Effect of Resistance Exercise on Skeletal Muscle Myopathy in Heart Transplant Recipients

Randy W. Braith, PhD, Peter M. Magyari, PhD, Gary L. Pierce, MS, David G. Edwards, PhD, James A. Hill, MD, Lesley J. White, PhD, and Juan M. Aranda, Jr., MD

The purpose of this study was to determine the efficacy of resistance exercise in reversing skeletal muscle myopathy in heart transplant recipients. Myopathy, engendered by both heart failure and immunosuppression with glucocorticoids, is a post-transplant complication. The sequelae of myopathic disease includes fiber-type shifts and deficits in aerobic metabolic capability. We randomly assigned patients to either 6 months of resistance exercise (training group; n = 8) or a control (control group; n = 7) group. Exercise was initiated at 2 months after transplant. Biopsy of the right vastus lateralis was performed before and after the 6-month intervention. Myosin heavy chain (MHC) composition was assessed using sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Biochemical assays were performed to determine citrate synthase, 3-hydroxyacyl-CoA-dehydrogenase, and lactate dehydrogenase activity. There were no group differences ($p \geq 0.05$) in MHC composition and enzymatic reserve at baseline. Improvements in the training group for citrate cynthase (+40%), 3-hydroxyacyl-CoA-dehydrogenase (+10%), and lactate dehydrogenase activity (+48%) were significantly greater ($p \leq 0.05$) than in the control group (+10%, −15%, and +20%, respectively). Oxidative type 1 MHC isoform concentration increased significantly in the training group (+73%, $p \leq 0.05$) but decreased in the control group (−28%; $p \leq 0.05$). Glycolytic type 2x MHC isoform increased significantly (17%; $p \leq 0.05$) in the control group but decreased (−33%; $p \leq 0.05$) in the training group. This is the first study to demonstrate that resistance training elicits myofibrillar shifts from less oxidative type II fibers to more oxidative fatigue-resistant type I fibers in heart transplant recipients. Resistance exercise initiated early in the post-transplant period is efficacious in changing skeletal muscle phenotype through increases in enzymatic reserve and shifts in fiber morphology.

(Am J Cardiol 2005;95:1192–1198)

Skeletal muscle myopathy is a hallmark of end-stage heart failure involving both morphologic shifts in fiber type[1–4] and histochemical changes in enzymatic reserve.[5,6] After orthotopic heart transplantation, immunosuppression regimens using bolus glucocorticoids cause further de novo deleterious effects on skeletal muscle.[7–11] No therapeutic intervention has been developed to prevent myopathic disease in heart transplant recipients. The purpose of this study was to determine if an intervention consisting of progressive resistance exercise, initiated early in the post-transplant period, would be efficacious in changing skeletal muscle phenotype through increases in enzymatic reserve and shifts in fiber morphology in heart transplant recipients. We used skeletal muscle biopsy to prospectively assess skeletal muscle morphology and enzymatic reserve in heart transplant recipients at 2 months after transplant and repeated the measurements after 6 months of progressive resistance exercise training or a control period.

From the Center for Exercise Science, College of Health and Human Performance and the College of Medicine, University of Florida, Gainesville, Florida; Lynchburg College, Lynchburg, Virginia; and the Department of Kinesiology, University of New Hampshire, Durham, New Hampshire. This report was supported by a grant from the American Heart Association, Dallas, Texas, to Dr. Braith. Manuscript received September 13, 2004; revised manuscript received and accepted January 10, 2005.

Address for reprints: Randy W. Braith, PhD, PO Box 118206, Center for Exercise Science, University of Florida, Gainesville, Florida 32611. E-mail: rbraith@hhp.ufl.edu.

METHODS

Subjects: Fifteen patients (n = 15) were recruited to participate in the study at the time they were listed with the United Network for Organ Sharing as candidates for orthotopic heart transplantation. Descriptive characteristics of heart transplant recipients are listed in Table 1. Before transplantation, patients were randomly and prospectively assigned either to a group that would participate in a 6-month program of resistance exercise training (n = 8) or to a control group that would not participate in resistance exercise (n = 7). Before transplantation, all subjects participated in a hospital-based physical therapy program consisting of mild walking and resistance exercises. After transplantation, all subjects participated in standard care home-based walking programs that were comparable in intensity and duration, but only the resistance training group performed specific supervised resistance exercises.

