

EFFECT OF SYMPATHETIC REINNERVATION ON CARDIAC PERFORMANCE AFTER HEART TRANSPLANTATION

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ABSTRACT

Background Late after cardiac transplantation, limited reinnervation of the transplanted heart may occur, but little is known about the effect of reinnervation on cardiac function and exercise performance.

Methods We quantified the extent of myocardial reinnervation noninvasively in 29 cardiac-transplant recipients, using positron-emission tomography and the catecholamine analogue [¹¹C]hydroxyephedrine. Global and regional ventricular function at rest and during standardized exercise testing was measured with the use of radionuclide angiography, and the results were compared with those in 10 healthy controls.

Results Sympathetic reinnervation, mainly in the anteroseptal wall, was present in 16 of the 29 transplant recipients. At rest, hemodynamic differences were not observed between the patients with reinnervation and those with denervation. However, the latter group had a shorter mean (\pm SD) exercise time (6.1 ± 1.5 minutes, vs. 8.2 ± 1.2 in the group with reinnervation; $P < 0.01$) and a lower peak heart rate (121 ± 13 vs. 143 ± 15 beats per minute, $P < 0.01$). The contractile response to exercise was significantly enhanced in transplant recipients with reinnervation and similar to that of normal controls. In a multivariate analysis, hydroxyephedrine retention was the only independent determinant of the exercise-induced increase in the ejection fraction.

Conclusions In heart-transplant recipients, the restoration of sympathetic innervation is associated with improved responses of the heart rate and contractile function to exercise. These results support the functional importance of reinnervation in transplanted hearts. (N Engl J Med 2001;345:731-8.)

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ALTHOUGH the capacity for exercise in heart-transplant recipients is improved after transplantation, it remains abnormal.¹⁻³ Impairments of chronotropic responsiveness and ventricular function have been regarded as major reasons for this problem.^{1,4,5} These impairments have been attributed primarily to sympathetic denervation of the allograft as a consequence of surgical interruption of postganglionic sympathetic fibers at the time of transplantation.⁶

Although it has long been thought that denervation is irreversible, there is evidence against this belief. In studies performed one to eight years after transplantation, invasive measurements of transcatheter nor-

epinephrine spillover,^{7,8} noninvasive imaging with radiolabeled catecholamine analogues,^{9,10} and electrophysiological determination of variability in the heart rate¹¹ have consistently shown partial sympathetic reinnervation of the allograft. In a recent longitudinal study, we showed that reinnervation is an ongoing process with different effects on various regions of the heart; reinnervation was not complete until 15 years after transplantation.¹²

Reinnervation affects the sensation of chest pain,¹³ regional regulation of myocardial blood flow,^{14,15} and substrate metabolism,¹⁶ but the functional importance of reinnervation is not known. Previous studies have examined impairments in exercise capacity, chronotropic responsiveness, and ventricular function in transplant recipients. None of these studies, however, used methods that could identify evidence of reinnervation.¹⁻⁵ We conducted a study to determine whether partial restoration of myocardial sympathetic innervation increases the capacity for exercise. We quantified the presence and extent of sympathetic reinnervation using positron-emission tomography (PET) with the catecholamine analogue [¹¹C]hydroxyephedrine, which is taken up and stored in presynaptic sympathetic-nerve terminals. We then examined the relation between reinnervation and allograft function at rest and during exercise, using noninvasive imaging with radionuclide angiography.

METHODS

Study Design

We studied 29 symptom-free, otherwise healthy cardiac-transplant recipients (6 women and 23 men). Their mean (\pm SD) age was 56 ± 10 years, and the mean interval between transplantation and enrollment in the study was 3.2 ± 2.1 years (range, 0.5 to 8.2). Nine of the patients had undergone transplantation because of ischemic cardiomyopathy, and the other 20 because of idiopathic cardiomyopathy. None of the patients had acute rejection, clinically significant transplant vasculopathy, or allograft dysfunction, as determined by clinical evaluation, echocardiography, coronary angiography, and endomyocardial biopsy before enrollment. None of the patients were taking medications known to interfere with presynaptic catecholamine uptake (e.g., antidepressants, clonidine, or reserpine). All other cardioactive drugs were discontinued.

