ethics committee. We studied only patients with stable chronic heart failure secondary to ischemic heart disease and without angina or arrhythmias.

Patients were aged 62.4 ± 2.6 years (range 43 to 75). Seven were in New York Heart Association functional class II and five were in class III. Radionuclide left ventricular ejection fraction was 24 ± 3.4% and maximal oxygen consumption was 12.1 ± 1.2 ml/kg per min (mean ± SEM). Four patients had undergone coronary artery bypass grafting. All patients were taking diuretic drugs (median furosemide dose 80 mg); 10 of the 12 were taking angiotensin-converting enzyme inhibitors. Pharmacologic treatment was stable for 3 months before and the duration of the study in all subjects. On entry into the trial, patients underwent a 2- to 4-week familiarization and baseline evaluation phase, during which reproducible exercise tests were obtained. Subsequently, all patients were randomized to 8 weeks of bicycle exercise or avoidance of exercise in a crossover design that we (15) have previously described. Our control group consisted of 15 healthy men aged 55.2 ± 2.8 years (range 33 to 68).

Exercise testing. Exercise tests were performed on a Tunturi Professional Ergometer. The upright bicycle tests were performed in 5-min stages, with 25-W increments to the limit of tolerance. All tests were performed before daily medication had been taken and were conducted by a neutral observer who had no knowledge of patient data. Oxygen consumption and carbon dioxide production were measured during the test (15). On the same day after 1 h of rest, a second exercise test was performed in the supine position, during which pulsed wave Doppler ultrasound measurements of ascending aorta blood velocity from the suprasternal approach were made at rest and at the end of each 5-min 25-W incremental stage of supine bicycle exercise test. Using a Pedof Doppler ultrasound generator (Vingmed) and our own laboratory-made computer-based fast Fourier transform spectral analyzer (20), stroke distance (the integral of velocity and time for the ejection period) was calculated; stroke volume was then determined from standard formulas and an echocardiographic measurement of aortic cross-sectional area (leading edge to leading edge immediately distal to the sinus of Valsalva).

Phosphorus-31 nuclear magnetic resonance spectroscopy. Studies were performed ≥4 h after eating. The details of the spectroscopy protocol have been previously described (21). Briefly, the patient lay supine with his right calf muscle placed over a 6-cm diameter surface coil in a 1.9-tesla, 60-cm bore superconducting magnet (Oxford Magnet Technology) interfaced to a Bruker Biospec spectrometer. Phosphorus-31 spectra were acquired at 32.7-MHz, using an interpulse delay of 2 s at pulse length of 60° (a 90° pulse at coil center was 80 μs).

All normal control subjects and patients with heart failure were studied at rest, during 0.7-Hz (40/min) plantar flexion until exhaustion and during recovery from exercise. A spectrum of 128 scans was collected at rest and 32 scans were accumulated for each exercise spectrum. Exercise was performed using a pedal connected by means of pulleys to an adjustable weight. The initial work load was set at 1.5 W and four exercise spectra (64 s each) were collected at this work load. Thereafter, the work load was increased by 0.5 W after each spectrum had been collected. Recovery was monitored for approximately 10 min, in which time four spectra each of 16 scans (32 s/spectrum) were collected at first and thereafter eight spectra of 32 scans (64 s/spectrum). The time-averaged free induction decays were apodized, subjected to exponential multiplication to yield a line broadening of 6 Hz and Fourier transformed. The relative concentrations of inorganic phosphate, phosphocreatine and the beta-phosphate of adenosine 5′-triphosphate (ATP) were determined by triangulation and corrected for differential saturation. Changes in phosphocreatine concentration during exercise were expressed by the ratio phosphocreatine/(phosphocreatine + inorganic phosphate); pH was calculated from the chemical shift difference between inorganic phosphate and phosphocreatine (22). The cytosolic free concentration of adenosine diphosphate (ADP) was calculated from the phosphocre-

atine/ATP ratio and pH, using the equilibrium constant for the creatine kinase reaction (22). Recovery half-times for phosphocreatine and ADP were calculated by graphic interpolation. The initial rate of phosphocreatine resynthesis after exercise was calculated from the phosphocreatine concentration during the last exercise (t = 0) and first recovery (midpoint = 0.27 min) spectra. This is a direct estimate of the rate of mitochondrial ATP synthesis and normally has a hyperbolic relation to cytosolic ADP (23). We therefore used the initial rate of phosphocreatine resynthesis and the ADP concentration at the end of exercise to calculate an apparent maximal rate of mitochondrial ATP synthesis (that is, the rate when ADP concentration is very high), making the assumption that the mitochondrial Km for ADP (that is the ADP concentration at which the oxidation rate is half-maximum) is not altered.