All heart transplant recipients had biatrial anastomosis at the time of transplantation and were receiving triple-drug immunosuppression therapy with cyclosporine, prednisone, and azathioprine. Cyclosporine dose was titrated to maintain whole blood trough levels of approximately 300 ng/ml. No subject re-

0002-9149/05/$–see front matter
doi:10.1016/j.amjcard.2005.01.048

TABLE 1 Descriptive and Muscle Metabolic Enzyme Activity Data for Transplant Recipients at Baseline and After Six Months of Resistance Exercise or a Control Period

	Age (yrs/sex)	Etiology of CHF	BMI (kg/m^2)	Time Before Txp (wks)	Baseline Enzyme Activity			Enzyme Activity After 6 Months		
					LDH	CS	HACoA	LDH	CS	HACoA
Trained patients										
1	64M	Ischemic	28.1	8	97.0	9.4	4.0	210.0	14.1	3.9
2	62M	Ischemic	22.1	23	78.0	10.7	3.3	151.0	14.3	3.9
3	51M	Ischemic	25.6	21	158.0	11.5	3.4	170.0	16.7	2.5
4	45M	IDC	28.8	1	66.0	10.5	4.2	160.0	13.7	3.6
5	49M	Ischemic	29.3	7	104.0	10.5	2.5	141.0	12.7	2.3
6	40M	IDC	29.9	16	159.0	9.0	2.8	167.0	15.6	5.6
7	50M	IDC	27.8	4	74.0	10.1	4.1	80.0	13.6	3.3
Mean ± SD	52 ± 2		27.4 ± 2.1	11 ± 4	105 ± 10	10.2 ± 0.6	3.5 ± 0.3	154 ± 15*†	14.4 ± 0.5*†	3.5 ± 0.4
Control patients										
1	57M	Ischemic	29.3	22	49.0	6.0	4.9	59.0	9.5	4.6
2	41M	Ischemic	26.8	17	106.0	14.0	4.1	148.0	16.4	3.4
3	54M	IDC	28.8	4	122.0	7.4	2.7	156.0	8.0	2.8
4	63M	IDC	30.5	12	134.0	9.9	4.6	165.0	8.3	3.2
5	62M	Ischemic	25.9	12	144.0	13.4	4.1	155.0	13.3	4.0
6	45M	Ischemic	24.3	3	114.0	12.9	2.1	149.0	8.8	1.5
Mean ± SD	53 ± 2		27.6 ± 2.3	12 ± 5	112 ± 13	10.6 ± 1.4	3.7 ± 0.7	139 ± 11*	10.7 ± 1.4	3.2 ± 0.2

*$p \leq 0.05$ baseline versus 6 months;†$p \leq 0.05$ trained versus control.
Units of enzyme activity are reported as mmol/g wet weight/min.
There were no significant differences between groups at study entry.
BMI = body mass index; CHF = congestive heart failure; CS = citrate cynthase; IDC = idiopathic dilated cardiomyopathy; Txp = transplantation.

quired a ventricular assist device as a bridge to transplantation, and no subject was confined to bed before transplantation. The protocol was approved by the institutional review board for the protection of human subjects at the University of Florida College of Medicine, and all subjects provided written informed consent before cardiac transplantation to participate in the study.

Muscle biopsy technique: Skeletal muscle tissue was extracted from the right vastus lateralis of each subject using a percutaneous needle at 2 months after transplantation and after 6 months of resistance exercise training or the control period. Subcutaneous 2% lidocaine hydrochloride was applied to the biopsy site and biopsy was performed using a modification of the Bergstrom technique.[12] This modification included application of suction using a 140-ml syringe, as described by Evans et al.[13] A transplant cardiologist, trained in the procedure, performed all muscle biopsies. Samples were immediately placed in 1.5-ml microcentrifuge tubes and snap-frozen in liquid nitrogen and then stored at −80°C until ultrastructural and biochemical analysis.