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ued at least 24 hours before enrollment. Immunosuppressive therapy was not interrupted.

The presence or absence and extent of reinnervation in various regions of the heart were determined noninvasively with the use of PET and [¹¹C]hydroxyephedrine. The results were compared with cardiac performance at rest and in response to a standardized, symptom-limited exercise test, as measured by electrocardiographically gated equilibrium radionuclide angiography within 24 hours of PET imaging. The results of radionuclide angiography were compared with those in a control group of 10 persons without clinical or electrocardiographic evidence of heart disease. The composition and mean age of the control group (two women and eight men, 53±12 years of age) were similar to those of the 29 patients. Before enrollment, all patients and controls signed written informed-consent forms approved by the ethics committee of the Technische Universität München, in Munich, Germany.

Sympathetic Reinnervation

[¹¹C]hydroxyephedrine was synthesized as previously described.¹⁷ Imaging was performed with the ECAT EXACT 47 or ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, Tenn.). After positioning of the patient, a 15-minute transmission scan was acquired for the correction of tissue attenuation. Myocardial perfusion was assessed qualitatively with the use of 370 MBq of [¹³N]ammonia or [¹¹C]acetate. After five half-lives to allow for decay of the perfusion tracer, 600 MBq of [¹¹C]hydroxyephedrine was injected, and dynamic imaging was performed, with a total of 14 frames (six of 30 seconds' duration, two of 60 seconds, two of 150 seconds, two of 300 seconds, and 2 of 600 seconds). Heart rate and blood pressure were monitored continuously.

Attenuation-corrected transaxial images were reconstructed by filtered backprojection. Volumetric sampling was performed to identify myocardial segments in the perfusion images and create polar maps of the distribution of the perfusion tracer throughout the entire left ventricle.¹⁹ The segments were then transferred to the hydroxyephedrine images. In addition, the arterial-input function was derived from a small circular region of interest in the left ventricular cavity in order to define the time course of radioactivity in arterial blood. On the basis of the dynamic PET images, myocardial hydroxyephedrine retention was calculated as the concentration in myocardial tissue at 40 minutes divided by the integral of the concentration in arterial blood, and also expressed in a polar map.^{10,12} Denervation was defined as a level of retention that was less than 7 percent per minute.^{10,12} The extent of reinnervation was quantified as the percentage of the polar map showing retention above this threshold. In addition, hydroxyephedrine retention was assessed in the anteroseptal, lateral, and inferior wall, reflecting the vascular territories of the left anterior descending, circumflex, and right coronary arteries.

Ventricular Function and Exercise Performance

Autologous erythrocytes were labeled with 800 to 1000 MBq of technetium-99m with the use of a combined *in vivo* and *in vitro* technique and reinjected after purification for repeated blood-pool imaging. After an interval of five minutes, to allow for equilibrium, patients were positioned in a semi-upright position on a bicycle table,¹⁸ and planar gated images at rest (frame mode, 24 segments of time for the cardiac cycle, three-minute acquisition) were acquired in the left anterior oblique view with the most clearly defined septum with the use of a small-field-of-view gamma camera (Basicam, Siemens, Erlangen, Germany).

A symptom-limited bicycle exercise test was performed according to a standardized protocol with an initial workload of 50 W. Gated scintigraphic imaging (with specifications similar to those for images acquired while the patient was at rest) was started after one minute, to allow for hemodynamic stabilization, and continued for three minutes. The workload was subsequently increased by 50 W every four minutes until the patient was too tired to continue. At each successive workload level, imaging was performed after a stabilization phase of one minute. The heart rate and blood

pressure were monitored and 12-lead electrocardiography was performed continuously.

Blood samples were obtained while the patient was at rest and immediately after maximal exercise for measurements of plasma norepinephrine and epinephrine by high-performance liquid chromatography.

Planar images were analyzed according to international standards¹⁸ with the use of commercially available software (Gaede, Freiburg, Germany). The global left ventricular ejection fraction was calculated in addition to regional ejection fractions in the anteroseptal, lateral, and inferoapical segments.

