Myocardial Efficiency and Sympathetic Reinnervation After Orthotopic Heart Transplantation
A Noninvasive Study With Positron Emission Tomography

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Background—The lack of cardiac catecholamine uptake and storage caused by sympathetic denervation may influence performance of the transplanted heart. Reinnervation, occurring late after transplantation, may partially resolve these effects. In this study, oxidative metabolism and its relation to cardiac work were compared in allografts and normal and failing hearts, and the effects of sympathetic reinnervation were evaluated.

Methods and Results—Twenty-seven nonrejecting, symptom-free transplant recipients, 11 healthy control subjects, and 10 patients with severe dilated cardiomyopathy underwent PET with 11C acetate for assessment of oxidative metabolism by the clearance constant kmono and radionuclide angiography or MRI for measurement of ventricular function, geometry, and work. Efficiency was estimated noninvasively by a work-metabolic index [WMI=(stroke volume×heart rate×systolic pressure)/k(mono)]. In 14 of 27 transplants, presence of regional reinnervation was identified with PET and the catecholamine analogue 11C hydroxyephedrine (extent, 24±14% of left ventricle). The WMI was comparable in normal subjects and reinnervated and denervated transplants (6.2±2.3 versus 4.9±2.0 versus 4.9±1.2·106 mm Hg·mL; P=NS) and significantly lower in cardiomyopathy patients (3.0±1.3·106 mm Hg·mL; P<0.001). For normal subjects and transplant recipients, the WMI was significantly correlated with afterload (peripheral vascular resistance; r=−0.65, P<0.01), preload (end-diastolic volume; r=0.78, P<0.01), and stroke volume (r=0.81, P<0.01) but not with hydroxyephedrine retention (transplants only; r=0.09, P=NS).

Conclusions—After transplantation, cardiac efficiency is improved compared with failing hearts and comparable to normal hearts. Differences between denervated and reinnervated allografts were not surveyed. Additionally, the dependency on loading conditions and contractility was preserved, suggesting that normal regulatory interactions for efficiency are intact and that sympathetic tone does not play a role under resting conditions. (Circulation. 2001;103:1881-1886.)

Key Words: transplantation □ myocardium □ nervous system, sympathetic □ tomography

After orthotopic heart transplantation, performance of the allograft may be influenced by a variety of factors. Prolonged hypothermic ex vivo storage,1 episodes of rejection,2 effects of immunosuppressive therapy,3 and transplant vasculopathy4 may all alter the functional and metabolic state. Myocardial sympathetic denervation as the result of surgical interruption of postganglionic nerve fibers is another factor that has been discussed to influence allograft performance by a reduction of local myocardial catecholamine uptake, storage, and release5,6 and an impaired responsiveness to adrenergic stimulation.6 Conversely, reappearance of innervation, which has been demonstrated late after transplantation,6,7 may resolve changes in the denervated heart. Reinnervation, however, has been shown to remain incomplete and regionally limited.8 Currently, little is known about its physiological importance and its effects on metabolism, function, and efficiency of the transplanted heart.

Mechanical efficiency of the ventricle is defined as the fraction of total expended metabolic energy that is converted into external contractile work10 and has been used successfully to describe beneficial therapeutic effects in patients with heart failure.11-13 By taking into account the energy cost for a given level of cardiac output, efficiency may also be a very sensitive parameter to characterize performance of the transplanted heart. It has been previously described that overall oxidative energy metabolism in the transplanted heart is comparable to normal hearts.14 The relation between oxidative metabolism and the level of cardiac work, however, has not yet been investigated in detail.

The aim of this study was therefore 2-fold: (1) to evaluate efficiency of the nonrejecting, orthotopically transplanted heart compared with the normal and failing heart and (2) to assess the role of sympathetic reinnervation for regulation of allograft efficiency.