Skeletal muscle morphologic procedures: Morphologic assessment of the skeletal muscle MHC fiber isoforms was performed using 10% sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (10%) as described by Bamman et al.[14] This technique yields clear separation of all 3 MHC chain isoforms (MHC I, IIa, IIx) in human skeletal muscle. In brief, muscle was homogenized using a glass micropestle in cold 100-mmol/L potassium phosphate buffer at 1:20 dilution and pH 7.4. Muscle homogenate was centrifuged at 700*g* for 10 minutes and the supernantant was removed and further diluted to 1:100, with 1.0 mol/L potassium phosphate buffer and used for enzyme assays. The myofibril pellet (insoluble protein) was resuspended and purified as described by Solaro et al.[15] Total protein concentration was determined as described by Bradford[16] and diluted in Laemmli sample buffer (Bio-Rad Laboratories, Hercules, California) to a final protein concentration of 0.2 μg/ml. Samples were boiled for 2 minutes and stored at −80°C until gel analysis. For analysis, 20 μl of sample was loaded in to minigels (30% acrylamide, 0.8% bis-acrylamide [37:1]; 1.5 mol/L tris base; 1 mol/L glycine; 10% SDS;100% glycerol; distilled water; 10% ammonium persulfate; TEMED) and run at 150 V for 20 hours in cold upper (diluted 6 ×) and lower running buffer (0.1 mol/L tris; 0.15 mol/L glycine; 10% SDS). Gels were stained with Rapid Coomassie Blue (Research Products International, Prospect, Illinois), and protein bands were captured on a Scientific Imaging System (Kodak 1D 3.6, New Haven, Connecticut) and each band analyzed for optical density. MHC isoforms were reported as relative percentages of each isoform.

Biochemical assay procedures: Biochemical enzyme assays were performed on 1:100 supernatant from the muscle homogenate to determine levels of activity of the oxidative enzymes citrate synthase and 3-hydroxyacyl-coenzyme A-dehydrogenase (HACoA), and the glycolytic enzyme lactate dehydrogenase (LDH). Citrate cynthase activity was determined by the spectrophotometric method described by Srere.[17] HACoA activity was described using the method by Smith.[18] LDH activity was determined using the method described by Bergmeyer et al.[19]

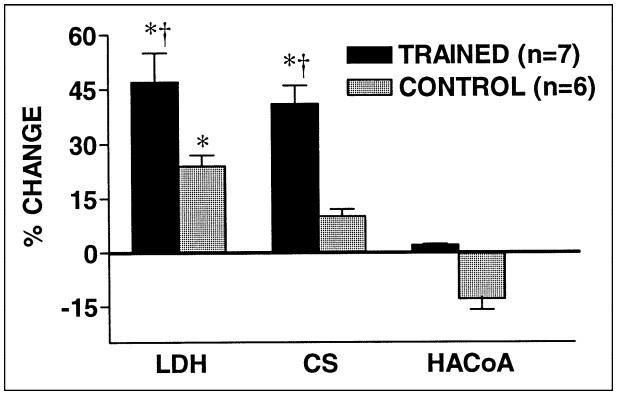

FIGURE 1. Percent change in skeletal muscle metabolic enzyme activity after 6 months of a progressive resistance exercise program (Trained) or a control period (Control). Data are expressed as mean value ± SEM. *p ≤0.05 versus baseline value; †p ≤0.05 training versus control group. CS = citrate synthase.

Skeletal muscle strength testing: Two months after heart transplantation, subjects in the training and control groups completed 2 tests designed to assess upper and lower body strength: (1) a dynamic variable resistance 1 repetition maximum (1-RM) bilateral knee extension strength test (MedX, Ocala, Florida); and (2) a dynamic variable resistance 1-RM dual-decline chest press strength test (MedX). Strength testing was performed by MedX technicians who were not aware of subject group assignment.

The 1-RM testing sessions began with the subject performing a warm-up set of 6 to 8 repetitions with a light weight. The initial 1-RM weights were standardized among subjects and represented 50% of body weight for bilateral knee extension and 30% of body weight for the dual decline chest press. When the weight was successfully lifted through the range of motion , the weight for the next trial was incremented by 2.3 to 9 kg. Two minutes of recovery time were allowed between 1-RM trials. The last weight successfully lifted through the full range of motion was considered the 1-RM. Most subjects reached their 1-RM in 3 to 5 trials. The 1-RM tests were repeated after 6 months of a resistance exercise training program or control period.