Subjective Assessment

All transplant recipients were asked to complete a questionnaire about their daily physical activity.²⁰ On the basis of the number of stairs climbed, the number of blocks walked, and the time spent engaged in exercise, a composite index of physical activity, expressed in kilocalories expended per week, was calculated.

Statistical Analysis

The data were analyzed with Statview software, version 5.0 (SAS Institute, Cary, N.C.). All differences between pairs of continuous variables were assessed by one-way analysis of variance and post hoc Fisher's protected least-significant-differences test.²¹ Differences in proportions between groups were analyzed with the chi-square test. Simple linear regression analysis was performed to determine the relation between pairs of continuous variables. In addition, a multivariate, stepwise linear regression analysis was performed to identify independent determinants of the ventricular response to exercise. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Sympathetic Reinnervation

Myocardial perfusion was homogeneous in all patients while they were at rest. Perfusion defects, defined as uptake of the perfusion tracer that was less than 50 percent of maximum, were not observed, confirming the integrity of the myocardium in all patients.

Global left ventricular retention of [¹¹C]hydroxyephedrine ranged from 2.2 to 7.0 percent per minute. Myocardial retention of the catecholamine analogue was moderately but significantly correlated with the interval between transplantation and participation in the study ($r=0.61$, $P<0.001$).

Sixteen of the transplant recipients had signs of reinnervation, defined as regional retention of hydroxyephedrine that exceeded the threshold of 7 percent per minute. The area of reinnervation ranged from 6 to 47 percent of the left ventricle (mean, 24±14) and was mainly located in the region of the left anterior descending artery, where hydroxyephedrine retention was substantially higher than it was in the regions of the left circumflex and right coronary arteries (Fig. 1). The other 13 transplant recipients had persistent denervation, with low retention of hydroxyephedrine in all vascular territories. The characteristics of the two groups of transplant recipients are shown in Table 1. The interval between transplantation and participation in the study was significantly longer in the group of patients with reinnervation than in the group with denervation. In addition, the do-