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All measurements were performed noninvasively on the basis of imaging with PET and the radiotracers $^{11}$C acetate and $^{18}$F hydroxyephedrine (HED). Clearance kinetics of $^{11}$C acetate were used to quantify tricarboxylic acid cycle flux, which is directly related to overall myocardial oxidative metabolism.$^{15}$ By a combination with noninvasive measures of cardiac function, a previously validated estimate of myocardial efficiency was derived.$^{14}$ Additionally, the norepinephrine analogue $^{11}$C HED was used in transplant recipients to quantify presence and extent of sympathetic reinnervation.$^{19}$

Methods

Patients and Study Design

The study group consisted of 27 patients (6 women, 21 men; age, 55±10 years) at various time points after orthotopic heart transplantation (0.5 to 8.2 years; mean, 3.1±2.2 years). For inclusion in the study, patients had to be symptom-free. The presence of acute rejection, significant graft vessel disease, or impaired allograft function was ruled out by clinical follow-up, echocardiography, coronary angiography, and endomyocardial biopsy. None of the patients received medication known to interfere with sympathetic catecholamine uptake (eg, antidepressants, clonidine, reserpine), whereas only 4 had $\beta$-adrenergic receptor blocking agents. $\beta$-Blockers and all other cardioactive drugs were discontinued at least 24 hours before the study, whereas immunosuppressive therapy based on cyclosporine A was not interrupted.

In addition, 2 age-matched control groups consisting of 11 healthy normal subjects (7 women, 4 men; age, 51±9 years) without clinical or ECG evidence of heart disease and 10 patients with severe chronic idiopathic dilated cardiomyopathy (2 women, 8 men; age, 53±11 years) were studied. Results of these control groups have been reported in a previous study.$^{16}$ Diagnosis of dilated cardiomyopathy was based on the absence of significant coronary artery disease and primary valvular disease during cardiac catheterization. Whereas healthy normal subjects had no medication, cardiomyopathy patients were studied under a standard therapy with $\beta$-blockers, furosemide because of symptomatic heart failure.

Before inclusion in the study, all patients signed written informed consent forms approved by the ethics committee of the medical faculty of the TU München.

PET

Tracers were synthesized as previously described.$^{17,18}$ PET imaging was performed with an ECAT EXACT 47 or ECAT EXACT HR + scanner (CTI/Siemens). After adequate positioning, a transmission scan of 10 to 15 minutes was acquired for correction of photon attenuation. To measure perfusion and oxidative metabolism, 300 to 400 MBq of $^{11}$C acetate was then injected as a slow bolus over 30 seconds, and a dynamic imaging sequence of 21 frames over 30 minutes (10×10, 1×60, 5×110, 3×180, and 2×300 seconds) was initiated. In transplant recipients, presence or absence of sympathetic reinnervation was assessed in the same session: After a break of 50 minutes to allow for decay of radioactivity, 600 MBq of $^{11}$C HED was injected, and a second dynamic imaging sequence (14 frames, 6×30, 2×60, 2×150, 2×300, 2×600 seconds) was acquired. Heart rate and blood pressure were monitored continuously throughout the imaging procedure by ECG and arm cuff measurements.

Assessment of Left Ventricular Function

Left ventricular (LV) function was measured noninvasively on the same day either before or directly after PET with tomographic radionuclide angiography (transplant recipients and cardiomyopathy patients) or cine MRI (healthy normal subjects). Both techniques have been shown to be reliable and reproducible, and results have been demonstrated to correlate closely.$^{19,20}$

For radionuclide ventriculography, autologous erythrocytes were labeled with 800 to 1000 MBq of $^{99m}$Tc by a combined in vivo/in vitro technique and reinjected after purification. After 5 minutes to allow for equilibrium, patients were positioned in a rotating triple-headed gamma camera (Multispect 3, Siemens), and an electrocardiographically gated tomographic acquisition was performed. MRI was performed with a 1.5-T Philips Gyroscan ACS2 or NT (Philips Medical Systems) with ECG-gated short-axis, multislice, multiphase cine gradient echo sequences.$^{20}$

Data Analysis

PET

Attenuation-corrected transaxial PET images were reconstructed by filtered backprojection. A previously validated volumetric sampling tool$^{21}$ was then applied to a summed data set of frames 11 to 12 of the imaging sequence for $^{11}$C acetate to create polar maps of static myocardial activity distribution at 2 to 4 minutes after injection. These polar maps were normalized to their maximum and used for qualitative assessment of regional myocardial perfusion.$^{22}$ Myocardial sectors defined by the polar map were then transferred to the whole dynamic sequence, and time-activity curves were obtained. The early phase of $^{11}$C acetate washout was fitted monoexponentially to obtain the constant $k_{\text{mono}}$ as a previously validated measure of oxidative metabolism,$^{19}$ expressed in another polar map. The average of $k_{\text{mono}}$ for the whole map was calculated to define global myocardial oxygen consumption.