Statistical analysis. Data were analyzed according to the recommendations of Hills and Armitage (24) for crossover trials. Analysis of variance (ANOVA) for repeated measures was used to detect the differences in terms of phosphocreatine utilization, acidification (pH) and ADP concentration during exercise before and after physical training. Repeated measures ANOVA was also used to analyze sequential changes at rest and during the part of the exercise completed both by control subjects and patients after physical training. The differences in recovery variables before and after training were assessed by the Wilcoxon signed-rank test and differences from control subjects by the Mann-Whitney *U* test. All values were expressed as mean value ± SEM.

Results

An example of the training-induced changes in phosphocreatine utilization at the same submaximal work load (2 W) for one of our subjects is depicted in Figure 1. There were no differences in muscle at rest with respect to muscle pH and phosphorus metabolite ratios (for example, phosphocreatine/ATP) in trained, detrained and control groups.

Differences between pre- and posttraining results. There was a small but significant improvement in plantar flexion exercise tolerance. Plantar flexion exercise time was 7.4 ± 0.7 min before training, increasing to 9.4 ± 0.8 min after training ($p < 0.002$).

After training there was significantly less phosphocreatine depletion during plantar flexion exercise ($p < 0.002$, ANOVA) (Fig. 2) and a significantly smaller increase in ADP ($p < 0.003$, ANOVA) (Fig. 3). In addition, the changes in muscle pH during exercise were not significantly different (Fig. 4), although a nonsignificant trend toward higher pH levels after training was apparent.

Training resulted in an acceleration in the recovery of phosphocreatine. After training, the half-time of phosphocreatine recovery was shorter (0.56 ± 0.17 vs. 0.89 ± 0.16 min, $p < 0.05$) and the initial rate of phosphocreatine resynthesis was faster (16 ± 2 vs. 11 ± 2 mmol/liter per min, $p < 0.05$), even though the end-exercise ADP concentration

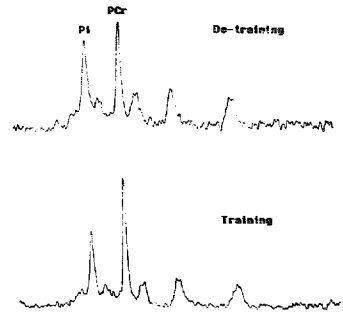
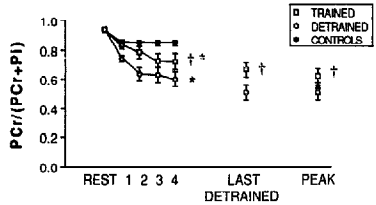


Figure 1. Phosphorus-31 nuclear magnetic resonance spectra of calf muscle during exercise at 2-W work load from a patient with chronic heart failure. From **left to right**, peaks are inorganic phosphate (Pi), phosphocreatine (PCr) and the gamma-, alpha- and beta-phosphates of adenosine triphosphate. Intracellular pH was calculated from the chemical shift difference between the inorganic phosphate and phosphocreatine peak. **Upper panel** shows spectrum obtained after detraining; **lower panel** shows the spectrum obtained after training during plantar flexion exercise at 2 W. The phosphocreatine level is higher and the inorganic phosphate level lower after physical training at the same work load.

(which drives phosphocreatine resynthesis) was, if anything, reduced (32 ± 4 vs. 51 ± 8 μmol/liter, $p = 0.06$). Thus, the estimated maximal rate of mitochondrial ATP synthesis, calculated from the initial phosphocreatine resynthesis rate

Figure 2. Effects of physical training on phosphocreatine (PCr) utilization. Phosphocreatine depletion during exercise is significantly improved by training at all matched submaximal work loads and even at peak exercise. *$p < 0.05$, comparison by analysis of variance of studies in control subjects. †$p < 0.05$, comparison of training and detraining studies by Wilcoxon signed-rank test. LAST DETRAINED = the highest work load achieved in the detraining study; 1 to 4 = the first four spectra (each 64 s) obtained at 1.5-W work load of plantar flexion exercise; PEAK = highest work loads achieved in detraining and training studies; Pi = inorganic phosphate; REST = muscle at rest; **closed circles** = control subjects; **open circles** = detrained patients; **open squares** = trained patients.



