A CONTROLLED TRIAL OF EXERCISE REHABILITATION AFTER HEART TRANSPLANTATION

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Abstract

Background In patients who have received a cardiac transplant, the denervated donor heart responds abnormally to exercise and exercise tolerance is reduced. The role of physical exercise in the treatment of patients who have undergone cardiac transplantation has not been determined. We assessed the effects of training on the capacity for exercise early after cardiac transplantation.

Methods Twenty-seven patients who were discharged within two weeks after receiving a heart transplant were randomly assigned to participate in a six-month structured cardiac-rehabilitation program (exercise group, 14 patients) or to undergo unstructured therapy at home (control group, 13 patients). Each patient in the exercise group underwent an individualized program of muscular-strength and aerobic training under the guidance of a physical therapist, whereas control patients received no formal exercise training. Cardiopulmonary stress testing was performed at base line (within one month after heart transplantation) and six months later.

Results As compared with the control group, the exercise group had significantly greater increases in peak oxygen consumption (mean increase, 4.4 ml per kilogram of body weight per minute [49 percent] vs. 1.9 ml per kilogram per minute [18 percent]; P=0.01) and workload (mean increase, 35 W [59 percent] vs. 12 W [18 percent]; P=0.01) and a greater reduction in the ventilatory equivalent for carbon dioxide (mean decrease, 13 [20 percent] vs. 6 [11 percent]; P=0.02). The mean dose of prednisone, the number of patients taking antihypertensive medications, the average number of episodes of rejection and of infection during the study period, and weight gain did not differ significantly between the groups.

Conclusions When initiated early after cardiac transplantation, exercise training increases the capacity for physical work. (N Engl J Med 1999;340:272-7.)

ALTHOUGH physical exercise has become an important part of standard therapy for patients who have had acute myocardial infarction and cardiac surgery, its role after heart transplantation has not been well defined.[1,2] Patients undergoing heart transplantation, like those undergoing coronary-artery bypass surgery, are affected by preoperative inactivity and postoperative deconditioning and can potentially benefit from exercise rehabilitation.

The denervated donor heart has altered physiologic responses to exercise that can impair exercise tolerance.[3-5] The question of whether the transplanted heart can tolerate the physiologic stress of exercise training after transplantation, coupled with the possibility that exercise might precipitate acute rejection of the transplant, may underlie the historical reluctance to prescribe exercise training after transplantation. However, the denervated heart has been shown to respond appropriately to exercise.[5-7] Moreover, several nonrandomized studies have suggested that exercise training increases the capacity for physical work after heart transplantation.[8-10]

Because a certain amount of improvement in exercise capacity is expected after surgery, it is unclear how much of these reported gains in physical-work capacity reflects the effects of exercise training as compared with the natural course of postoperative recovery. Therefore, we undertook a randomized, prospective study to assess the effect of exercise training provided in a cardiac-rehabilitation program on measurements of physical-work capacity and activities of daily living among patients who had undergone heart transplantation.

METHODS

Patients

Thirty-six consecutive patients underwent heart transplantation by the midatrial-cuff technique between August 1992 and June 1993. Nine patients were not enrolled in the study; five patients had multiple medical limitations after prolonged hospitalization, and four patients declined to participate. Within two weeks after transplantation, informed consent was obtained from the remaining 27 patients, who were randomly assigned (by selection of sealed envelopes) either to a group that participated in an exercise training program in an outpatient cardiac-rehabilitation setting (exercise group, 14 patients) or to a control group (13 patients). The control group received written guidelines for exercise but participated in no formal, supervised exercise sessions after discharge from the hospital.

All the patients were treated with triple-drug immunosuppression, including cyclosporine, azathioprine, and prednisone. The dosage of prednisone was initially 1 mg per kilogram of body weight per day, given in divided doses, and was gradually de-

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creased to 0.1 mg per kilogram per day by six months after transplantation. Episodes of cardiac rejection were treated with an oral bolus dose of prednisone and then tapered doses and, for clinically severe rejection, with OKT3 murine monoclonal antibody (muromonab-CD3). Episodes of rejection and infection were recorded, and blood pressure, renal function, and weight gain were evaluated in both groups of patients during the study. Cardiac function was assessed with echocardiography and right-heart catheterization at base line and at a six-month follow-up examination.