In transplant recipients, myocardial activity of $^{11}$C HED was also sampled volumetrically. Additionally, the arterial input function was derived from a small circular region of interest in the LV cavity. Myocardial HED retention was calculated as activity at 40 minutes divided by the integral of the arterial blood curve.$^{7}$ On the basis of results in denervated hearts,$^{7}$ myocardium showing HED retention <7% per minute was defined as denervated. The global extent of reinnervation was quantified by the percentage of polar map showing retention above this threshold.$^{9}$

Ventricular Function

For radionuclide angiography, tomographic data were also reconstructed by filtered backprojection, and the volumetric sampling tool was used for detection of endocardial borders in end-systolic and end-diastolic phases, allowing calculation of regional endocardial shortening in a polar map, and of global LV volumes. Magnetic resonance images were analyzed by commercially available software (MASS, University of Leiden, The Netherlands). Contours for endocardial borders were drawn manually in every phase of slices from apex to just below the valve plane. Then, end-diastolic and end-systolic volumes were calculated from the summation of these slices in end-diastolic and end-systolic phases.

Calculation of Hemodynamic Parameters and Estimation of Myocardial Efficiency

Cardiac output was obtained by multiplying stroke volume times heart rate. Systemic vascular resistance (SVR) was estimated as mean arterial blood pressure divided by cardiac output and converted to dyncm$^{-5}$s$^{-1}$.LV stroke work was estimated by a stroke work index (SWI), the product of stroke volume and peak systolic blood pressure.$^{13}$

Mechanical efficiency of the left ventricle, defined as the relation between cardiac work and oxygen consumption, was noninvasively estimated by combining stroke work data with data from $^{11}$C acetate PET. As previously validated,$^{13}$ the work-metabolic index (WMI) was calculated by

$$\text{WMI} = \frac{\text{SWI} \times \text{HR}}{k_{\text{mono}}}, \text{mm Hg} \cdot \text{mL}$$

where $k_{\text{mono}}$ is the myocardial clearance constant for $^{11}$C acetate derived from PET, SWI the stroke work index, and HR the heart rate.

Statistical Analysis

Values are expressed as mean±SD. Differences between patient groups were assessed by 1-way factorial ANOVA and the post hoc
Fisher’s protected least significant differences test. Simple linear regression analysis was performed to describe the relation between continuous variables. A value of $P < 0.05$ was defined as significant.

**Results**

**Sympathetic Reinnervation in Transplant Recipients**

In transplants, maximal LV HED retention ranged from 3.4% to 16.1% per minute and was significantly correlated with time after transplantation ($r=0.59; P<0.001$). Fourteen of 27 patients showed HED retention above the threshold of 7% per minute, indicating sympathetic reinnervation. The extent of reinnervation in these patients ranged from 9% to 47% of the left ventricle (mean, 24±6). Thirteen of 27 transplant recipients remained sympathetically denervated. Both groups were matched for age (56±6 years for denervated versus 55±12 years for reinnervated patients; $P<0.70$) and the number of previously documented rejection episodes (1±1 versus 1±1; $P=0.97$).

**Hemodynamics, Ventricular Function, and Loading Conditions**

Table 1 displays hemodynamic parameters for both groups of transplant recipients compared with normal subjects and cardiomyopathy patients. Importantly, differences between reinnervated and denervated transplant recipients were not observed.

Compared with cardiomyopathy patients and normal subjects, the baseline heart rate was higher in transplant recipients. LV ejection fraction and volumes were comparable in transplants and normal subjects, except for a slightly lower end-diastolic volume and stroke volume in both transplant groups, whereas cardiomyopathy patients showed reduced ejection fraction and elevated volumes, as expected. SVR was substantially elevated in cardiomyopathy patients and was only marginally higher in innervated transplants compared with normal subjects.

Finally, cardiac work, estimated by the SWI, was significantly higher in both transplant groups compared with cardiomyopathy patients. Because of the difference in stroke volume, the SWI was slightly lower in transplants compared with normal subjects.