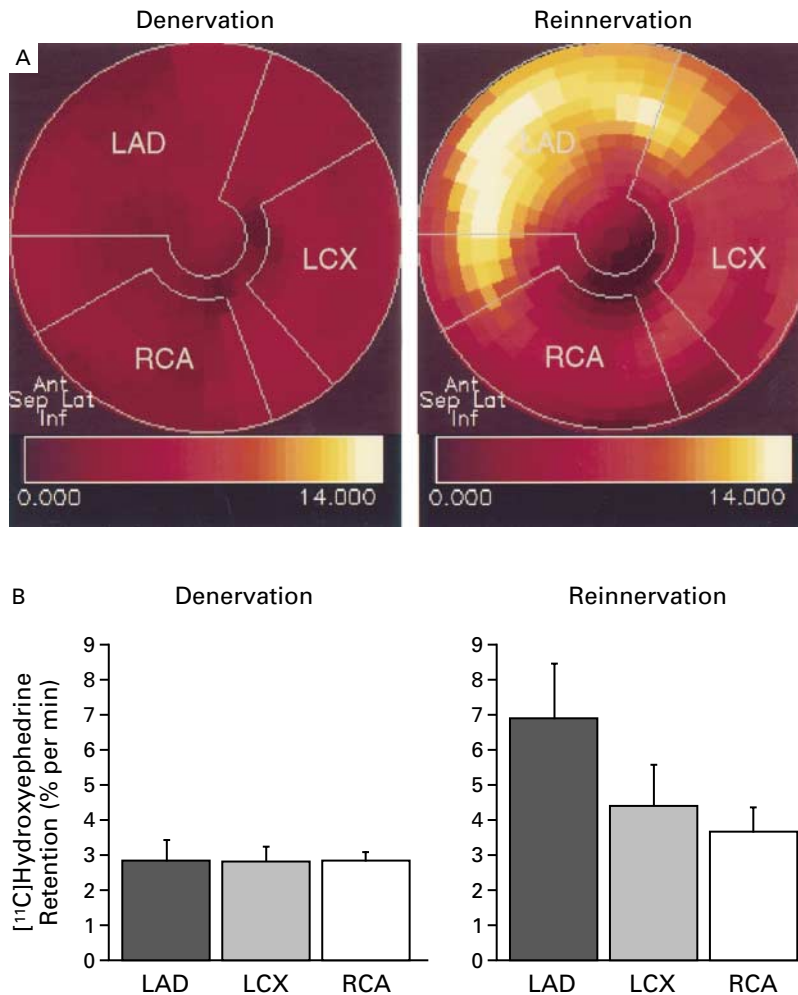


Figure 1. Left Ventricular Retention of the Catecholamine Analogue [^{11}C]Hydroxyephedrine in Transplant Recipients with Denervation and Those with Reinnervation.

The polar maps in Panel A show the level of [^{11}C]hydroxyephedrine retention (percent per minute) in one patient with denervation and one with reinnervation. The apex is in the center, the base in the periphery, the anterior wall (Ant) on top, the septum (Sep) on the left, the lateral wall (Lat) on the right, and the inferior wall (Inf) on the bottom. The patient with denervation has low levels of [^{11}C]hydroxyephedrine retention in all regions (dark red), whereas the patient with reinnervation has a high level of [^{11}C]hydroxyephedrine retention (yellow) in the basal anteroseptal wall, indicating partial restoration of catecholamine-uptake sites. LAD denotes left anterior descending artery, LCX left circumflex artery, and RCA right coronary artery. Panel B shows that in the group of transplant recipients with reinnervation, the mean level of [^{11}C]hydroxyephedrine retention was significantly higher in the territory of the left anterior descending artery (anteroseptal region) than in the territories of the left circumflex artery (lateral wall) or the right coronary artery (inferior wall). $P < 0.001$ for both comparisons. The level of [^{11}C]hydroxyephedrine retention was homogeneously low in the patients with denervation. T bars indicate standard deviations.

nors were significantly younger in the group with reinnervation.

Systemic Hemodynamics and Exercise Tolerance

At base line, the hemodynamic values and tolerance of exercise did not differ significantly between the transplant recipients with reinnervation and those

with denervation (Table 2). The heart rate was significantly higher in both groups than in the controls, as were the rate–pressure product and diastolic pressure. The systolic pressure did not differ significantly among the three groups.

Overall exercise time was significantly longer in the group of patients with reinnervation than in the group

TABLE 1. CHARACTERISTICS OF THE TRANSPLANT RECIPIENTS.*

CHARACTERISTIC	ALL PATIENTS (N=29)	DENERVATION GROUP (N=13)	REINNERVATION GROUP (N=16)
Age (yr)	56±10	56±9	56±12
Interval since surgery (yr)	3.2±2.1	1.7±1.6	4.4±1.7†
Age at transplantation (yr)	53±11	54±9	52±13
Age of donor (yr)	37±15	45±15	31±13‡
Prior rejection episodes (no.)	1±1	1±1	1±1
Global HED retention (%/min)	4.2±1.5	2.8±0.4	5.3±1.0‡
Reinnervated area (% of ventricle)	13±16	0	24±14‡

*Plus-minus values are means ±SD. HED denotes [¹¹C]hydroxyephedrine.

†P=0.02 for the comparison with the denervation group.

‡P<0.001 for the comparison with the denervation group.

with denervation; the values were lower in both groups than in the control group. The maximal workload was lowest in the group of transplant recipients with denervation.

Reduced exercise performance was significantly associated with a reduced peak heart rate in the group of patients with denervation, but the peak heart rate did not differ significantly between the group with reinnervation and the control group. The results were similar for the association of systolic pressure and the rate-pressure product with exercise performance.

Left Ventricular Function

The global and regional ejection fractions at rest did not differ significantly among the group of patients with denervation, the group with reinnervation, and the control group (Table 3). During peak exercise, the global ejection fraction was significantly lower in the denervation group than in the reinnervation and control groups; the values were similar in the latter two groups. To eliminate any effects of differences in maximal exercise capacity, the response of the ejection fraction to exercise was normalized and compared at an identical workload of 50 W, with similar results (Table 3 and Fig. 2).