Exercise Program

At the time of entry into the structured, six-month program of rehabilitative exercise, patients in the exercise group were evaluated by a physical therapist for overall muscle strength, joint flexibility, and aerobic endurance. On the basis of these findings, a supervised program of exercise was developed by the therapist according to each patient's specific needs. Strengthening exercises consisted primarily of closed-chain resistive activities (e.g., bridging [lifting of hips with knees flexed in a supine position], half-squats, and toe raises) and abdominal exercises (curl-ups and pelvic tilts). Flexibility exercises, which emphasized chest expansion and thoracic mobility, included side stretches, trunk twists, scapula squeezes, and shoulder rolls. Aerobic exercises consisted of walking on a motorized treadmill or pedaling on a bicycle ergometer (Cybex, Ronkonkoma, N.Y.), as well as arm movements on an ergometer (Cybex). The duration and intensity of aerobic-exercise sessions were increased to meet the patient's tolerance, with a goal of at least 30 minutes of continuous exercise at a moderate intensity.

Patients initially visited the cardiac-rehabilitation clinic one to three times weekly (some were unable to attend more than once each week because of transportation difficulties) and received specific instructions for exercising at home. The frequency of cardiac rehabilitation sessions was gradually reduced to one every two weeks as patients became more independently involved in their home exercise programs. Patients who had rejection were instructed not to exercise until a follow-up endomyocardial biopsy showed resolution of rejection, which usually required two weeks.

Before discharge from the hospital, patients in both groups received written guidelines specifying the following exercises to be performed at home: shoulder circles, 10 times forward and 10 times backward; shoulder retraction, 10 slow repetitions of inhaling while bringing the elbows back and exhaling while bringing them forward; trunk twists, 10 times in each direction; side bends, 10 times in each direction; half-squats, 10 to 20 repetitions; and toe raises, 10 to 20 repetitions. Patients also received the following written guidelines for walking: first week after discharge, walk without stopping for 5 to 10 minutes three or four times a day at a comfortable pace; second week, walk 10 to 15 minutes three times a day at a comfortable pace; third week, walk 15 to 20 minutes twice a day at a comfortable pace; fourth week, walk 20 to 30 minutes once a day at a comfortable pace; fifth week, walk 30 to 40 minutes once a day at a comfortable pace; and sixth week, continue walking 30 to 40 minutes every day while increasing the pace.

Measurements

Cardiopulmonary Exercise Testing

All the patients underwent a cardiopulmonary exercise stress test that is routinely administered in our laboratory within one month after cardiac transplantation and again six months after transplantation. Cardiopulmonary exercise stress tests were conducted by bicycle ergometry. During testing, the electrocardiogram was monitored continuously and the blood pressure was measured regularly. For maximal cardiopulmonary exercise stress testing, the patient first cycled at 50 to 70 rpm with no workload for three minutes. Then the workload was incrementally increased by 10 W every minute until the patient's ability to exercise became limited by symptoms. This point was taken as peak oxygen consumption (peak aerobic capacity).

During exercise testing, expired gas was collected and analyzed with a gas analyzer (Medical Graphics System 2001, Kalamazoo, Mich.). The cardiopulmonary exercise measurements permitted determination of peak oxygen consumption, workload, ventilatory equivalent for carbon dioxide, ventilatory equivalent for oxygen, exercise time, time to estimated threshold of lactic acidosis as determined by the V-slope method (the V slope is the point of a nonlinear increase in carbon dioxide production during exercise), resting heart rate, peak heart rate, resting blood pressure, peak blood pressure, and minute ventilation. The primary end points of this study were the differences between the two groups of patients in the results of cardiopulmonary exercise stress testing at one month and six months after transplantation.

Muscle Strength

A secondary end point of this study was leg strength, as reflected by hip-girdle weight transfer, which was evaluated by means of the sitting-to-standing test at base line and the six-month follow-up. This test was initially developed as a clinical tool to assess the ability of patients with orthopedic limitations due to osteoarthritis to rise from a chair 10 times.[11] Because many of our patients were unable to rise from a chair 10 times, we modified this test by recording the number of times each patient could rise from a chair to a standing position within a 60-second period.

