Effects of Cardiac Transplantation on Bioenergetic Abnormalities of Skeletal Muscle in Congestive Heart Failure

John R. Stratton, MD; Graham J. Kemp, BM, BCh; Richard C. Daly, MD; Sir Magdi Yacoub, FRCS; Bheeshma Rajagopalan, FRCP, DPhil

**Background** Patients with advanced heart failure have bioenergetic abnormalities of skeletal muscle metabolism during exercise. Using $^{31}$P magnetic resonance spectroscopy, we sought to determine whether skeletal metabolic responses to exercise are normalized by orthotopic cardiac transplantation.

**Methods and Results** Four groups were studied: healthy normal volunteers ($n=9$), subjects awaiting heart transplantation ($n=10$), subjects $<6$ months (mean, 4 months) after transplant ($n=9$), and subjects >6 months (mean, 15 months) after transplant ($n=8$). None of the posttransplant patients had biopsy evidence of rejection at the time of study. There were no significant differences in age, preoperative functional class, or symptom duration among the three patient groups. Metabolic responses were monitored in the dominant arm during incremental weight pull exercise and 10 minutes of recovery by $^{31}$P magnetic resonance spectroscopy, with measurement of pH and the phosphocreatine (PCr)/[PCR+iorganic phosphate (Pi)] ratio, an index of PCr concentration. In addition, based on recovery data, the rate of PCr resynthesis was calculated as a measure of oxidative metabolism that is independent of work level, recruitment, or muscle mass, and the effective maximal rate of mitochondrial ATP synthesis ($V_m$) was determined. Analysis was by ANOVA. There were no differences between groups in pH or PCr/[PCR+Pi] at rest. Compared with the normal control group, the pretransplant group had a decreased exercise duration (11.3±2.5 versus 15.0±1.3 minutes, $P=.02$), a lower submaximal exercise PCr/(PCr+Pi) ratio (0.58±0.11 versus 0.76±0.08, $P<.05$), a reduced PCr resynthesis rate (13±6 versus 22±9 mmol/L per minute, $P<.05$), and a lower calculated $V_m$ (26±14 versus 53±26 mmol/L per minute, $P<.05$). In the group studied early after transplantation, all the changes noted in the pretransplant group persisted and were if anything somewhat worse. In the group studied late after transplantation, there was a significant improvement in the PCr resynthesis rate compared with the early-posttransplant group (27±6 late versus 15±6 mmol/L per minute early, $P<.05$) and statistically nonsignificant trends toward improvements in submaximal exercise pH (6.86±0.24 late versus 6.72±0.24 early) and submaximal PCr/(PCr+Pi) ratio (0.56±0.14 late versus 0.44±0.15 early) and $V_m$ (45±21 late versus 33±15 mmol/L per minute early). However, compared with normal subjects, exercise duration and submaximal PCr/(PCr+Pi) were still reduced in the late-posttransplant group.

**Conclusions** Despite successful heart transplantation, skeletal muscle abnormalities of advanced heart failure persist for indefinite periods, although partial improvement occurred at late times. The persistent abnormalities may contribute to the reduced exercise capacity that is present in most patients after transplantation. (*Circulation*. 1994;89:1624-1631.)

**Key Words** • transplantation • magnetic resonance imaging • spectroscopy • exercise • metabolism • heart failure, congestive

