Regional Differences in Sympathetic Reinnervation After Human Orthotopic Cardiac Transplantation

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Background. In the majority of humans ≥1 year after cardiac transplantation, cardiac norepinephrine (NE) stores reappear, suggesting late sympathetic reinnervation.

Methods and Results. To determine whether there are regional differences in reinnervation, we measured markers of sympathetic reinnervation of the sinus node (SN) and left ventricle (LV) in five early transplant recipients (<4 months after cardiac transplantation), 45 late transplant recipients (≥1 year after cardiac transplantation), and seven normally innervated control patients. SN reinnervation was defined as an increase in heart rate by more than five beats per minute after injection of tyramine into the artery supplying the SN. LV reinnervation was defined as a measurable LV NE release after left main coronary injection of 4 µg/kg tyramine. In 13 patients with previously known LV reinnervation, regional LV reinnervation was assessed by NE release after subselective injection of tyramine (4 µg/kg) into the proximal left anterior descending and circumflex arteries. Five of five patients ≤4 months after cardiac transplantation had no change in heart rate and no LV NE release, confirming early, total denervation. In contrast, ≥1 year after cardiac transplantation, tyramine caused a heart rate increase (eight to 49 beats per minute) in 32 of 45 patients and LV NE release in 33 of 45. Although LV NE release was correlated with the change in heart rate in late cardiac transplantation recipients (r=.61), eight of 45 had only heart rate response, nine had only LV NE release, and four had neither. In late cardiac transplantation recipients with LV reinnervation, tyramine caused NE release from both the anterior descending and circumflex perfusion fields in 10 of 14, but one of 14 patients released NE only after circumflex tyramine and three of 14 only after left anterior descending tyramine stimulation. Tyramine caused a marked heart rate increase and LV NE release in all control patients.

Conclusions. Sympathetic reinnervation after cardiac transplantation is regionally heterogeneous. SN reinnervation is not associated necessarily with LV reinnervation, and LV reinnervation can involve the anterior and posterior walls together or separately. (Circulation 1993;88:165-171)
rate of sinus node depolarization, and to find out if sinus node reinnervation was predictive of left ventricular reinnervation.

**Methods**

**Patient Selection**

Three groups of patients were evaluated. The first group was composed of five consecutive patients who had undergone orthotopic cardiac transplantation within 4 months (mean, 3.0±0.4 months; range, 2 to 4 months) of the study. All patients underwent uncomplicated transplantation (two for ischemic coronary artery disease and three for idiopathic cardiomyopathy) and were studied at the time of routine, scheduled baseline angiography. All patients were treated with cyclosporine A, azathioprine, and glucocorticoid immunosuppression, as described previously.11 Three patients were treated with antihypertensive drugs (a calcium channel antagonist in one, an angiotensin converting enzyme inhibitor in one, and both in another).

The second group was composed of 45 consecutive patients who were studied ≥1 years after transplantation (mean, 37±3 months; range, 12 to 86 months) at the time of routine annual coronary angiography. Twenty-three of these patients underwent transplantation for ischemic heart disease, 18 patients for idiopathic cardiomyopathy, two for valvular heart disease, and one patient each for viral and familial cardiomyopathy. All patients were treated with chronic immunosuppressive therapy similar to that described above. Twenty-three patients received antihypertensive drugs (in 20, a calcium channel antagonist and in six, an angiotensin converting enzyme inhibitor). Additionally, eight patients received low-dose aspirin therapy (≤650 mg daily) and all took oral calcium supplements.

The third group was composed of seven control patients undergoing coronary angiography for the diagnosis of a chest pain syndrome in whom we presumed normal cardiac innervation. Three patients had mild to moderate atherosclerotic coronary artery disease and four had no discernible coronary artery disease.

Patients were excluded from any of the groups if they were taking a β-adrenoreceptor antagonist or if they had diabetes mellitus, amyloidosis, or other diseases that could impair peripheral neural function. All studies were approved by the University of Minnesota Institutional Review Board, and each patient was studied after informed consent.

**Catheterization Protocol**

Patients were brought to the cardiac catheterization laboratory in a fasting state after premedication with diazepam (5 to 10 mg orally). Right heart catheterization, measurement of cardiac output (thermodilution method), right ventricular endomyocardial biopsy, and coronary angiography were performed in all transplant recipients. The coronary sinus was then cannulated with a 5F catheter. The aortic blood pressure was measured from the coronary angiographic catheter (flushed with saline), and the ECG was recorded continuously.