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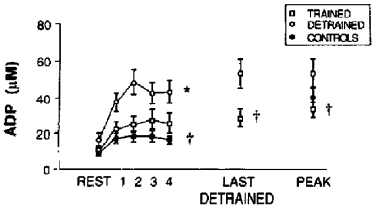

Figure 3. Effects of physical training on adenosine diphosphate (ADP). Physical training produced a significant reduction in ADP levels at all matched submaximal work loads and even at peak exercise. *Comparison by ANOVA of studies in control subjects; †comparison of trained and detrained studies by Wilcoxon signed-rank test (both $p < 0.05$). Abbreviations and format as in Figure 2.

and end-exercise ADP concentration, was increased after training (33 ± 6 vs. 20 ± 3 mmol/liter per min, $p < 0.01$). The decrease after training in the half-time of ADP recovery did not reach significance (0.25 ± 0.04 vs. 0.32 ± 0.07 min, p = NS).

Comparisons between patients and control subjects. Compared with control subjects, untrained patients with chronic heart failure had a significantly increased ADP concentration ($p < 0.005$), increased phosphocreatine depletion ($p < 0.0001$) and increased acidification ($p < 0.04$) during exercise at 1.5 W, which was the highest work load that all control subjects and patients with chronic heart failure managed to perform (Fig. 2 to 4).

There was no significant difference in pH and cytosolic free ADP concentration between control subjects and patients with chronic heart failure after training during exercise at 1.5 W. However, phosphocreatine depletion was significantly less in the control subjects ($p < 0.05$) (Fig. 2 to 4).

There was no significant difference between trained or untrained patients and control subjects in recovery half-time

Figure 4. Effects of physical training on pH. Training did not induce any significant difference in pH changes during plantar flexion exercise. *Comparison by ANOVA of studies in control subjects ($p < 0.05$). Abbreviations and format as in Figure 2.

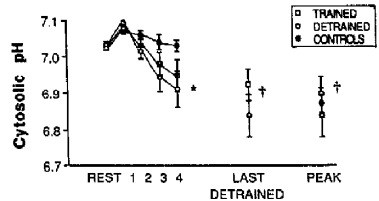

Table 1. Correlations Between Cardiac Performance and Skeletal Muscle Metabolism

Variable	VO_2max (ml/kg per min)	Cardiac Output at 50 W (liters/min)
Minute 4 of exercise		
PCr/(PCr + Pi)	0.5	0.5
pH	0.4	0.5
[ADP]	0.1	0.1
Recovery half-time		
PCr	0.3	0.1
ADP	0.3	0.6

Shown are the correlation coefficients describing the relation between the fractional improvement (achieved by physical training) in each pair of measurements. None of the correlations reached significance. [ADP] = adenosine diphosphate (ADP) concentration; PCr = phosphocreatine; Pi = inorganic phosphate; VO_2max = maximal oxygen consumption.

of phosphocreatine (0.61 ± 0.08 min in control subjects or ADP (0.29 ± 0.04 min in control subjects). However, in detrained subjects both the initial rate of phosphocreatine resynthesis and the calculated maximal rate of ATP synthesis during recovery were significantly lower (both $p < 0.003$) than in control subjects (20 ± 2 and 39 ± 3 mmol/liter per min, respectively, in control subjects); there was no significant difference between trained subjects and control subjects with respect to these measurements.

Thus, physical training in patients with chronic heart failure partially corrected skeletal muscle metabolic abnormalities. However, the plantar flexion exercise time of 9.4 ± 0.8 min after training was still shorter ($p < 0.001$) than the exercise time of 19.7 ± 1.18 min achieved by control subjects.

Correlations between cardiac performance and skeletal muscle metabolism. Physical training induced an improvement in functional capacity and exercise tolerance in patients with chronic heart failure. Maximal oxygen consumption measured during upright bicycle exercise was increased by training from 12.2 ± 1.3 to 14.1 ± 1.5 ml/kg per min ($p < 0.004$) and the bicycle exercise duration was increased from 12.7 ± 1.7 to 15.8 ± 2.1 min ($p < 0.002$). Cardiac output at rest was not significantly increased by training (5.7 ± 0.5 compared to 5.0 ± 0.4 liters/min before training), whereas cardiac output at 50 W was significantly increased by training from 6.1 ± 0.6 to 6.9 ± 0.7 liters/min ($p < 0.05$). There was no significant correlation, however, between improvement in bicycle or plantar flexion exercise performance and training-induced changes in skeletal muscle metabolism (Table 1), nor was there a significant correlation between improvements in estimated maximal rate of phosphocreatine resynthesis and the phosphocreatine/(phosphocreatine + inorganic phosphate) at minute 4 of exercise (r = 0.5, p = NS).