Skeletal muscle metabolic responses to exercise are abnormal in patients with congestive heart failure.¹ By magnetic resonance spectroscopy, patients with congestive heart failure have abnormally rapid depletion of phosphocreatine (PCr) and greater intracellular acidosis during exercise of arm or leg skeletal muscles.²⁻⁸ Patients in more advanced heart failure have more deranged skeletal muscle metabolism,⁵⁻⁹ suggesting that the changes in peripheral muscle may be important determinants of exercise performance in heart failure. This contrasts with the findings from hemodynamic studies, in which there has been a notable dissociation between ejection fraction and other hemodynamic measurements and exercise tolerance.⁹⁻¹⁰ The abnormal skeletal muscle metabolism during exercise in patients with congestive heart failure is not due solely to a limitation in blood flow⁵⁻⁶,¹¹ or differences in muscle bulk or the degree of atrophy.⁵⁻⁶,¹² Based on biopsies of resting muscle, several histological and biochemical changes have been described, including fiber atrophy, a decrease in the percentage of type I fibers, an increase in the percentage of type IIb fibers, a decrease in the oxidative enzymes succinate dehydrogenase and citrate synthetase, and a decrease in the enzyme β-hydroxyacyl coenzyme A dehydrogenase, which mediates β-oxidation of fatty acids.¹³,¹⁴ However, these histological and biochemical changes measured at rest did not correlate with $^{31}$P metabolic responses measured during exercise.¹³ The underlying cause of the abnormal skeletal muscle metabolism is uncertain,¹ and the extent to which the changes are reversible is largely unknown. However, we...
and others have recently documented that exercise training protocols, which have minimal effects on cardiac function, can at least in part reverse the skeletal muscle metabolic abnormalities.\textsuperscript{15-17} Whether heart transplantation reverses the skeletal muscle abnormalities has not been determined. Exercise capacity, although improved after heart transplantation, does not totally normalize.\textsuperscript{18-21} In one study, maximal oxygen uptake was only 60% of predicted normal in patients studied a mean of 14 months after transplantation.\textsuperscript{21} The cause of reduced exercise capacity after heart transplantation is unclear, but continued skeletal muscle abnormalities might contribute.

The purpose of this study was to determine whether the improvement in central hemodynamics caused by successful heart transplantation is associated with improvements in skeletal muscle metabolic responses to exercise in patients with congestive heart failure. Metabolic responses to exercise were assessed during progressive exercise by \textsuperscript{31}P magnetic resonance spectroscopy in normal control subjects, in patients with heart failure on the waiting list for transplantation, and in patients early (<6 months) or later (>6 months) after successful orthotopic heart transplantation.

Methods

Subjects

Four groups of subjects were studied. Ten subjects with chronic congestive heart failure who were on the heart transplant waiting list were studied. Nine subjects who were early (>6 months) after orthotopic heart transplantation and eight subjects who were late (>6 months) after orthotopic heart transplantation were studied. For comparison, nine age-matched normal control subjects (50±4 years old, eight men and one woman) were also studied. All subjects gave informed consent according to a protocol approved by the local ethics committee.

Exercise Testing Protocols for Magnetic Resonance Spectroscopy Studies

The muscle of the dominant arm was studied. Before testing, the body of the flexor digitorum superficialis was identified and a 2-cm-diameter circular area marked with a pen. Incremental exercise was done with the patient supine with the arm extended into the magnet and consisted of pulling a lever connected by a pulley to a bucket at a rate of 40 pulls per minute. The weight of the bucket was kept constant at 0.75 kg for 4.8 minutes and then increased by 0.25 kg/min every 1.2 minutes until the subject stopped exercising because of fatigue.\textsuperscript{5,8}

Magnetic Resonance Spectroscopy Methods

Studies were conducted in a 1.9-T, 20-cm-bore horizontal superconducting magnet (Oxford Instruments, Oxford, UK) connected to a Biospec spectrometer (TMR 32, Oxford Research System, Oxford). A surface coil 2.5 cm in diameter was placed over the flexor digitorum superficialis muscle. After magnetic field homogeneity was optimized by use of the proton signal, \textsuperscript{31}P spectra were collected at rest, during the incremental exercise protocol, and during the first 12 minutes of recovery as previously described.\textsuperscript{5,8} The initial resting spectrum was obtained as the sum of 256 scans, and subsequent exercise spectra used 32 scans. During recovery from exercise, four 16-scan spectra were collected, followed by four 32-scan spectra, followed by two 64-scan spectra. The time between scans during exercise was 1.25 minutes. During recovery, the time between spectra was 0.6 minute for the first four spectra, then 1.25 minutes for the next four spectra, and 2.5 minutes for the final two spectra.