**Assessment of sinus node reinnervation.** Sympathetic reinnervation of the sinus node was assessed by injecting tyramine (Sigma F+D Division, St Louis, Mo) sequentially into the left and right coronary arteries and measuring the consequent change in heart rate. Four micrograms per kilogram of tyramine was injected into the right coronary artery, and 8 μg/kg was injected into the left coronary artery. This dose of tyramine was chosen because previous dose-response studies in dogs showed that left coronary boluses of 8 to 10 μg/kg caused no significant changes in arterial blood pressure but resulted in a marked cardiac norepinephrine release (approximately twofold that elicited by 55 μg/kg of intravenously administered tyramine). The dose was adjusted to 1 μg/kg for nondominant right arteries. The heart rate was recorded for 1 minute before and ≥2 minutes after each tyramine injection (until heart rate returned to basal levels). After the study, the major coronary artery supplying the sinus node artery was assessed by an experienced angiographer who had no knowledge of the experimental data.

To assess the effect of tyramine on sinus node rate, the maximal heart rate within the first 2 minutes after tyramine injection (averaged over three beat periods) was subtracted from the heart rate measured during the 1-minute period preceding tyramine injection. To assess the normal variability in heart rate measurement, basal heart rate was measured twice over a 3-minute period in 17 late transplant recipients. The maximal change in heart rate without intervention was 2±1 beat per minute (mean±SD; range, –3 to +4). Consequently, a change in heart rate of plus five beats per minute was deemed a measurable response to tyramine (ie, outside the 99% confidence limits of normal variability).

**Assessment of global left ventricular norepinephrine release.** In all transplant recipients and four normally innervated control patients, the presence of norepinephrine stores in the left ventricle as a whole was assessed by measuring cardiac release of norepinephrine after left coronary injection of tyramine (8 μg/kg). Before left main coronary artery tyramine injection, paired blood samples for plasma norepinephrine concentration assay were collected from the coronary sinus and aorta. Thirty seconds, 1 minute, and 2 minutes after tyramine injection, paired blood samples were obtained again. The coronary sinus sample was obtained approximately 5 to 7 seconds after the aortic sample was drawn to allow for the transit time of blood through the coronary circulation. Less than 35 mL of blood was drawn for norepinephrine assays. We have shown previously that peak norepinephrine release after intravenous tyramine administration occurs 30 seconds to 1 minute after tyramine administration.

**Assessment of regional left ventricular norepinephrine release.** Fourteen of the late transplant recipients who were studied in the above protocols and who were known to have return of left ventricular norepinephrine stores were studied again during their next annual catheterization. In these patients and in three normally innervated control patients, subselective coronary injection of tyramine was used to detect whether or not norepinephrine stores were present in the anterior and/or posterior left ventricle. After systemic anticoagulation with heparin (to achieve an activated clotting time of ≥300 seconds), a 7F angioplasty guiding catheter (Cordis, Miami, Fla) was advanced into the left coronary ostium. A 3F, two-lumen catheter (NuMed, Hopkinton, NY) then was advanced with the aid of a guide wire through the guiding catheter into the proxi-
mal left anterior descending or circumflex coronary artery. Paired blood samples for norepinephrine analysis were then obtained from the aorta (via the guiding catheter) and coronary sinus. After collection of resting blood samples, tyramine (4 μg/kg) was infused into the proximal coronary (left anterior descending or circumflex) through the subselective 3F catheter. Paired aortic and coronary sinus blood samples were obtained at 30 seconds, 1 minute, and 2 minutes after the tyramine bolus. After a waiting period of at least 8 minutes, blood samples for norepinephrine assay were obtained again from the coronary sinus and aorta to establish that norepinephrine release from the tyramine bolus had dissipated. We have shown previously that measurable norepinephrine release lasts for <7 minutes after intravenous tyramine injection.\(^5\) After collection of aortic and coronary sinus blood samples to confirm that norepinephrine levels had returned to the basal state, the remaining left coronary branch was then injected with tyramine, and similar paired blood samples were obtained.