**Global $^{11}$C Acetate Kinetics and Myocardial Efficiency**

Early uptake of $^{11}$C acetate as a measure of myocardial perfusion was homogeneous in all subjects. Perfusion defects, defined as regional uptake <50% of the individual maximum, were not observed.

The clearance constant $k_{\text{mono}}$ as a measure of oxidative metabolism was not different in innervated and denervated transplant recipients and was comparable to normal subjects ($0.060±0.015$ per minute in normal subjects versus $0.055±0.014$ per minute in denervated transplants and

**Figure 1.** Comparison of oxidative metabolism ($k_{\text{mono}}$) and WMI as estimates of efficiency in denervated (denerv) and reinnervated (reinnerv) transplant recipients, patients with dilated cardiomyopathy (DCM), and normal subjects.
0.060±0.010 per minute in reinnervated transplants; \( P=\text{NS} \), whereas it was significantly lower in cardiomyopathy patients (0.040±0.011 per minute, \( P<0.001 \)) (Figure 1).

The WMI as an estimate of cardiac efficiency was also similar in denervated and innervated transplant recipients and comparable to normal subjects (6.2±2.3·10^6 mm Hg·mL in normal subjects versus 4.9±1.2·10^6 mm Hg·mL in denervated and 4.9±2.0·10^6 mm Hg·mL in reinnervated transplants; \( P=\text{NS} \) but significantly reduced in cardiomyopathy patients (3.0±1.3·10^6 mm Hg·mL; \( P<0.01 \)) (Figure 1).

**Determinants of Myocardial Efficiency**

For normal subjects as well as transplant recipients, the WMI was significantly inversely correlated with SVR as a measure of afterload and positively correlated with end-diastolic volume as an estimate of preload. Additionally, there was a positive correlation with stroke volume as a measure of contractility (Figure 2). The interrelation between these parameters in subgroups is shown in Table 2.

Parameters of sympathetic reinnervation such as mean HED retention (Figure 3) were not correlated with the WMI in transplant recipients.

### TABLE 2. Correlation Coefficients for Determinants of Cardiac Efficiency in Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>WMI</th>
<th>SVR</th>
<th>LVEDV</th>
<th>LV Stroke Volume</th>
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</thead>
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<tr>
<td>Reinnervated transplants (n=14)</td>
<td></td>
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<tr>
<td>SVR</td>
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<td></td>
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<tr>
<td>LVEDV</td>
<td>0.94*</td>
<td>-0.74*</td>
<td></td>
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<tr>
<td>LV stroke volume</td>
<td>0.95*</td>
<td>-0.72*</td>
<td>0.98*</td>
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<tr>
<td>Global HED retention</td>
<td>0.28</td>
<td>-0.12</td>
<td>0.25</td>
<td>0.31</td>
</tr>
<tr>
<td>Denervated transplants (n=13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>LVEDV</td>
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<tr>
<td>LV stroke volume</td>
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<td>-0.81*</td>
<td>0.84*</td>
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<tr>
<td>Global HED retention</td>
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<td>0.40</td>
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<tr>
<td>Normal subjects (n=11)</td>
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<tr>
<td>SVR</td>
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<tr>
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<tr>
<td>LV stroke volume</td>
<td>0.68*</td>
<td>-0.69*</td>
<td>0.91*</td>
<td></td>
</tr>
</tbody>
</table>

LVEDV indicates left ventricular end-diastolic volume.

*\( P<0.05 \).

### Regional Analysis of Catecholamine Uptake, Oxidative Metabolism, and Wall Motion

In addition to global analysis, HED retention, qualitative perfusion, \( k(\text{mono}) \), and endocardial shortening were regionally analyzed by regions of interest encompassing the vascular territories for the left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA).

Results are summarized in Table 3. Reinnervation occurred mainly in the LAD territory, where the difference in HED retention between denervated and reinnervated transplants was highly significant. Smaller but also significant differences were observed for the LCX and RCA. Despite these differences in HED retention, no regional differences for perfusion, \( k(\text{mono}) \), or endocardial shortening were observed between groups.