Analysis of regional ejection fractions (at a workload of 50 W) showed that the differences in overall ventricular function were mainly due to changes in the anteroseptal region (corresponding to the area of the left anterior descending artery, where reinnervation begins). As with the global values, the ejection fraction during exercise in this region was lower in the denervation group than in the reinnervation and control groups, which had similar values. The ejection fraction in the lateral region did not differ significantly among the three groups. In the inferoapical region, which remained denervated in all the transplant recipients, the peak ejection fraction was lower in both transplantation groups than in the control group (Fig. 3).

Plasma Catecholamines

Plasma catecholamine levels were similar in the denervation and reinnervation groups at rest (norep-

TABLE 2. SYSTEMIC HEMODYNAMIC VALUES AND EXERCISE TOLERANCE.*

VARIABLE	DENERVATION GROUP (N=13)	REINNERVATION GROUP (N=16)	CONTROL GROUP (N=10)
At rest			
Heart rate (beats/min)	89±9†	90±14†	79±11
Systolic pressure (mm Hg)	130±16	128±10	125±5
Diastolic pressure (mm Hg)	86±9†	89±8‡	79±7
Rate-pressure product	11,468±980†	11,491±2139†	9822±1535
During exercise			
Exercise time (min)	6.1±1.5‡§	8.2±1.2‡	9.8±1.6
Maximal workload (W)	108±28‡	128±26	145±28
Peak heart rate (beats/min)	121±13‡§	143±15	142±17
Systolic pressure (mm Hg)	172±22¶	190±21	189±21
Diastolic pressure (mm Hg)	87±13	96±11	87±16
Rate-pressure product	20,804±2619‡§	27,267±4137	27,013±5051

*Plus-minus values are means ±SD.

†P<0.05 for the comparison with the control group.

‡P<0.01 for the comparison with the control group.

§P<0.01 for the comparison with the reinnervation group.

¶P<0.05 for the comparison with the reinnervation group.

TABLE 3. GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION.*

EJECTION FRACTION	DERIVATION GROUP (N=13)	REINNERVATION GROUP (N=16)	CONTROL GROUP (N=10)
	percent		
At rest			
Global	67±6	66±7	68±6
Regional			
Anteroseptal	53±14	57±14	56±14
Lateral	90±8	89±11	82±7
Inferoapical	61±12	60±13	68±14
During exercise			
Peak			
Global	70±8†‡	78±6	82±5
Increase from base line	3±5†‡	12±4	14±4
Workload of 50 W			
Global	69±7†‡	76±6	80±6
Increase from base line	2±4†‡	10±4	12±4
Regional			
Anteroseptal	54±16†‡	71±14	77±11
Lateral	91±8	95±15	85±8
Inferoapical	66±12†	73±6§	82±10

*Values are means ±SD.

†P<0.001 for the comparison with the control group.

‡P<0.01 for the comparison with the reinnervation group.

§P=0.03 for the comparison with the control group.

inephrine, 2.9 ± 2.7 and 2.1 ± 1.0 nmol per liter, respectively; $P=0.29$; and epinephrine, 0.1 ± 0.1 and 0.2 ± 0.1 nmol per liter, respectively; $P=0.43$) and after peak exercise (norepinephrine, 7.3 ± 2.6 and 7.1 ± 3.6 nmol per liter, respectively; $P=0.87$; and epinephrine, 0.3 ± 0.2 and 0.4 ± 0.3 nmol per liter; $P=0.48$).

Relation between Exercise Performance and Reinnervation

In the transplant recipients, overall hydroxyephedrine retention was significantly correlated with the change in the global ejection fraction in response to stress — that is, the difference between the value at rest and the value during exercise ($r=0.61$, $P<0.001$) (Fig. 4). In a univariate analysis, the increase in the ejection fraction was also correlated with the interval since transplantation ($r=0.59$, $P<0.001$), the increase in the heart rate ($r=0.45$, $P=0.02$), the overall exercise time ($r=0.56$, $P=0.002$), and the maximal workload ($r=0.38$, $P=0.04$). There was no correlation between the change in the ejection fraction and the patient's age, the age at transplantation, the donor's age, the number of previous rejection episodes, the body-mass index, the heart rate at rest, the ejection fraction at rest, or the plasma catecholamine levels.