Resistance exercise training protocol: Supervised resistance exercise training was initiated at 2 months after transplantation, which permitted sufficient time for recovery from surgical sternotomy.[11] The 6-month training regimen consisted of upper and lower body exercise 2 days/week using MedX variable resistance machines. All training sessions involved 1 transplant recipient supervised by 1 exercise specialist certified in the proper use of MedX equipment. Before resistance exercise sessions, subjects walked for 5 minutes at low intensity on a treadmill. A single set consisting of 10 to 15 repetitions was completed for each exercise. The initial training resistance represented 50% of

TABLE 2 Composition of Skeletal Muscle Myosin Heavy Chain (MHC) Isoforms in the Trained and Control Groups After Six Months of Resistance Exercise or a Control Period

	Baseline Muscle Composition			Muscle Composition After 6 Months		
	MHC	MHC2a	MHC2x	MHC	MHC2a	MHC2x
Trained patients						
1	28.7	41.2	30.0	45.6	32.9	21.5
2	20.4	32.8	46.8	22.7	33.3	43.9
3	24.0	40.0	36.0	37.0	33.3	29.6
4	17.0	40.1	42.9	23.0	61.0	20.8
5	5.8	24.8	69.4	13.1	33.0	53.9
6	12.6	35.6	51.8	44.2	32.5	23.3
7	17.0	42.7	40.4	32.0	43.8	24.3
Mean ± SD	17.9 ± 6.8	36.7 ± 2.4	45.3 ± 8.2	31.0 ± 5.3*†	38.5 ± 2.6	31.0 ± 5.1*†
Control patients						
1	29.0	36.0	34.8	21.0	19.0	60.0
2	26.6	33.1	40.3	25.4	37.6	37.0
3	16.0	31.0	53.2	9.0	31.0	59.8
4	26.0	30.0	44.0	16.0	37.0	46.9
5	37.0	21.0	42.5	31.0	31.0	37.8
6	28.0	25.0	47.0	13.5	22.8	63.7
Mean ± SD	27.1 ± 6.0	29.3 ± 3.2	43.6 ± 3.3	19.3 ± 6.6*	29.6 ± 4.9	51.0 ± 6.5*

Values are percentage of total MHC content.
*p ≤0.05 baseline versus 6 months;†p ≤0.05 trained versus control groups.
MHC2a = myocin heavy chain 2a isoform; MHC2x = myocin heavy chain 2x isoform.

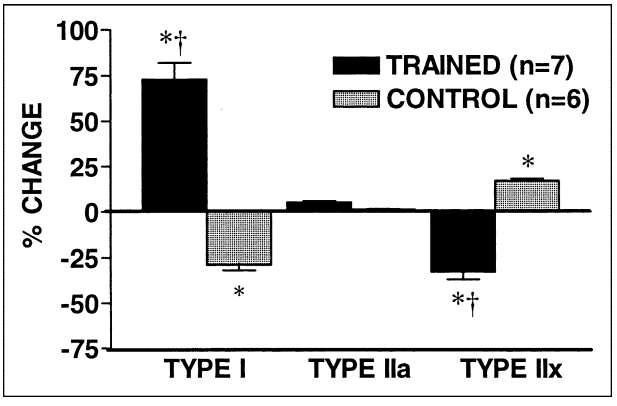

FIGURE 2. Percent change in the composition of MHC isoforms after 6 months of a progressive resistance exercise program (Trained) or a control period (Control). Data are expressed as mean value ± SEM. *p ≤0.05 versus baseline value; †p ≤0.05 training versus control group.

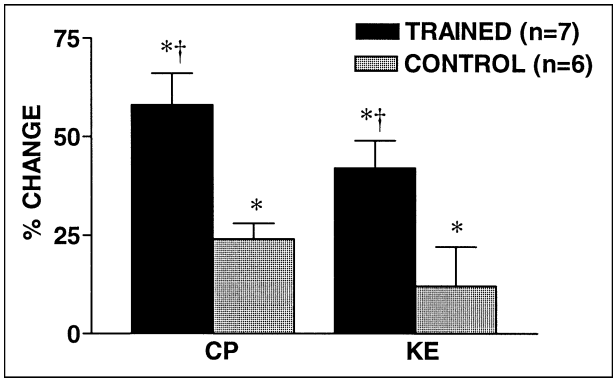

FIGURE 3. Percent change in chest press (CP) strength and knee extension (KE) strength after 6 months of a progressive resistance exercise program (Trained) or a control period (Control). Data are expressed as mean value ± SEM. *p ≤0.05 versus baseline value; †p ≤0.05 training versus control group.

1 repetition maximum. Subjects were not permitted to exceed 15 repetitions. Rather, when 15 repetitions were successfully achieved, the resistance was increased by 5% to 10% at the next training session. Thus, the exercise prescription strived to have subjects use the greatest resistance possible to complete 15 repetitions.