Statistical Analysis

The distribution of the patients' characteristics, the results of cardiopulmonary exercise testing at base line, the changes in the cardiopulmonary exercise measurements between the base-line evaluation and the six-month follow-up, and postoperative characteristics were evaluated by means of prespecified analyses. The frequency distributions and mode were examined for all the categorical measures. For all the continuous measures, the mean; the 25, 50, 75, and 95 percent quantiles; the standard deviations; and the minimal and maximal values were examined. Fisher's exact test was used for categorical measures, and the paired t-test was used for continuous measures. For all tests, a two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Characteristics of the Patients at Base Line

The differences in base-line characteristics between the exercise and control groups were not statistically significant, although more patients in the control group (seven) than in the exercise group (four) had coronary artery disease before transplantation (Table 1). The length of time from a patient's appearance on the waiting list for a transplant to transplantation was longer in the exercise group than in the control group, and more patients in the exercise group required transplantation on an urgent basis, but these differences were also not statistically significant (Table 1). Patients tolerated exercise training with no adverse clinical events. The patients randomly assigned to receive supervised exercise training participated in a mean (±SD) of 17±10 supervised exercise sessions (range, 4 to 36). The most important factor limiting program attendance was commuting distance to the rehabilitation site.

Course after Transplantation

Table 2 summarizes the patients' clinical course after transplantation. Factors that may have had an effect on exercise capacity and function, including

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	EXERCISE GROUP (N=14)	CONTROL GROUP (N=13)
Mean age — yr		
Recipient	55±8	50±12
Donor	32±15	25±10
Female sex — no. (%)	3 (21)	5 (38)
Mean body-surface area — m²	1.8	1.8
White race — no. (%)	10 (71)	11 (85)
Coronary artery disease before transplantation — no. (%)	4 (29)	7 (54)
Mean cold ischemic time — min†	178±43	176±55
Time on transplant waiting list — mo	6±5	3±4
Status I — no. (%)‡	2 (14)	0

*Plus–minus values are means ±SD. There were no statistically significant differences between the groups.

†Mean cold ischemic time is the average time between removal of the heart from the donor and transplantation in the recipient.

‡Status I indicates a priority (urgent) status for patients on the heart-transplant waiting list; these patients have heart failure and are dependent on the support of assistive devices or inotropic agents in the intensive care unit.

TABLE 2. POSTOPERATIVE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	EXERCISE GROUP (N=14)	CONTROL GROUP (N=13)
Dose of prednisone (mg/day)		
At 3 mo	12±3	14±4
At 6 mo	9±4	11±5
Hypertension requiring medication (no. of patients)†	8	11
Rejection episodes during study (no.)	0.7±1.0	1.1±1.8
Infection episodes during study (no.)	0	0
Increase in weight (kg)	8±6	8±9
Left ventricular ejection fraction by echocardiography (%)		
At base line	61	55
At 6 mo	60	55
Results of right-heart catheterization		
At base line		
Right atrial pressure (mm Hg)	3±2	5+2
Pulmonary-artery pressure (mm Hg)	23±5	25±4
Pulmonary-capillary wedge pressure (mm Hg)	8±3	10±3
Cardiac output (liters/min)	5.3±1.1	5.2±1.3
At 6 mo		
Right atrial pressure (mm Hg)	2±2	4±4
Pulmonary-artery pressure (mm Hg)	21±3	24±7
Pulmonary-capillary wedge pressure (mm Hg)	5±2	9±5
Cardiac output (liters/min)	5.0±0.5	5.2±1.6

*Plus–minus values are means ±SD. There were no statistically significant differences between the groups.

†Medications included calcium-channel blockers and angiotensin-converting–enzyme inhibitors.

the mean dose of prednisone, the number of patients taking antihypertensive medications (calcium-channel blockers and angiotensin-converting–enzyme inhibitors), the number of rejection episodes, and the number of infections, did not differ significantly between groups. Patients in both groups gained similar amounts of weight during the study period. Echocardiographic findings and the results of right-heart catheterization at base line and at the six-month follow-up were similar in the two groups (Table 2).

Cardiopulmonary Exercise Tests

Base-line measurements of each exercise variable were similar in the two groups (Table 3). For both groups, changes in cardiopulmonary exercise-test measurements from base line to the six-month follow-up revealed improvements in cardiopulmonary function. However, the improvement in the exercise group was significantly greater than that in the control group for both peak oxygen consumption (mean increase, 4.4 ml per kilogram per minute [49 percent] vs. 1.9 ml per kilogram per minute [18 percent]) and workload (mean increase, 35 W [59 percent] vs. 12 W [18 percent]), and a greater reduction in the ventilatory equivalent for carbon dioxide (13 [20 percent] vs. 6 [11 percent]) (Table 3). In addition, there were trends in the exercise group toward increased exercise time, increased time to the estimated threshold of lactic acidosis, a greater reduction in the ventilatory equivalent for oxygen, and lower resting heart rate. The increase in the rate at which patients could rise from sitting was significantly greater in the group receiving physical exercise training than in the control group (Table 3).