Quantitative analysis of the time-averaged spectra was performed by previously described methods.\textsuperscript{22-24} Peak areas were measured by manual triangulation and corrected for saturation and triangulation artifacts by comparison with fully relaxed spectra in separate experiments. Cytosolic inorganic phosphate (P\textsubscript{i}) and PCr concentrations in mmol/L (ie, mmol/L per liter cell water) were calculated from the metabolite ratios \textsuperscript{P\textsubscript{i}}/ATP and PCr/ATP, on the assumption that [ATP] was normal at 8.2 mmol/L.\textsuperscript{25} The combined triangulation/saturation correction factors used were 1.52 for PCr and 1.44 for P\textsubscript{i}. Changes in PCr were normalized to minimize the effects of variations in signal intensity by the ratio of PCr/(PCr+P\textsubscript{i}). Intracellular pH was calculated from the chemical shift of P\textsubscript{i} relative to PCr,\textsuperscript{25,26} (Fig 1). Free [ADP] (\mu mol/L cell water) was calculated at end exercise from the creatine kinase equilibrium\textsuperscript{25,27} as [ADP]=([total creatine]/[PCr]−1)[ATP]/(K[H\textsuperscript{+}]), where [total creatine] is taken as normal at 42.5 mmol/L\textsuperscript{25,28} and K is the equilibrium constant (1.66×10\textsuperscript{5} L/mol). For kinetic analysis, data were assigned to the midpoint of the acquisition interval.
Analysis of PCr recovery after exercise has been proposed as a measure of muscle oxidative capacity that is independent of muscle mass, recruitment, and workload.\(^1\)\(^2\) To analyze mitochondrial function in recovery, we measured the initial rate of PCr resynthesis (dPCr/dt) in mmol/L per minute, using the slope of PCr/(PCr+P\(_\text{i}\)) (per minute) (calculated from the end-exercise spectrum and the first two recovery spectra) times the resting P\(_\text{i}\)/PCr concentration in mmol/L. This method is designed to be independent of signal loss or gain during the experiment and provides an estimate of mitochondrial ATP synthesis.

The apparent effective maximal rate of mitochondrial ATP synthesis (V\(_\text{max}\)) was also calculated by previously described methods.\(^29\) ATP production during recovery from exercise is essentially entirely oxidative. Therefore, the rate of PCr resynthesis after exercise is a measure of mitochondrial ATP synthesis. There is substantial evidence that the rate of mitochondrial ATP synthesis (which we call V) is related to cytosolic [ADP] according to a hyperbolic (Michaelis-Menten) relation: 

\[ V = \frac{V_{\text{max}}}{1 + (K_m/\text{[ADP]})} \]

where V is half-maximal at [ADP]=K\(_m\) (\(=30 \mu\text{mol/L cell water}\)) and has a maximum value (V\(_\text{max}\)) of \(=40 \text{ mmol/L cell water per minute}\).\(^29\) This relation holds during exercise\(^30\) and during recovery\(^29\) as well as in isolated mitochondria.\(^3\) Since the rate of ATP turnover in resting muscle is small compared with that during exercise and early recovery, we can take the rate of PCr resynthesis as an estimate of oxidative ATP synthesis rate, V. Mitochondrial oxidation can in principle be affected by abnormalities in K\(_m\), in V\(_\text{max}\), or in [ADP]. Since the K\(_m\) for ADP is probably a property of the mitochondrial adenine nucleotide translocase,\(^30\) it is reasonable to assume that the K\(_m\) is not altered by disease states leading to an abnormality of mitochondrial numbers or capacity. Thus, for the above equation, apparent mitochondrial V\(_\text{max}\) is estimated from the initial rate of PCr resynthesis as calculated above and the end-exercise [ADP]: 

\[ V_{\text{max}} = \text{PCr resynthesis rate} \times \{1 + (K_m/\text{[ADP]})\} \]

Statistical Analysis

Data were analyzed by ANOVA across the four groups, with post hoc subgroup testing using the Fisher test when the overall ANOVA P value was \(\leq 0.05\). A value of \(P \leq 0.05\) was considered significant. Submaximal exercise was defined as stage 5 of the incremental protocol. All data are expressed as the mean±SD in the text and tables and as the mean±SEM in the figures.