Variables that were correlated in the univariate analysis were entered into a multivariate, stepwise linear regression model in order to identify independent

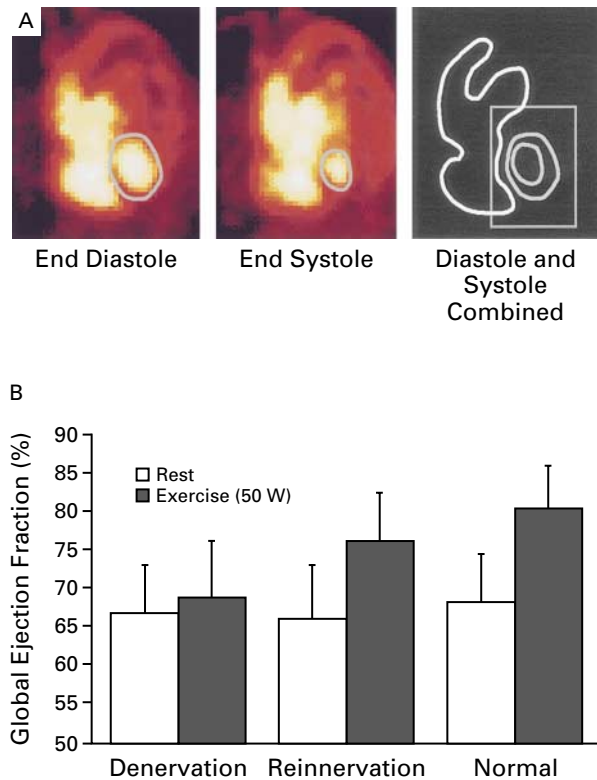


Figure 2. Global Left Ventricular Ejection Fraction as Determined by Gated Radionuclide Angiography.

Panel A shows images in the left anterior oblique view of the left ventricle of a normal subject at rest, with regions of interest circled in the end-diastolic and end-systolic frames and the results of the two frames combined in the right-hand portion of the panel. The large area of radioactivity is a composite of the atria, right ventricle, and great vessels. Panel B shows the left ventricular ejection fraction at rest and during exercise (a 50-W workload) in the patients with denervation, those with reinnervation, and normal subjects. During exercise, the ejection fraction was lower in the patients with denervation than in those with reinnervation or the normal subjects ($P<0.01$ for both comparisons); the ejection fraction did not differ significantly between the patients with reinnervation and the normal subjects. T bars indicate standard deviations.

determinants of the functional response to exercise. In the final model, overall hydroxyephedrine retention was the only independent determinant of the inotropic response to exercise; the interval since transplantation, heart rate, exercise time, and maximal workload were not significantly associated with hydroxyephedrine retention.

Daily Physical Activity

Although multiple factors may have affected the subjective data on daily physical activity, there was a trend toward higher values for the physical-activity index in the reinnervation group than in the denervation group (3340 ± 3056 vs. 2021 ± 876 kcal per week, $P=0.09$).