The following exercises were performed in order: chest press, knee extension, pull-down, seated leg curl, shoulder press, seated triceps dip, biceps curl, and lumbar extension. Special precautions were taken to ensure adequate maintenance of blood pressure in preload-dependent cardiac denervated heart transplant recipients. Upper body exercises were alternated with lower body exercises in an attempt to prevent blood pooling. Subjects with symptoms of transient hypotension walked 2 minutes between exercises or performed standing calf raises.

Glucocorticoid therapy: Heart transplant recipients all received 1,000 mg of methylprednisolone (Solumedrol, Pharmacia & UpJohn, New York, New York) intravenously during the transplantation surgery and 375 mg/24 hours of methylprednisolone intravenously on the first postoperative day. Methylprednisolone was reduced to 250 mg/24 hours on the second postoperative day and to 125 mg/24 hours on the third postoperative day. Oral prednisone (1 mg/kg body weight/day) was initiated on the fourth postoperative day. During the first 6 weeks after transplantation, the daily prednisone dose was tapered by 20 mg each week in transplant recipients who remained rejection free. The daily prednisone dose was further reduced by 10 mg after week 6, and by 5 mg after week 8. Thereafter, in the absence of rejection,

the daily prednisone dose was decreased by 2.5 mg every 2 weeks until prednisone was discontinued or rejection occurred. Episodes of acute rejection, as determined by routine surveillance endomyocardial biopsy, were treated with enhanced immunosuppression, including increased doses of intravenous methylprednisolone or oral prednisone.

Statistical analysis: Descriptive characteristics were compared between groups using analysis of variance. The temporal pattern of MHC isoform percentage, enzyme concentrations, and skeletal muscle strength at 2 and 8 months after transplantation were compared using analysis of variance. Analysis of variance was performed using the SAS general linear model procedure (SAS Institute, Cary, North Carolina). An α level of $p < 0.05$ was required for statistical significance.

RESULTS

One patient randomized to the training group was prevented from completing the postoperative training protocol due to sinus bradyarrhythmia, and 1 patient randomized to the control group was lost due to noncardiac mortality. Data from those subjects were not included in the statistical analyses. Descriptive characteristics of the remaining 13 subjects are listed in Table 1. The 2 groups did not differ ($p \geq 0.05$) with respect to age, height, weight, and the duration of time on the United Network for Organ Sharing waiting list before heart transplantation.

Activity of the muscle metabolic enzymes (reported as mmol/g wet muscle weight/min) did not differ ($p \geq 0.05$) between groups at baseline. Absolute enzyme values are presented in Table 1 and relative changes in muscle enzyme activity are presented in Figure 1. LDH enzyme activity levels increased significantly ($p \leq 0.05$) in both the control (112 ± 13 to 139 ± 11 mmol/g wet weight/min) and trained (105 ± 10 to 154 ± 15 mmol/g wet weight/min) groups, but the magnitude of increase in LDH activity in the trained group was twofold greater ($p \leq 0.05$). Citrate synthase enzyme activity increased significantly in the trained group (10.5 ± 0.6 to 14.4 ± 0.5 mmol/g wet weight/min) but did not change ($p \geq 0.05$) in the control group (9.5 ± 2.1 to 10.6 ± 1.4 mmol/g wet weight/min). HACoA enzyme activity did not change significantly ($p \geq 0.05$) in either the control or trained groups.

Skeletal muscle MHC isoform composition (fraction represented by type I, type IIa, and type IIx) did not differ ($p \geq 0.05$) between the 2 groups at baseline. Absolute changes in MHC composition are presented in Table 2, and relative changes in skeletal muscle MHC isoform composition are shown in Figure 2. The 6-month resistance exercise program elicited a significant ($p \leq 0.05$) increase in fatigue-resistant MHC type I fibers (+73%) and a concurrent significant decrease in highly fatigable MHC type IIx fibers (−33%). In contrast, the control group experienced a further significant reduction in oxidative fatigue-resistant MHC type I fibers from baseline (−29%) and a further significant increase in glycolytic fatigue-prone MHC type IIx fibers from baseline values (+17%).

Criterion measures of upper (chest press) and lower body (knee extension) strength were significantly ($p \leq 0.05$) improved after the 6-month intervention in both groups. However, the magnitude of upper body strength improvement in the trained group was 2.5-fold greater (from 187 ± 36 before to 289 ± 63 lbs after training on 1-RM test) than the control group (from 130 ± 52 before to 164 ± 53 lbs after control period on 1-RM test), and the magnitude of lower body strength improvement in the trained group was fourfold greater (from 214 ± 19 before to 300 ± 24 lbs after training on 1-RM test) than in the control group (from 180 ± 11 before to 203 ± 10 lbs after control period on 1-RM test). Relative changes in strength are presented in Figure 3.