### Results

#### Patient Characteristics

Patient characteristics are summarized in Table 1. Coronary artery disease was the underlying cause of heart failure in the majority of patients. All posttransplantation patients were receiving cyclosporine. The mean dose was 390±120 mg/d in the early group and 360±160 mg/d in the late group. Azathioprine was used in eight of the early-posttransplant group (mean dose, 95±38 mg/d) and in seven of the late-posttransplant group (mean dose, 73±46 mg/d). In the early-posttransplant group, five subjects received prednisone (mean dose, 21±20 mg/d), and in the late group, three received prednisone (mean dose, 10±25 mg/d).

All posttransplant patients had a myocardial biopsy on the day before testing, and none had evidence of rejection. None of the patients had a prior history of severe rejection, and only one subject, in the early-posttransplant group, had a prior history of a single episode of histologically graded moderate rejection.

The mean New York Heart Association functional class at the time of study was 2.7±1.3 in the pretransplant group and 1.2±0.4 in the early- and 1.1±0.7 in the late-posttransplant groups. The mean ejection fraction in the two groups studied after transplantation was normal. Thus, the posttransplantation patients had successful transplantation as judged by a lack of significant rejection, a good functional class, and normal resting left ventricular systolic function.

#### Rest, Submaximal Exercise, and End-Exercise pH and PCr/(PCr+P\(_\text{i}\))

At rest, there were no differences between groups in pH or PCr/(PCr+P\(_\text{i}\)) (Table 2, Fig 1).

During submaximal exercise, defined as stage 5, pH was significantly different between groups (\(P<.05\)) (Figs 1 and 2), with all three patient groups having lower values than normal control subjects. Submaximal exercise PCr/(PCr+P\(_\text{i}\)) was also different between groups (\(P<.0001\)), with all three patient groups having lower values than normal control subjects (Fig 3).

### Table 1. Characteristics of the Pretransplant and Posttransplant Groups

<table>
<thead>
<tr>
<th>No. studied</th>
<th>Pretransplant</th>
<th>Early Posttransplant</th>
<th>Late Posttransplant</th>
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<th>Pretransplant</th>
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<td>54±6</td>
<td>47±14</td>
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<th>Pretransplant</th>
<th>Early Posttransplant</th>
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<td>81±12</td>
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<th>Pretransplant</th>
<th>Early Posttransplant</th>
<th>Late Posttransplant</th>
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<th>Late Posttransplant</th>
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<th>Pretransplant</th>
<th>Early Posttransplant</th>
<th>Late Posttransplant</th>
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<td>18±9</td>
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<tr>
<td>NA</td>
<td>64±12</td>
<td>70±10</td>
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<th>Systolic BP, mm Hg</th>
<th>Pretransplant</th>
<th>Early Posttransplant</th>
<th>Late Posttransplant</th>
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<td>109±17</td>
<td>134±12</td>
<td>123±16</td>
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<table>
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<th>Heart rate, bpm</th>
<th>Pretransplant</th>
<th>Early Posttransplant</th>
<th>Late Posttransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>71±19</td>
<td>96±8</td>
<td>96±8</td>
<td></td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; CAD, coronary artery disease; IDCM, idiopathic dilated cardiomyopathy; EF, ejection fraction; BP, blood pressure; bpm, beats per minute; and NA, not applicable.
Exercise duration was significantly shorter in all three patient groups compared with normal control subjects ($P<.001$). At the end of exercise, the PCR/(PCR+Pi) ratio was not different between groups, whereas the pH was higher in the three patient groups compared with normal subjects ($P<.01$).