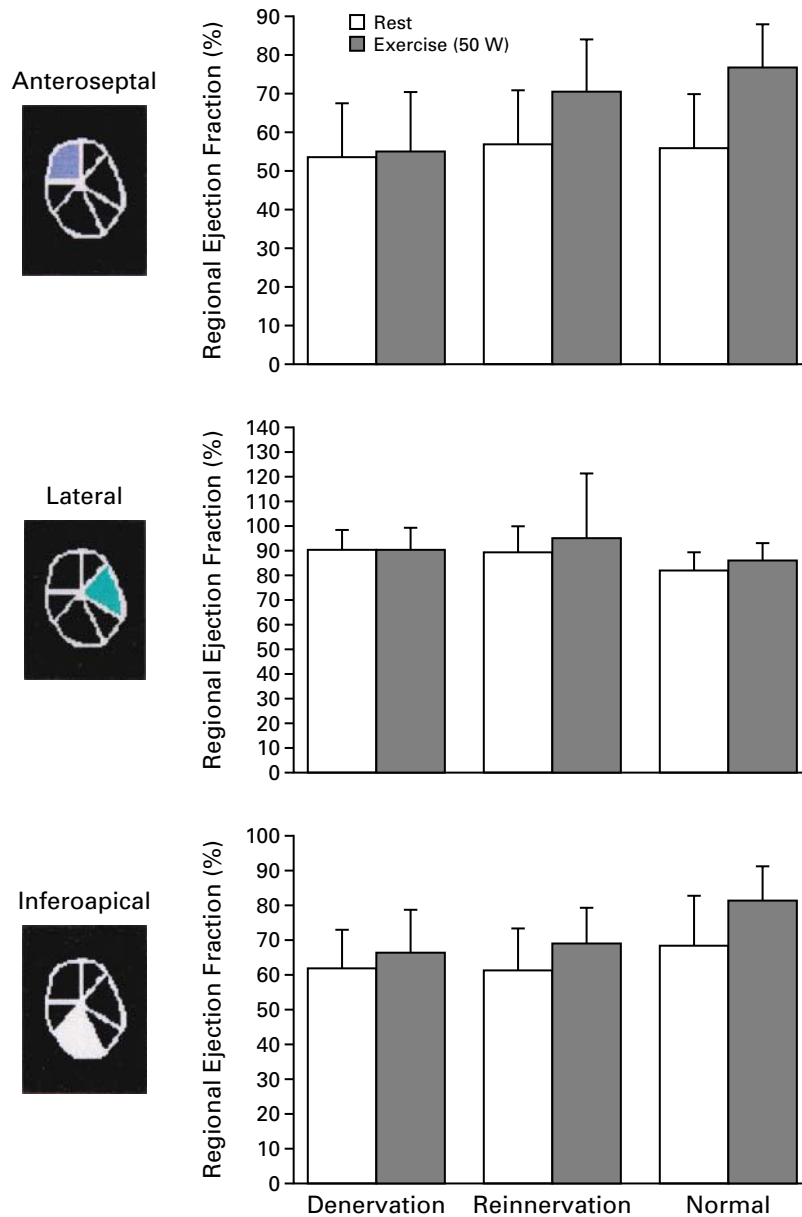


Figure 3. Regional Ejection Fraction in the Anteroseptal, Lateral, and Inferoapical Segments, Derived from Radionuclide Angiography.

During exercise, the ejection fraction in the anteroseptal segment, where reinnervation initially occurs, was significantly lower in the patients with denervation than in those with reinnervation or the normal subjects ($P < 0.01$). In the inferoapical segment, the ejection fraction was significantly lower in the patients with denervation and in those with reinnervation than in the normal subjects ($P < 0.01$ for the first comparison, and $P = 0.03$ for the second). T bars indicate standard deviations.

DISCUSSION

Our findings confirm that sympathetic reinnervation occurs in heart transplants. In our study, the group of patients with reinnervation had undergone transplantation earlier than the group of patients with denervation and had received hearts from younger

donors. However, myocardial catecholamine uptake and storage were associated with the ventricular inotropic response to exercise independently of these and other factors. Together with an improvement in the chronotropic response to exercise, an increase in the inotropic response resulted in significantly better

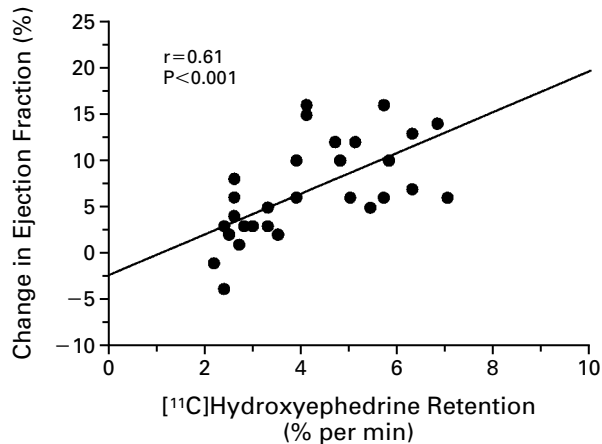


Figure 4. Overall Retention of [^{11}C]hydroxyephedrine in Relation to the Change in the Global Left Ventricular Ejection Fraction during Exercise.