Discussion

^{31}P nuclear magnetic resonance abnormalities. This study demonstrates that in patients with moderate to severe ischemic chronic heart failure, an exercise training program at

home improves skeletal muscle energetics, exercise performance, hemodynamics, ventilation and autonomic function (15,16).

The smaller increase in phosphocreatine and increase in ADP during exercise suggest an increased capacity for oxidative ATP synthesis after physical training as a result of an increase in either mitochondrial content or activity (25). The acceleration in phosphocreatine resynthesis is consistent with this view, and the increase in the inferred maximal rate of ATP synthesis suggests an approximately 50% improvement. It has recently been demonstrated (26) that the volume density of mitochondria in muscle and the surface density of mitochondrial cristae are reduced in chronic heart failure.

Changes in pH during exercise are a balance between the effects of lactic acid production and buffering, and an important component of buffering during exercise is the consumption of protons by the net hydrolysis of phosphocreatine (27). Training produces no significant change in the pH response during exercise compared with detraining in patients with chronic heart failure. This could be because both phosphocreatine depletion (reflected in changes in the phosphocreatine/(phosphocreatine + inorganic phosphate) ratio [Fig. 2]) and lactic acid production are reduced after training. However, despite similar phosphocreatine depletion in the trained and control subjects (Fig. 2), trained subjects with chronic heart failure show significant acidosis during exercise (Fig. 4). This observation suggests that the patients with chronic heart failure may continue to have increased lactate production even after training.

Possible biochemical mechanisms. Further insight into the biochemical mechanism underlying these training-induced bioenergetic changes is provided by measurements of muscle enzymatic activity in our previously reported experimental model (18). Rats with heart failure responded to a physical training program by increasing levels of the mitochondrial oxidative enzyme citrate synthase and the mitochondrial cytoplasmic enzyme glutamate pyruvate amino transferase. Training is known to induce an increase in the level of glutamate pyruvate amino transferase, which catalyzes the generation of alanine and ketoglutarate from pyruvate and glutamate, thus reducing the formation of lactic acid during exercise (and therefore acidification of the muscle during exercise) and providing oxaloacetate for the first step of the Krebs cycle (28,29). Reduced glutamate pyruvate amino transferase activity in chronic heart failure might be another biochemical mechanism explaining the improvement in skeletal muscle abnormalities and exercise capacity in our patients with chronic heart failure.

Apart from muscle conditioning, there are other possible explanations of the training induced improvement in skeletal muscle oxidative capacity. Lipkin et al. (30) and more recently Miyagi et al. (31) reported evidence consistent with reduced skeletal muscle mass and strength in chronic heart failure. Thus, in chronic heart failure, each fiber might be subjected to an increased load, resulting in a greater change in the phosphocreatine/(phosphocreatine + inorganic phosphate) ratio and muscle pH. The NMR spectroscopic changes during exercise seen in our patients after training, therefore, could have resulted from performing the same work with more muscle. That this is not the only mechanism has been recently shown in a study (19) in which localized skeletal muscle training produced beneficial NMR spectroscopic responses at submaximal work loads without any associated change in muscle mass. Moreover, in our recent experimental study (18), no significant difference in muscle mass was found in rats with congestive heart failure randomly allocated to either training or nontraining compared with values in sham-operated rats despite the significant training-induced improvement in skeletal muscle metabolism assessed with ^{31}P NMR spectroscopy and enzymatic assays. Also, a recent study (32) has shown that atrophy contributes only modestly to reduced exercise capacity and altered muscle metabolism in chronic heart failure.

It is a particular advantage of measurements of phosphocreatine recovery kinetics that they are independent of muscle mass (32). We and others (32) have shown that phosphocreatine resynthesis is impaired in chronic heart failure, and the present data show that this is improved by training. A novel feature of the present analysis is the estimation of the maximal rate of mitochondrial ATP synthesis by using the known relation between phosphocreatine resynthesis and ADP concentration (23). This represents the inferred rate of ATP synthesis at saturating ADP concentrations and is (in accordance with standard biochemical usage) the mitochondrial effective maximal rate of mitochondrial ATP synthesis (*Vmax*). This takes into account the relation between ATP synthesis and ADP concentration (23) and addresses questions of mitochondrial capacity and control more directly than does the recovery half-time.