**Measurement of plasma norepinephrine concentration.** Blood samples obtained from the coronary sinus and aorta were centrifuged immediately at 2000 rpm for 12 minutes. The plasma was decanted and frozen at −70°C. Plasma norepinephrine concentration was determined subsequently by a radioenzymatic method described elsewhere (Cat-a-kit, Amersham, Inc.).\(^2\)

**Assessment of cardiac norepinephrine release.** Cardiac release or uptake of norepinephrine was assessed by subtracting the norepinephrine concentration in the blood entering the heart via the aorta from the norepinephrine concentration in the blood leaving the heart via the coronary sinus ([NE]\(_{a-cs}\)−[NE]\(_{c-a}\)), the cardiac norepinephrine gradient). The effect of an intervention on the cardiac norepinephrine gradient was assessed by subtracting the gradient during control conditions from the cardiac norepinephrine gradient during the intervention (Δ[NE]\(_{a-cs}\)−[NE]\(_{c-a}\)). The method of assessing peak cardiac norepinephrine release has been described elsewhere.\(^3\)

In a previous study of 17 patients, a repeat set of paired samples was obtained within 1 minute (without intervention) to assess the measurement variability of the cardiac norepinephrine gradient.\(^4\) The mean difference of the paired measurements of the cardiac norepinephrine gradient (Δ[NE]\(_{a-cs}\)−[NE]\(_{c-a}\)) obtained within 1 minute of each other was 5±46 pg/mL (mean±SD). The likelihood that an intervention in a single patient would spuriously cause >143 pg/mL rise in plasma norepinephrine concentration between the coronary sinus and aorta was less than 1% (3 SD). Hence, a measured cardiac norepinephrine release of >143 pg/mL in response to an intervention was taken as evidence of a measurable norepinephrine release (ie, >3 SD from the measurement variability).

**Statistical Analysis**

Data are presented as mean±SEM (with a range), except where stated otherwise. Differences between group means were analyzed using ANOVA (STATVIEW \(^\text{II}\)). Linear regression was assessed by the least-squares method, and correlation was expressed as a Pearson correlation coefficient (\(r\) value).

**Results**

**Sinus Node Reinnervation**

In early transplant recipients, intracoronary tyramine did not change heart rate (mean change, 1.0±0.4 beats per minute; range, zero to two beats per minute; see Fig 1). In late transplant recipients, however, injection of tyramine into the artery perfusing the sinus node caused heart rate to increase by an average of 15±2 beats per minute (range, −2 to 49 beats per minute, \(P<.05\) versus early after transplantation). In 32 of 45 late transplant recipients, heart rate rose by more than five beats per minute (mean increase, 20±2 beats per minute). After injection of tyramine into the artery perfusing the sinus node in normally innervated control patients, heart rate rose even more (+49±9 beats per minute; range, 35 to 74 beats per minute; \(P<.05\) versus early and late after transplantation).

In patients with a significant change in heart rate after tyramine (increase of more than five beats per minute), the peak heart rate occurred 80±4 seconds (range, 40 to 107 seconds) after tyramine injection and fell to normal over 3 to 5 minutes. In each group, injection of tyramine into the artery not perfusing the sinus node artery failed to cause a significant change in heart rate (Fig 1).

In transplant recipients, the magnitude of heart rate increase in response to tyramine injection was significantly correlated with the time elapsed since transplantation (Δheart rate=0.35 time since transplantation [in months]+1.5; \(r=0.52\); \(P<.001\); see Fig 2).

The mean heart rate change in late transplant recipients taking calcium channel antagonist drugs (11±3 beats per minute) tended to be less than that measured in patients who were not taking the drug (17±3 beats per minute), but the difference was not significant (\(P=.13\)). Of late transplant recipients taking calcium channel antagonists, six of 13 had a significant heart rate increase after tyramine compared with 13 of 19 patients not taking the drug (\(P=.63\)).

**Global Left Ventricular Reinnervation**

Early after transplantation, no patient had a measurable left ventricular release of norepinephrine (see Fig 3 and Table 1). Of the 45 patients studied ≥1 year after transplantation, 33 had a measurable left ventricular release of norepinephrine. The average peak ventricular norepinephrine release (Δ[NE]\(_{a-cs}\)−[NE]\(_{c-a}\)) for all late trans-
plant recipients was 456±60 pg/mL (range, 36 to 1563 pg/mL). In all patients, the maximal transcardiac norepinephrine gradient occurred within 1 minute of tyramine injection. In all normal patients, left main coronary injection of tyramine caused a rapid and marked release of cardiac norepinephrine (Table 1). Peak left ventricular norepinephrine release was similar in patients taking calcium channel antagonist drugs (593±163 pg/mL) and those who did not (620±184 pg/mL).