### Discussion

In summary, performance of the transplanted heart was significantly improved compared with the failing heart and was comparable to healthy individuals. Normal regulatory mechanisms for efficiency, namely the dependency on load-
ing conditions and contractility, remained intact after transplantation, whereas the presence or absence of sympathetic reinnervation did not have an influence under resting conditions.

The concept of efficiency, which includes not only information about cardiac output but also about the concomitant energy cost, has been mainly used in heart failure to understand and optimize effects of medical therapy. Efficiency is usually quantified by complex invasive measurements of cardiac work and oxygen consumption, which limit its clinical application. Recently, however, an approach for noninvasive estimation based on PET imaging with $^{11}$C acetate has been introduced and validated. In the present study, this noninvasive method was applied to characterize effects of heart transplantation as a therapeutic option for terminal heart failure. After transplantation, a variety of factors may affect cardiac work, oxygen consumption, and thus efficiency.

First, the hemodynamic situation of the transplanted heart is different. The baseline heart rate is elevated, mainly because of a lack of parasympathetic control of the sinus node. Blood pressure and ventricular afterload also may be increased as the result of elevated plasma catecholamine levels or due to effects of cyclosporine immunosuppression. Despite hemodynamic differences, however, efficiency of transplant allografts remained within the normal range in the present study. Furthermore, the relation between efficiency and loading conditions as well as contractile state, a previously described normal regulatory interaction, remained intact after transplantation. Efficiency was also significantly improved compared with failing hearts, so that results of previous studies reporting only minor improvements in exercise performance after transplantation cannot be attributed to a lack of improvement of cardiac efficiency.

Second, the metabolic profile of the transplanted heart may differ from normal hearts. It has previously been shown that nonrejecting allografts utilize higher amounts of glucose as a substrate. This observation was largely attributed to sympathetic denervation and led to the conclusion that the transplanted heart may be metabolically inefficient, requiring greater amounts of substrate to maintain cardiac work. Consistent with previous work, however, overall flux through the tricarboxylic acid cycle as the final common pathway for all substrates was found to be comparable to normal subjects in the present study, suggesting a substrate shift from fatty acids to glucose rather than an overall increased energy demand as explanation for higher glucose utilization rates. Normal values for the WMI give further evidence against the hypothesis of general metabolic inefficiency after transplantation.

Progressive transplant vasculopathy and repeated myocardial damage caused by acute rejection are major complications after transplantation and may alter allograft performance. The present study, however, was designed to characterize cardiac efficiency in transplant recipients with an uncomplicated course and to evaluate the additional role of sympathetic reinnervation. Patients with acute rejection, vasculopathy, or allograft failure were excluded. Future studies may focus on effects of these short- and long-term complications, and new therapeutic approaches may be optimized with serial noninvasive measurements of efficiency.

With the use of different techniques, a variety of previous studies have demonstrated that sympathetic reinnervation of both sinus node and myocardium does occur late after transplantation. It has also been shown that reinnervation remains regionally heterogeneous. Consistently, with the use of PET methodology, which allows direct detection of reappearing myocardial catecholamine uptake and storage, evidence of incomplete reinnervation was found in the present study. Previous work has shown that sympathetic reinnervation contributes to partial restoration of exercise capacity and plays a role for regulation of myocardial blood flow and metabolism. In the present study, however, cardiac work, oxygen consumption, and efficiency at rest were not different between reinnervated and denervated transplant recipients. Additionally, there was no regional difference for contractile performance or oxygen consumption in reinnervated and denervated territories. These results further confirm that efficiency of the allograft is mainly regulated by intrinsic mechanisms other than sympathetic innervation and that reappearance of sympathetic nerve terminals does not play a major regulatory role under resting conditions.

Conclusions
Cardiac work, oxygen consumption, and efficiency of the transplanted heart are similar to normal hearts at rest and are significantly improved compared with the failing heart. In-
trinastic regulatory interactions between efficiency, preload, afterload, and contractility remain intact despite sympathetic denervation early after transplantation. Additionally, the occurrence of sympathetic reinnervation did not have global or regional effects on oxidative metabolism, contractile function, and efficiency at rest. The performance of physical exercise is of limited feasibility during PET imaging because of the high likelihood of motion artifacts; therefore, further studies with other techniques may be performed in the future to evaluate the physiological role of reinnervation under stress conditions.

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