Acute allograft rejection was determined by endomyocardial biopsy and graded using the International Society for Heart and Lung Transplantation system. We enhanced immunosuppression only for the International Society for Heart and Lung Transplantation grade 3A or 3B rejection. A total of 8 acute rejection episodes in the control group and 7 episodes in the training group were treated with enhanced glucocorticoids. Oral prednisone was enhanced ($100 \text{ mg} \times 3$ days with rapid taper) for 4 of the rejection episodes in the control group and 3 episodes in the training group. Methylprednisolone was administered intravenously (1 g/day for 3 days or 500 mg/day for 3 days) for 4 rejection episodes in the control group and 3 episodes in the training group. Total prednisone consumption at 8 months after transplantation was not different ($p \geq 0.05$) in the control ($11{,}182 \pm 1{,}1341$ mg) and training ($10{,}523 \pm 1{,}211$ mg) groups. No patient failed to respond to glucocorticoid therapy, and none had evidence of noncellular rejection or hemodynamic compromise.

DISCUSSION

Skeletal muscle myopathy develops during chronic heart failure,[1–6] and the sequelea of myopathic disease persist indefinitely after heart transplantation.[7–11] The first principal finding of this study was that resistance training elicited myofibrillar shifts from less oxidative type II fibers (32% decrease in type IIx MHC isoform) in the vastus lateralis to more oxidative fatigue resistant type 1 fibers (73% increase in type I MHC isoform) in heart transplant recipients. In contrast, heart transplant recipients who participated only in self-monitored aerobic walking exercise experienced further decreases in oxidative fatigue-resistant type 1 fibers (29% decrease in type I MHC isoform) and further increases in less oxidative type II fibers (17% increase in type IIx MHC isoform).

The second principal finding of this study was that resistance exercise training elicited increases in oxidative and glycolytic skeletal muscle metabolic enzymes. Significant ($p \leq 0.05$) increases in LDH, a marker of glycolytic activity, were observed in both the resistance training and control groups after the 6-month intervention period. However, the magnitude

of increase in LDH was 2.5-fold greater in the resistance exercise group (48% vs 20%, respectively, $p \leq 0.05$). Citrate synthase, a marker of oxidative Kreb cycle activity, was also significantly ($p \leq 0.05$) increased in the resistance training group (+40%) after 6 months of resistance exercise but did not change ($p \geq 0.05$) in the control group (Figure 2). HACoA activity, a marker of fat oxidation, did not change significantly ($p \geq 0.05$) in either group.

No studies have evaluated the possible therapeutic benefits of progressive resistance exercise in heart transplant recipients who experience skeletal myopathic disorders. Three investigations have studied skeletal muscle morphology and biochemistry before and after heart transplantation in patients who did not participate in resistance exercise training. Schaufelberger et al[20] obtained serial skeletal muscle biopsy samples from the vastus lateralis in patients (n = 10) before, 1 to 3, and 6 to 9 months after heart transplantation. All patients participated in a post-transplantation supervised stationary cycling program. Citrate synthase activity was decreased in patients (5.6 ± 1.5 mol/g wet wt./min) versus controls (8.1 ± 1.6 mol/g wet wt./min) at baseline and did not change after transplantation. Patients had decreased numbers of capillaries in contact with each fiber versus controls at baseline (2.6 ± 0.5 vs 3.5 ± 1.0; p = 0.039), which persisted after transplantation. Skeletal muscle strength in patients did not improve significantly from baseline values.[20] Bussieres et al[10] obtained skeletal muscle biopsy specimens (vastus lateralis) in 12 patients before, and at 3 and 12 months after heart transplantation. Fiber-type analysis revealed a predominance of highly fatigable type II fibers before transplantation (66%), and the ratio was not changed 1 year after transplantation despite a 9-month intervention consisting of calisthenic-type exercises. Stratton et al[9] used P-31 magnetic resonance spectroscopy to monitor noninvasively skeletal muscle metabolism in a cross-sectional study consisting of 3 groups of cardiac patients: (1) patients awaiting heart transplantation (n = 10), (2) heart transplant recipients <6 months after transplant (n = 9), and (3) heart transplant recipients >6 months after transplant (n = 8). Compared with age-matched normal subjects, heart transplant recipients who were studied late after transplantation (group mean = 15 months after transplant) during dominant arm weight pull exercise continued to have increased depletion of phosphocreatine, higher muscle pH, and less rapid resynthesis of phosphocreatine during recovery from exercise. All the P-31 magnetic resonance spectroscopy markers were suggestive of diminished type I MHC isoform and diminished mitochondrial oxidative phosphorylation. The available evidence clearly indicates that intrinsic abnormalities in skeletal muscle persist after heart transplantation and that myopathic disease may contribute to the impaired exercise capacity observed in heart transplant recipients.