Selective tyramine infusion into either the left or right coronary arteries did not change the aortic blood pressure, although early transplant recipients had a slightly higher basal diastolic pressure (Table 1). In all patients, the peak norepinephrine gradient occurred ≤1 minute after tyramine injection.

Relation Between Sinus Node and Global Left Ventricular Reinnervation

All normally innervated control patients had both left ventricular release of norepinephrine and a rise in heart rate after tyramine injection into the artery perfusing the sinus node, confirming sympathetic innervation of both the left ventricle and the sinus node. The early transplant recipients had neither a heart rate change nor left ventricular release of norepinephrine after tyramine injection, suggesting complete denervation in each patient.

FIG 3. Scatterplot of peak cardiac release of norepinephrine ([NE]Cs−Ao) in response to injection of tyramine into the left main coronary artery (abscissa) compared with change in heart rate after tyramine injection into the sinus node perfusion field (ordinate).

FIG 4. Bar graph shows frequency of sinus node and left ventricular reinnervation in late transplant recipients.

Twenty-four (53%) late transplant recipients had evidence of both left ventricular and sinus node reinnervation (see Fig 4). In nine (20%) late allograft recipients, however, left ventricular norepinephrine release was found in the absence of any tyramine-induced change in heart rate, suggesting isolated left ventricular reinnervation. Conversely, eight (18%) late transplant patients had evidence of sinus node reinnervation but no left ventricular norepinephrine release, suggesting isolated sinus node reinnervation. In four patients (9%), neither left ventricular nor sinus node reinnervation was detected, suggesting total, persistent denervation.

In late transplant recipients, there was a weak relation between the magnitude of heart rate change and the peak left ventricular norepinephrine release after tyramine stimulation (Δheart rate=0.021Δ[NE]Cs−Ao+5.0; r=.61; P<.001).

Regional Left Ventricular Sympathetic Reinnervation

Normally innervated nontransplanted patients had a large norepinephrine release from both the left anterior descending and circumflex artery perfusion fields (see Table 2 and Fig 5). Of the 14 late reinnervated transplant recipients in whom tyramine was subselectively injected, 10 (77%) had a measurable norepinephrine release from both perfusion fields. In three patients, however, release could be measured only in the left anterior descending territory and in one, only in the circumflex distribution.

The ratio of peak norepinephrine release ([NE]Cs−Ao) after circumflex tyramine injection to peak release after left anterior descending tyramine injection varied widely. This ratio, however, was similar in normally innervated control patients and in late transplant recipients (see Table 2 and Fig 5).

Between subselective intracoronary tyramine injections, the transcardiac norepinephrine gradient ([NE]Cs−Ao) fell to within 143 pg/mL of the initial basal level in all patients, suggesting that norepinephrine release lasted <8 minutes.

Discussion

These studies demonstrate that sympathetic reinnervation after cardiac transplantation is regionally heterogeneous. Reinnervation of the sinus node did not imply necessarily that the left ventricle is reinnervated and the reverse, although there was a weak relation between left ventricular and sinus node reinnervation. Similarly, reinnervation within the left ventricle oc-
TABLE 1. Peak Left Ventricular Norepinephrine Release After Left Coronary Tyramine Injection (8 μg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Basal conditions</th>
<th>After tyramine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aortic pressure</td>
<td>ΔAortic pressure</td>
</tr>
<tr>
<td></td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
</tr>
<tr>
<td></td>
<td>[NE]c₅ (pg/mL)</td>
<td>[NE]c₅ (pg/mL)</td>
</tr>
<tr>
<td></td>
<td>Systolic/Diastolic</td>
<td></td>
</tr>
<tr>
<td>Transplant recipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 Months after</td>
<td>5/128±12</td>
<td>340±54</td>
</tr>
<tr>
<td>cardiac transplantation</td>
<td>93±15*</td>
<td>313±39</td>
</tr>
<tr>
<td></td>
<td>27±29</td>
<td>5±3</td>
</tr>
<tr>
<td>≥1 Year after</td>
<td>45/131±4</td>
<td>400±29</td>
</tr>
<tr>
<td>cardiac transplantation</td>
<td>1±2</td>
<td>8±11</td>
</tr>
<tr>
<td>Normal patients</td>
<td>4/142±13</td>
<td>313±129</td>
</tr>
<tr>
<td></td>
<td>70±3</td>
<td>1±2</td>
</tr>
</tbody>
</table>