Retention of [^{11}C]hydroxyephedrine was determined by positron-emission tomography, and the left ventricular ejection fraction by radionuclide angiography.

exercise performance in the innervation group than in the denervation group, suggesting a benefit of sympathetic reinnervation in the transplanted heart.

The adrenergic pathway has an important role in the regulation of myocardial contractility. The release of catecholamines results in the activation of cardiomyocyte β -adrenergic receptors, which is followed by an increase in tissue cyclic AMP, activation of protein kinases, and an increase in the intracellular calcium level.²² This cascade ultimately leads to augmented contractility through increases in the contraction rate and peak force.²³ As a consequence of surgical denervation, presynaptic nerve terminals disappear, and myocardial storage of the neurotransmitter norepinephrine is depleted.⁶ The denervated transplanted heart therefore has to rely on circulating catecholamines in adapting cardiac output to increased demand. Our results, like those of previous studies,^{4,24,25} suggest that this adaptation is limited and is not sufficient to achieve a normal heart rate and contractility in response to exercise. Thus, the capacity for exercise is diminished.

As a result of sympathetic reinnervation, presynaptic nerve terminals reappear in the myocardium, and local uptake and storage of catecholamines are reestablished. Previous studies have suggested that restitution of sympathetic innervation has positive effects on the physiologic regulation of myocardial blood flow¹⁴ and metabolism.¹⁶ It has also been shown that reinnervation, as demonstrated by PET, is associated with increased tyramine-induced arteriovenous norepinephrine spillover, supporting the pharmacologic functionality of noninvasively detected nerve termi-

nals.²⁶ At rest, the effects of reinnervation on global cardiac contractility appear to be negligible.²⁷ Our findings suggest, however, that under conditions of stress, resulting in sympathetic stimulation, the restoration of innervation is important for an adequate contractile response. A previous study has shown that transplant recipients with reinnervation have a greater capacity for exercise than do those with denervation.²⁸ Our study shows that reinnervation is an independent determinant of the improvement in exercise capacity.

The overall density of postsynaptic adrenergic receptors and intracellular signal transduction have been shown to remain intact in transplant recipients with denervation.²⁹ However, there is evidence of a shift from β_1 to β_2 receptors.³⁰ Moreover, beta-blockade appears to accentuate the impairment in ventricular performance after transplantation.³¹

We found that in addition to the improvement in contractile function, the response of the heart rate to exercise was enhanced in transplant recipients with evidence of reinnervation, suggesting improved function of the sinus node. The spatial resolution of clinical PET scanners does not currently allow visualization of the atrial wall or sinus node. However, our findings suggest that reinnervation of ventricular myocardium is correlated, at least in part, with reinnervation of the sinus node. A recent study involving invasive measurements of arteriovenous norepinephrine spillover in vessels supplying the sinus node underscored the importance of sinus-node reinnervation for an improved chronotropic response to exercise in transplant recipients.³²

A variety of factors other than innervation may influence ventricular performance and exercise capacity after transplantation. Prolonged cold ischemia of allografts,³³ rejection episodes, or perimyocytic fibrosis due to cyclosporine therapy³⁴ may contribute to myocardial stiffness and impair contractile function in response to exercise. Hypertension induced by immunosuppressive therapy or occult ischemia due to transplant vasculopathy may also play a part. Finally, peripheral deconditioning and skeletal-muscle abnormalities due to prior heart failure have been identified as contributors to a reduced capacity for exercise.⁴ In addition to the incomplete pattern of reinnervation,¹² these factors may account for the finding that the capacity for exercise in transplant recipients with reinnervation, although improved, does not return to a normal level.

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