Diminished peak oxygen uptake (VO_{2peak}) is a consistent finding in heart transplant recipients indefinitely after transplantation, with VO_{2peak} values approaching only ~60% to 70% of age-matched norms at 18 months after transplantation.[21,22] The mechanisms responsible for attenuated VO_{2peak} in heart transplant recipients have been described extensively and include reduced cardiac index due to chronotropic incompetence and diastolic dysfunction,[23] endothelial dysfunction,[24,25] and impaired pulmonary diffusion capacity.[26,27] However, previous data from our laboratory[7] suggest that skeletal myopathic disease may be a particularly important determinant of exercise capacity in heart transplant recipients. In fact, skeletal muscle myopathy may preclude objective measurement of VO_{2peak} in heart transplant recipients because treadmill and cycle ergometer testing devices place considerable demands on strength and oxidative capacity of leg skeletal muscle. Untrained heart transplant recipients (aged 51 ± 9 years) exhibit maximal quadriceps strength values (normalized for lean body mass) that are comparable to values achieved by untrained and sedentary 70- to 79-year-old subjects.[7] Furthermore, quadriceps strength is highly correlated with VO_{2peak} in heart transplant recipients (r = 0.90) compared with that in age-matched normal control subjects (r = 0.65).[13] Leg strength accounted for 81% of the variability in VO_{2peak} among heart transplant recipients, whereas only accounting for 42% of the variability in healthy age-matched controls.[7] Thus, VO_{2peak} in subjects with normal leg strength is likely restricted by cardiovascular function, whereas in heart transplant recipients, myopathy of leg muscles may be a primary factor limiting aerobic power and optimal performance of the transplanted heart. We speculate that reported decrements in aerobic power can be attributed, in part, to leg strength in heart transplant recipients being only 60% to 70% of matched controls.

A limitation of this study is that the number of patients investigated was small. Prospective and longitudinal studies involving adherence to a supervised exercise regimen and serial biopsy measurements involve considerable patient burden and limit patient enrollment. Another limitation of this study is that no central hemodynamic parameters were measured. Cardiac output increases after transplant but is lower than in normal subjects at maximal exercise,[28] and the tachycardic heart rate response during exercise is attenuated.[29] What contribution these alterations in cardiac performance may have made to the results noted in this study is unknown.

1. Drexler H, Reide U, Munzel T. Alterations of skeletal muscle in chronic heart failure. *Circulation* 1992;85:1751–1759.

2. Okita K, Yonezawa K, Nishijima H. Skeletal muscle metabolism limits exercise capacity in patients with chronic heart failure. *Circulation* 1998;1886–1891.

3. Schaufelberger M, Erikson B, Grimby G, Held P, Swedberg K. Skeletal muscle alterations in patients with chronic heart failure. *Eur Heart J* 1997;18:971–980.

4. Vescovo G, Serafini F, Dalla Libera L. Skeletal muscle myocin heavy chain composition in CHF: correlation between the magnitude of the isoenzymatic shift, exercise capacity, and gas exchange measurements. *Am Heart J* 1998;135: 130–137.

5. Ralston M, Merola A, Leier C. Depressed aerobic enzyme activity of skeletal muscle in severe chronic heart failure. *J Lab Clin Med* 1991;117:370–372.

6. Sullivan J, Green H, Cobb F. Altered skeletal muscle metabolic response to exercise in chronic heart failure. *Circulation* 1991;84:1597–1607.

7. Braith RW, Limacher MC, Leggett SH, Pollock ML. Skeletal muscle strength in heart transplant recipients. *J Heart Lung Transplant* 1993;12:1018–1023.