DISCUSSION

This prospective, randomized study of heart-transplant recipients, initiated early in the postoperative period, demonstrated that patients who participated in an exercise training program increased their capacity for physical work as compared with control patients who did not undergo training.

Although physical exercise is clearly warranted for patients after bypass surgery or after acute myocardial infarction, the role of exercise in the treatment of patients who have undergone cardiac transplantation is less well defined.[1,2] In recipients of cardiac transplants, exercise capacity is influenced by the denervation that occurs during transplantation surgery, which reduces the overall response to exercise as compared with that of normal volunteers.[3-5] Specifically, the chronotropic response at the peak of effort is reduced.[6,7] At peak exercise after cardiac transplantation, the rise in circulating catecholamines is normal or increased,[12,13] and the responsiveness of the sinoatrial node to beta-adrenergic stimulation is also normal or increased; therefore, the attenuated response of the peak heart rate to exercise after trans-

TABLE 3. CHANGES FROM BASE LINE TO SIX MONTHS IN CARDIOPULMONARY EXERCISE-TEST RESULTS.

VARIABLE	EXERCISE GROUP (N=14)			CONTROL GROUP (N=13)			P VALUE
	BASE LINE	6 MONTHS	DIFFERENCE (% CHANGE)*	BASE LINE	6 MONTHS	DIFFERENCE (% CHANGE)*	
Peak oxygen consumption (ml/kg/min)	9.2	13.6	+4.4 (+49)	10.4	12.3	+1.9 (+18)	0.01
Workload (W)	59	94	+35 (+59)	66	78	+12 (+18)	0.01
Ventilatory equivalent for carbon dioxide	66	53	−13 (−20)	54	48	−6 (−11)	0.02
Ventilatory equivalent for oxygen	79	67	−12 (−15)	64	60	−4 (−6)	0.09
Duration of exercise (min)	6.9	9.0	+2.1 (+30)	7.2	8.3	+1.1 (+15)	0.07
Time to estimated lactic acidosis threshold (min)	1.8	3.3	+1.5 (+83)	2.3	2.3	0	0.09
Resting heart rate (beats/min)	90	100	+10 (+11)	91	109	+18 (+20)	0.06
Peak heart rate (beats/min)	102	125	+23 (+23)	107	134	+27 (+25)	0.25
Systolic blood pressure at rest (mm Hg)	126	121	−5 (−4)	130	114	−16 (−12)	0.20
Peak systolic blood pressure (mm Hg)	141	148	+7 (+5)	139	148	+9 (+6)	0.46
Minute ventilation	38	45	+7 (+18)	46	62	+16 (+35)	0.10
Sitting-to-standing rate (no./min)†	10.6	23.9	+13.3 (+125)	12.3	17.9	+5.6 (+46)	0.02

*Plus signs denote an increase, and minus signs a decrease.

†The sitting-to-standing rate is the number of times per minute a patient could rise from a sitting position to a standing position.

plantation most likely reflects the lack of direct innervation of the sinoatrial node.[5,14] In addition to the peak heart rate, the peak cardiac output and peak left ventricular ejection fraction during exercise have been reported to be impaired in patients who have undergone heart transplantation.[3,4]

Peak oxygen consumption is greatly diminished in cardiac-transplant recipients, and it has been reported that 57 percent of such patients are still in New York Heart Association functional class II, III, or IV one year after transplantation.[10] Maximal work output, peak oxygen consumption, and the time to the lactic acidosis threshold are reduced, resulting in symptoms of early fatigue.[4,8] Kavanagh[15] has reported that during submaximal effort, heart-transplant recipients have increases in minute ventilation, perceived exertion, and the ventilatory equivalent for oxygen, and the absolute ventilatory threshold for oxygen is reduced. These findings indicate that exercise capacity may be limited in cardiac-transplant patients. In the current study, gas-exchange data in our population were similar to those reported by Kavanagh.