All values are mean±SEM unless stated otherwise. [NE]c₅, plasma norepinephrine concentration in the aorta; [NE]c₅-A₀, plasma norepinephrine concentration in the coronary sinus; Δ[NE]c₅-A₀, [NE]c₅-[NE]c₅-A₀; Δ[NE]c₅-A₀ (after tyramine) = ([NE]c₅-A₀ during basal conditions). *P<.05 vs normal. †P<.05 vs early after transplantation.

curred with approximately equal overall frequency in the perfusion fields of the circumflex and left anterior descending arteries, but in individual patients, norepinephrine release was found in the posterior or anterior walls separately or together. The time course of sinus node reinnervation was similar to that of left ventricular reinnervation, becoming detectable about 1 year after transplantation and increasing in magnitude thereafter. Finally, these studies demonstrate that release of norepinephrine from reinnervating neurons can substantially increase the rate of sinus node depolarization, suggesting that direct neuronal stimulation can have a physiological effect.

Potential Limitations

We used the heart rate change induced by tyramine to assess sinus node reinnervation and release of norepinephrine to reflect left ventricular reinnervation. It is possible that these tests had different sensitivities in detecting reinnervation. Both methods, however, appear to be sensitive markers of reinnervation. Peak coronary sinus norepinephrine concentration after left coronary injection of tyramine in normal patients can exceed 10 000 pg/mL, suggesting that intracoronary tyramine causes intense neural stimulation. A study in animals showed that a 10-μM dose of tyramine can reduce myocardial norepinephrine concentration by 45%. Moreover, injection of tyramine into the sinus node artery of normally innervated patients caused heart rate to rise markedly (mean, 49±9 beats per minute) even without parasympathetic blockade, also suggesting intense stimulation and response. Hence, it is unlikely that we failed to detect measurable reinnervation using either test because the stimulus was too small.

It is possible however, that sinus node dysfunction could have attenuated the heart rate change induced by tyramine in late transplant recipients. Transplantation-induced sinus node dysfunction has been shown previously, particularly in patients surviving many years after transplantation. Our studies, nevertheless, show that the heart rate response to tyramine increased significantly with time, suggesting that sinus node dysfunction was not a major factor modulating the heart rate response to sinus node stimulation. It is possible, however, that we underestimated the frequency of sinus node reinnervation in late transplant recipients. Furthermore, possible occult sinus node dysfunction underscores the potential inaccuracy of using the responses of the sinus node to predict ventricular reinnervation.

It is also possible that drug treatment with calcium channel antagonists reduced the heart rate response to tyramine, although in the patients we studied there was no significant difference in mean heart rate change after tyramine in patients taking calcium channel antagonists and those not receiving the drug. If an effect exists, it is probably related to a direct drug effect on sinus node

TABLE 2. Indexes of Regional Left Ventricular Sympathetic Reinnervation

<table>
<thead>
<tr>
<th></th>
<th>Δ[NE]c₅-A₀ (pg/mL)</th>
<th>Δ[NE]c₅-A₀ after</th>
<th>Δ[NE]c₅-A₀ after left</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left anterior</td>
<td>Circumflex</td>
<td>anterior descending</td>
</tr>
<tr>
<td></td>
<td>Descending</td>
<td></td>
<td>tyramine</td>
</tr>
<tr>
<td></td>
<td>Mean±SEM</td>
<td>Mean±SEM</td>
<td>Mean±SEM</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>Range</td>
<td>Range</td>
</tr>
<tr>
<td>Transplant recipients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 Year after cardiac</td>
<td>479±79*</td>
<td>285±46*</td>
<td>0.71±0.16†</td>
</tr>
<tr>
<td>transplantation</td>
<td>0–1080</td>
<td>25–506</td>
<td>0.28–0.8</td>
</tr>
<tr>
<td>Normal patients</td>
<td>1756±126</td>
<td>1916±879</td>
<td>1.04±0.40</td>
</tr>
<tr>
<td></td>
<td>1584–2002</td>
<td>975–3673</td>
<td>0.56–1.84</td>
</tr>
</tbody>
</table>

[NE]c₅-A₀, plasma norepinephrine concentration in the coronary sinus minus plasma norepinephrine concentration in the aorta. Δ[NE]c₅-A₀ = ([NE]c₅-A₀ after tyramine) minus ([NE]c₅-A₀ during basal conditions). *P<.05 vs normal patients. †A single value of * (where Δ[NE]c₅-A₀ after left anterior tyramine=0) was excluded from calculation of the mean.
depolarization rather than through modulation of neuronal norepinephrine release, because left ventricular norepinephrine release was almost identical in patients with and without drug treatment.