8. Khaleeli A, Edwards R, Gohil K, McPhail G, Rennie M, Round J, Ross E. Corticosteroid myopathy: a clinical and pathological study. *Clin Endocrinol (Oxf)* 1983;18:155–166.
9. Stratton J, Kemp G, Daily R, Yacoub M, Rajagopalan B. Effects of cardiac transplantation on bioenergetic abnormalities of skeletal muscle in CHF. *Circulation* 1994;89:1624–1631.
10. Bussieres L, Pflugfelder P, Taylor A, Noble E, Kostuk W. Changes in skeletal muscle morphology and biochemistry after cardiac transplantation. *Am J Cardiol* 1997;78:630–634.
11. Braith RW, Welsch MA, Mills RM, Keller JW, Pollock ML. Resistance exercise prevents glucocorticoid-induced myopathy in heart transplant recipients. *Med Sci Sports Exerc* 1998;30:483–489.
12. Bergstrom J. Muscle electrolytes in man. *Scand J Clin Lab Med* 1962;14: 511–513.
13. Evans WJ, Phinney SD, Young VR. Suction applied to a muscle biopsy maximizes sample size. *Med Sci Sports Exerc* 1982;14:101–102.
14. Bamman MM, Clarke MS, Talmadge RJ, Feeback DL. Enhanced protein electrophoresis technique for separating human skeletal muscle myosin heavy chain isoforms. *Electrophoresis* 1999;20:466–468.
15. Solaro RJ, Pang DC, Briggs FN. The purification of cardiac myofibrils with triton x-100. *Biochem Biophys Acta* 1971;245:259–262.
16. Bradford M. A rapid sensitive method for the quantification microgram quantities of protein utilizing the principle of protein dye binding. *Anal Biochem* 1976;72:248–254.
17. Srere P. Reactions on the cycle: citrate synthase. In: Lowastein JM, ed. Methods of Enzymology. New York: Academic Press, 1969:3–5.
18. Smith L. Spectrophotometric assay of cytochrome c oxidase. In: Glick D ed. Methods of Biochemical Analysis. New York: lnterscience, 1955;427–435.
19. Bergmeyer H, Bernt E, Hess B. Methods of Enzymatic Analysis. New York: Academic Press, 1965:736–741.
20. Schaufelberger M, Eriksson BO, Lonn L, Rundqvist B, Sunnerhagen KS, Swedberg K. Skeletal muscle characteristics, muscle strength and thigh muscle area in patients before and after cardiac transplantation. *Eur J Heart Failure* 2001;3:59–67.
21. Kavanagh T, Yacoub M, Mertens D. Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation. *Circulation* 1988; 77:162–171.
22. Braith RW, Wood CE, Limacher MC. Abnormal neuroendocrine responses during exercise in heart transplant recipients. *Circulation* 1992;86: 1453–1463.
23. Rudas L, Pflugfelder P, Kostuk W. Comparison of hemodynamic responses during dynamic exercise in the upright and supine postures after orthotopic cardiac transplantation. *J Am Coll Cardiol* 1990;16:1367–1373.
24. Andreassen AK, Kvernebo K, Jorgensen B, Simonsen S, Kjekshus J. Exercise capacity in heart transplant recipients: relation to impaired endothelium-dependent vasodilation of the peripheral microcirculation. *Am Heart J* 1998;136:320–328.
25. Patel AR, Kuvin JT, Pandian NG, Smith JJ, Udelson JE, Mendelsohn ME, Konstam MA, Karas RH. Heart failure etiology affects peripheral vascular endothelial function after heart transplantation. *J Am Coll Cardiol* 2001;37:195–200.
26. Braith RW, Limacher MC, Mills RM, Leggett SH, Pollock ML, Staples ED. Exercise-induced hypoxemia in heart transplant recipients. *J Am Coll Cardiol* 1993;22:768–776.
27. Ville N, Mercier J, Varray A, Albat B, Messner-Pellenc P, Prefaut C. Exercise tolerance in heart transplant patients with altered pulmonary diffusion capacity. *Med Sci Sports Exerc* 1998;30:339–344.
28. Braith RW, Plunkett MB, Mills RM. Cardiac output responses during exercise in volume-expanded heart transplant recipients. *Am J Cardiol* 1998;81:1152–1156.
29. Braith RW, Clapp L, Brown T, Brown C, Schofield R, Mills RM, Hill JA. Rate-responsive pacing improves exercise tolerance in heart transplant recipients: A pilot study. *J Cardiopulmonary Rehabil* 2000;20:377–382.