The PCR resynthesis rate varied significantly between groups ($P<.001$) (Table 3), being lowest in the pretransplant and early-posttransplant groups, and highest in the late-posttransplant group (Fig 4). End-exercise [ADP] varied significantly between groups ($P<.01$), being highest in the late-posttransplant group. $V_{\text{max}}$ also differed between groups ($P=.03$), with the pretransplant and early-posttransplant groups having the most abnormal values (Fig 5).

**Comparison of Early- and Late-Posttransplant Groups**

Compared with the early-posttransplant group, the late group showed trends toward improvements in submaximal values of pH and PCR/(PCR+Pi) and in $V_{\text{max}}$, which were not statistically significant. The PCR resynthesis rate was significantly higher in the late-posttransplant group compared with the early-posttransplant group, but this was associated with a supranormal drive to mitochondrial ATP production, as reflected by the significantly higher end-exercise [ADP] in the late-posttransplant group. However, compared with normal control subjects, the late-posttransplant group still had a reduced exercise duration and a lower PCR/(PCR+Pi) at submaximal exercise (both $P<.05$).

**Discussion**

The present study demonstrates that the metabolic abnormalities in exercising skeletal muscle in patients with congestive heart failure persist, in large part, after successful heart transplantation. In the early-posttransplantation group studied a mean of 4 months after successful heart transplantation, the increased acidification and PCR utilization during exercise, as well as the reduced PCR resynthesis rate in recovery, suggest a continued decreased capacity for oxidative metabolism and a continued increased reliance on glycolysis.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Bar graph shows that pH at submaximal exercise was significantly different between groups, with the three patient groups (pretransplant [Pre] and early and late posttransplant) all tending to have lower values than normal subjects.
Although the late-posttransplant group showed some evidence of improvement in exercising skeletal muscle metabolic measures, one of the most striking findings was the continued abnormal exercise responses in this group, who were a mean of 15 months and a median of 10 months after transplantation. The persistently abnormal responses in the late-posttransplant group included a decreased maximal exercise duration ($P<.05$ versus normal subjects), a persistently reduced submaximal exercise PCr/(PCr+Pi) ($P<.05$), and a trend toward a lower submaximal pH and $V_{max}$. In addition, although the rate of PCr resynthesis in the late group was not significantly different from control subjects, the PCr resynthesis rate was maintained only by a higher than normal end-exercise [ADP], which is the drive for mitochondrial ATP production. This is reflected in the $V_{max}$, which is slightly reduced.

The explanation for the persistent metabolic abnormalities after otherwise successful heart transplantation is not clear from this study. There are several possibilities, but none sufficiently explain our findings. First, the skeletal muscle defect may be permanent and irreversible by the time that a patient is ill enough to require transplantation. Arguing against this possibility is the clear-cut symptomatic improvement and relief of fatigue that occurs after transplantation. In addition, we and others have demonstrated that in congestive heart failure, the metabolic defect is not fixed but can be improved by exercise training. A second possibility is that the forearm skeletal muscle continues to be deconditioned. As noted above, several studies have documented that the metabolic abnormality of exercising skeletal muscle in heart failure can be ameliorated by training; thus, continued inactivity after transplantation potentially could lead to persistent skeletal muscle defects. We think this explanation is unlikely, since nearly all the posttransplant patients had resumed a normal lifestyle. In addition, patients with the chronic fatigue syndrome have no consistent abnormalities by $^3$P magnetic resonance spectroscopy exercise testing of their forearm muscles. Thus, even marked inactivity, as occurs in patients with the chronic fatigue syndrome, does not lead to abnormalities of forearm metabolism during exercise. A third potential explanation for our findings might be reduced blood flow to the exercising muscles. Although reduced blood flow can cause metabolic abnormalities in exercising muscle, reduced blood flow alone is unlikely to explain our findings in the patient groups for several reasons: (1) plethysmographic measures of forearm blood flow have not been different in patients with heart failure and control subjects in several studies; (2) differences between patients with heart failure and control subjects persist even during ischemic exercise; (3) forearm vasodilator reserve returns to normal by 4 months after transplantation; and (4) submaximal supine exercise cardiac output is normal late after transplantation.