Possible neural and vascular mechanisms. Wilson et al. (2,33) reported impairment in blood flow during exercise in patients with heart failure. Although inadequate blood flow could produce the NMR spectroscopic changes observed in our patients, there is strong evidence from blood flow measurements (9,21,34) and studies during ischemic exercise (8) that these metabolic events cannot be fully explained by changes in limb blood flow. These human data confirm the finding in previous experimental studies (35) that there is no difference in blood flow between trained and sedentary rats with myocardial infarction. Minotti et al. (19) in their localized forearm exercise training study in patients with chronic heart failure showed improvement in muscle energetics independently of limb blood flow or central cardiovascular response. Also, the same investigators (36) more recently reported that reduced muscle endurance is independent of exercise blood flow and suggested that structural or biochemical changes, or both, in muscle may contribute to exercise intolerance in chronic heart failure. However, despite these findings, redistribution of blood flow within the leg to perfuse the exercising muscles more effectively cannot be excluded as a cause of the decreased exercise tolerance (37).

A contribution of peripheral neural adjustments to the metabolic changes after training also cannot be excluded.

These may be related to either alterations in recruitment of motoneurons with endurance training or increased sensitivity of $beta_2$ muscle metabolic receptors compatible with the reduced sympathetic activity we have observed with training (16).

Conclusions. To what extent these muscle changes influence the exercise capacity of patients remains to be determined. The lack of correlation between the training-induced improvement in exercise performance and indexes of skeletal muscle metabolism seen in Table 1 indicates that other peripheral factors may be limiting exercise in these patients. Once skeletal muscle changes are corrected, peripheral vascular, autonomic or pulmonary factors may intervene to restrict the improvement in exercise tolerance. Training is also specific to the training task and because we trained our patients on a bicycle and tested with plantar flexion exercise, the changes may be disparate (38). This view is also supported by the finding that in patients with chronic heart failure, training almost completely corrected the skeletal muscle metabolic abnormalities observed in comparison with findings in age-matched control subjects but only partially corrected the reduced plantar flexion exercise tolerance. Further prospective trials early in the evolution of heart failure are necessary to show whether some of the secondary changes could be ameliorated by avoidance of physical deconditioning.