Previous studies of heart-transplant recipients have suggested that exercise training can increase the capacity for physical work.[8-10] Savin et al.[8] initially reported that five heart-transplant recipients undergoing a four-month exercise program of stationary cycling increased their peak work output by 45 percent and their peak oxygen consumption by 18 percent. Kavanagh et al.[9] selected 36 patients a mean (±SD) of 7±6 months after heart transplantation to participate in a program of walking and jogging that lasted 16±7 months. At the conclusion of this exercise program, patients progressed to walking or jogging an average distance of 24 kilometers per week at an average pace of 8.5 minutes per kilometer. In addition, these patients increased their body mass by 5.5 percent (including a 3.2 percent increase in lean tissue mass), resting heart rate by 3.6±10.7 beats per minute, peak heart rate by 12.7±16.7 beats per minute, peak work output by 49 percent, and peak oxygen consumption by 27 percent, whereas the heart rate at rest decreased by 3.6±10.7 beats per minute.

The largest study, conducted by Niset et al.,[10] involved 62 patients who had undergone cardiac transplantation. Symptom-limited exercise stress tests performed approximately one month postoperatively and again after one year of exercise training revealed increases in maximal oxygen consumption (a 33 percent increase), peak heart rate (11 percent), and peak systolic blood pressure (18 percent) and a reduction in the ventilation quotient for oxygen (a 25 percent decrease) during submaximal exercise. The results of these studies are noteworthy because they indicate that patients who have received cardiac transplants can successfully participate in exercise training.

However, the interpretation of these studies is limited by the lack of a nonexercising control group. Therefore, it remains uncertain whether increases in physical work capacity after exercise training reflect the recovery of work capacity that we also found in our nonexercising group. In addition, the interpretation of these earlier results is limited by the lack of a uniform time frame after transplantation for initiating the training. Moreover, these study groups comprised selected patients who tended to be highly motivated to pursue the exercise training.

Early after heart transplantation, skeletal-muscle weakness resulting from atrophy and high doses of corticosteroids may also limit the ability to exercise.[16,17] Many exercise variables improve later, once the patient's muscle mass and physical condition are restored. Although the sitting-to-standing rates did increase between the base-line evaluation and the six-month follow-up in the control group, the increase among the exercising patients was almost three times as large, a difference we attribute in part to the exercise program.

Exercise training increases the capacity for physical work without increasing the peak heart rate; that is, after training, a person can do more work than before, at the same level of exertion. Because increases in peak oxygen consumption and peak heart rate were seen in both groups at the six-month follow-up, the increase in physical capacity could be attributed to the patient's ability to exercise with greater effort rather than to a physiologic training effect. However, evidence that a physiologic training effect did occur is the improvement in the lactic acidosis threshold after exercise training. This increase represents the effect of having achieved a greater capacity for physical work rather than the ability to perform at a greater level of exertion.

Episodes of acute rejection may affect both systolic and diastolic cardiac function and may limit exercise tolerance. Chan et al.[18] reported a decrease in coronary-artery flow reserve in patients who had acute rejection after heart transplantation; the flow reserve returned to base-line levels after successful antirejection therapy. This finding implies that acute rejection can impair coronary blood flow during exercise. For this reason, patients who had episodes of rejection were requested to refrain from physical exercise and did not undergo exercise testing until the episode resolved. Exercise training was well tolerated by our participating patients, and the training itself did not increase the incidence of rejection.

The small size of this study limits the strength of the results. However, the end points of exercise capacity are relatively objective and suggest important differences between the two study groups. Although the difference was not statistically significant, the time spent by the exercise group on the waiting list for a heart transplant was longer than that spent by the control group, and there were more patients who required transplantation urgently in the exercise group. This would tend to bias the results against the exercise group, because they had a longer time to become debilitated and because more of them were severely ill. Finally, it is possible that the larger number of patients in the exercise group who had a pretransplantation diagnosis of coronary artery disease influenced the study results. However, in three large registry studies, a pretransplantation diagnosis of coronary artery disease was not found to increase mortality, rejection, or infection to a substantial degree.[19-21]

This study demonstrates the benefit of exercise training initiated early after cardiac transplantation to improve physical work capacity. The practical implications of these results are that improved work capacity can be achieved in a structured, individualized exercise program. By implication, increased exercise capacity may lead to participation in more strenuous activities and thus to a better quality of life, since more activities can be performed. Therefore, exercise training should be considered standard postoperative care for heart-transplant recipients.

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