A fourth potential explanation for the persistent muscle abnormalities might be side effects caused by the antirejection medications required after transplan-

### Table 3. End-Exercise [ADP], PCr Resynthesis Rates, and $V_{max}$

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects</th>
<th>Pretransplant</th>
<th>Early Posttransplant</th>
<th>Late Posttransplant</th>
<th>$P$ (ANOVA)</th>
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<tbody>
<tr>
<td>End-exercise [ADP], $\mu$mol/L</td>
<td>25±21</td>
<td>36±19</td>
<td>43±34</td>
<td>72±36*</td>
<td>.01</td>
</tr>
<tr>
<td>PCr resynthesis, mmol/L per minute</td>
<td>22±9</td>
<td>13±6*</td>
<td>15±6</td>
<td>27±6†</td>
<td>.001</td>
</tr>
<tr>
<td>$V_{max}$, mmol/L per minute</td>
<td>53±26</td>
<td>26±14*</td>
<td>33±15*</td>
<td>45±21</td>
<td>.03</td>
</tr>
</tbody>
</table>

PCr indicates phosphocreatine; $V_{max}$, maximal rate of mitochondrial ATP synthesis.

* $P<.05$ vs normal subjects.
† $P<.05$ vs early.
‡ $P<.05$ vs pretransplant.
tion. Corticosteroids, which were used in eight of the posttransplantation patients, can cause both a steroid myopathy and muscle wasting; however, abnormal metabolic findings were also present in the 10 patients in this study who were not receiving steroids. Azathioprine, which was used in 15 of the posttransplantation subjects, has not to our knowledge been described as causing skeletal muscle toxicity.

Cyclosporine may affect skeletal muscle.\textsuperscript{36-38} Two potential patterns of clinically overt muscle damage have been described, both of which are rare, with an estimated overall incidence rate of only 0.22\%,\textsuperscript{38} In one, a myopathy occurs without evidence of rhabdomyolysis but associated with myalgia and weakness. The second pattern is associated with rhabdomyolysis. Further, in animal models and possibly in humans, cyclosporine may potentiate the skeletal muscle toxicity of other drugs, such as the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors,\textsuperscript{38,39} which could lead to impaired skeletal muscle energy metabo-

![Graph](image1.png)

**Fig 4.** Bar graph shows that the phosphocreatine resynthesis rate (mmol/L per minute) was significantly different between groups, with the pretransplant group (Pre) being significantly lower than normal. The late-posttransplant group was significantly improved compared with the early-posttransplant group, suggesting that some late improvement in oxidative capacity does occur.

![Graph](image2.png)

**Fig 5.** Bar graph shows that the effective maximal rate of mitochondrial ATP synthesis ($V_{\text{max}}$) was significantly reduced in the pretransplant (Pre) and early-posttransplant subjects compared with normal subjects. In the late-posttransplant group, $V_{\text{max}}$ was not significantly different from normal.
described. Thus, although overt skeletal muscle damage caused by cyclosporine is quite rare, it is possible that cyclosporine contributes to milder subclinical defects that are detectable by spectroscopic testing. Further studies of the effects of cyclosporine on skeletal muscle are needed.

**Clinical Implications**

Exercise capacity, although improved after heart transplantation, does not totally normalize. In a study by Stevenson et al., maximal oxygen uptake was only 60% of predicted normal in patients studied a mean of 14 months after transplantation. The causes of reduced exercise capacity are unclear. Possible causes include central defects (reduced maximal heart rate, stroke volume, and cardiac output) and increased myocardial stiffness. Additionally, the present study raises the possibility that peripheral skeletal muscle defects, which do not reverse with otherwise successful heart transplantation, might also contribute to abnormal exercise capacity.

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**References**

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