References

1. Zelis R, Nellis SH, Longhurst J, Lee G, Mason DT. Abnormalities in the regional circulations accompanying congestive heart failure. Prog Cardiovasc Dis 1975;18:181–99.
2. Wilson JR, Martin JL, Schwartz D, Ferraro N. Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. Circulation 1984;69:1079–87.
3. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure: muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation 1989;80:769–81.
4. Wilson JR, Martin JL, Ferraro N. Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: role of cardiac pump dysfunction as determined by the effect of dobutamine. Am J Cardiol 1984;53:1308–15.
5. Wilson JR, Martin JL, Ferraro N, Weber KT. Effect of hydralazine on perfusion and metabolism in the leg during upright bicycle exercise in patients with heart failure. Circulation 1983;68:425–32.
6. Franciosa JA, Goldsmith SR, Cohn JN. Contrasting immediate and long-term effects of isosorbide dinitrate on exercise capacity in congestive heart failure. Am J Med 1980;69:559–66.
7. Massie BM, Conway M, Yonge R, et al. ^{31}P nuclear magnetic resonance evidence of abnormal skeletal muscle metabolism in patients with congestive heart failure. Am J Cardiol 1987;60:309–15.
8. Massie BM, Conway M, Rajagopalan, et al. Skeletal muscle metabolism during exercise under ischemic conditions in congestive heart failure: evidence for abnormalities unrelated to blood flow. Circulation 1988;78: 320–6.
9. Wiener DH, Fink LI, Maris J, Jones RA, Chance B, Wilson JR. Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow. Circulation 1986;73:1127–36.
10. Sullivan MJ, Green HJ, Cobb FR. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. Circulation 1990;81:518–27.
11. Mancini DM, Coyle E, Coggan A, et al. Contribution of intrinsic skeletal muscle changes to ^{31}P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. Circulation 1989;80:1338–46.
12. Adamopoulos S, Coats AJS. Peripheral abnormalities in chronic heart failure. Postgrad Med J;1991:67(suppl 1):S74–80.
13. Coyle EF, Martin WH, Sinacore DR, Joyner MJ, Hagberg JM, Holloszy JO. Time course of loss of adaptations after stopping prolonged intense endurance training. J Appl Physiol 1984;57:1857–64.
14. Green HJ, Thompson JA, Daub BD, Ranney DA. Biochemical and histochemical alterations in skeletal muscle in man during a period of reduced activity. Can J Physiol Pharmacol 1980;58:1311–6.
15. Coats AJS, Adamopoulos S, Meyer TE, Conway J, Sleight P. Effects of physical training in chronic heart failure. Lancet 1990;335:63–6.
16. Adamopoulos S, Coats AJS, McCance A, et al. Physical training improves autonomic balance in chronic heart failure (abstr). Eur Heart J 1990;11(suppl):244.
17. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction: hemodynamic and metabolic effects. Circulation 1988;78:506–15.
18. Adamopoulos S, Brunotte F, Coats AJS, et al. Skeletal muscle metabolism in experimental heart failure: effects of infarct size and physical training (abstr). J Am Coll Cardiol 1991;17(suppl):158A.
19. Minotti JR, Johnson EC, Hudson TL, et al. Skeletal muscle response to exercise training in congestive heart failure. J Clin Invest 1990;86:751–8.
20. Murphy C, Coats A, Conway J, Colditz P, Rolphe P. Doppler ultrasound signal analysis based on the TMS320 signal processor. J Biomed Eng 1988;10:127–9.
21. Arnolda L, Conway M, Dolecki M, et al. Skeletal muscle metabolism in heart failure: a ^{31}P nuclear magnetic resonance spectroscopy study of leg muscle. Clin Sci 1990;79:583–9.
22. Taylor DJ, Bore PJ, Styles P, Gadian DG, Radda GK. Bioenergetics of intact human muscle: a ^{31}P nuclear magnetic resonance study. Mol Biol Med 1983;1:77–94.
23. Kemp GJ, Taylor DJ, Radda GK. Control of phosphocreatine resynthesis during recovery from exercise in human skeletal muscle. NMR Biomed (in press).
24. Hills M, Armitage P. The two-period cross-over clinical trial. Br J Clin Pharmacol 1979;8:7–20.
25. Dudley GA, Tullson PC, Terjung RL. Influence of mitochondrial content on the sensitivity of respiratory control. J Biol Chem 1987;262:9109–14.
26. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation 1992;85:1751–9.
27. Kemp GJ, Taylor DJ, Styles P, Radda GK. The production, buffering and efflux of protons in human skeletal muscle during exercise and recovery. NMR Biomed (in press).
28. Mole PA, Baldwin KM, Terjung RL, Holloszy JO. Enzymatic pathways of pyruvate metabolism in skeletal muscle: adaptations to exercise. Am J Physiol 1973;224:50–4.
29. Holloszy JO. Adaptation of muscular tissue to training. Prog Cardiovasc Dis 1976;18:445–8.
30. Lipkin D, Jones D, Round J, Poole-Wilson P. Abnormalities of skeletal muscle in patients with chronic heart failure. Int J Cardiol 1988;18:187–95.
31. Miyagi K, Asanoi H, Ishizaka S, Kameyama T, Sasayama S. Loss of skeletal muscle mass is a major determinant of exercise intolerance in chronic heart failure (abstr). Circulation 1991;84(suppl II):II-74.
32. Mancini DM, Walter G, Reichek N, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992;85:1364–73.
33. Wilson JR, Falcone R, Ferraro N, Egler J. Mechanism of skeletal muscle underperfusion in a dog model of low-output heart failure. Am J Physiol 1986;251:H227–35.
34. Massie BM, Conway M, Yonge R, et al. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. Circulation 1987;76:1009–19.
35. Munch TI, Moore RL, Leathers DJ, Bruno A, Zelis R. Endurance training in rats with chronic heart failure induced by myocardial infarction. Circulation 1986;74:431–41.
36. Minotti JR, Oka RK, Wells LM, Christoph I, Massie BM. Is abnormal muscle endurance in congestive heart failure independent of blood flow? (abstr). Circulation 1991;84(suppl II):II-73.
37. Mackie BG, Terjung RL. Influence of training on blood flow to different skeletal muscle fiber types. J Appl Physiol 1983;55:1072–8.
38. Rube N, Secher NH. Effect of training on central factors in fatigue following two- and one-leg static exercise in man. Acta Physiol Scand 1990;141:87–93.