A fourth potential problem is that the magnitude of response to tyramine stimulation might not reflect the magnitude of sympathetic reinnervation. In our opinion, the response to a standardized dose of tyramine (adjusted for body weight) probably provides a semiquantitative index of reinnervation. In animals, there exists a clear relation between the amount of tyramine injected into the coronary artery and the resultant peak release of norepinephrine and peak increase in heart rate.\textsuperscript{13,14} In preliminary studies in humans, we have shown a relation between the response to tyramine and the consequent physiological effect.\textsuperscript{15,16} Moreover, the mechanism of action of tyramine (direct displacement of norepinephrine from large secretory granules in the nerve terminal) would suggest a dose-response effect.\textsuperscript{17}

In fact, we found that the response (norepinephrine release or increase in heart rate) increased over time in late transplant survivors. This would be expected if reinnervation is ongoing (as shown in animals).\textsuperscript{10} Conversely, however, treatment with cyclosporine (or possibly glucocorticoids) might have reduced the rate of reuptake of norepinephrine after release, increasing the fraction of norepinephrine making its way into the vascular space.\textsuperscript{16,19} Additionally, it is possible that reinnervating sympathetic nerve terminals or cyclosporine alter the rate of presynaptic catabolism of norepinephrine released from large neuronal vesicles, thereby changing the fraction of vesicular norepinephrine released to the vascular space.\textsuperscript{20}

An additional limitation is that we assessed regional left ventricular reinnervation by measuring the change in transcardiac norepinephrine gradient that followed subselective injection of tyramine into the left anterior descending or circumflex arteries. The release of norepinephrine into either perfusion field was diluted by the venous drainage from the rest of the heart. This factor would have reduced the sensitivity of the test and would have made more difficult the detection of norepinephrine release from individual perfusion fields. Similarly, an increase in heart rate after circumflex infusion of tyramine could have increased coronary blood flow and diluted the norepinephrine concentration in the vein. This potential lack of sensitivity, however, reinforces the finding that the vast majority of patients had a measurable norepinephrine release in both the anterior and the posterior perfusion territories and that both fields must have been in part reinnervated.

Finally, coronary reinnervation might have caused coronary blood flow to decrease in response to tyramine by causing coronary constriction. The effect would have been to increase the concentration of norepinephrine in the venous effluent of the branch under study and to a lesser extent in the coronary sinus. Coronary constriction could occur only in the presence of reinnervation, and although it would increase the sensitivity of the test, the improvement in sensitivity would be appropriate.

Our findings contrast somewhat with positron emission tomographic imaging studies of the sympathetic nervous system reported by Schwaiger et al.\textsuperscript{21} They found evidence of sympathetic reinnervation only in the anterior left ventricular base. Our studies, however, suggest that both the anterior and posterior left ventricular perfusion fields are usually involved in reinnervation in most patients, although we found a trend for the left anterior descending perfusion field to release more norepinephrine than the circumflex field. It is possible that the sensitivity of the positron imaging method used by Schwaiger et al (\textsuperscript{11}C-hydroxyephedrine) may not have been able to detect reinnervation in the sinus node or atria because these tissues are below the sensitivity of the method (resolution or isotope). It is also possible that in our patients, some of the norepinephrine released after circumflex injection of tyramine originated in the anterolateral left ventricular wall perfused by the proximal circumflex marginal branches. Also, because of the factors outlined above and the relatively small number of patients in whom subselective coronary studies were done, the absolute ratio of norepinephrine release in the circumflex and left anterior descending fields cannot be specified with certainty from our data.
**Implications of the Study**

First, the sinus node frequently has sympathetic reinnervation after transplantation. Investigators using late transplant recipients as "denervated" controls in studies assessing neural function will need to demonstrate persistent denervation. Second, the response of the sinus node to stimulatory maneuvers cannot be taken as evidence for (or lack of) reinnervation of the remainder of the heart. Similarly, left ventricular reinnervation may vary regionally. Return of afferent sensation to one perfusion field does not indicate necessarily that the adjacent field is reinnervated and that an ischemic event would be sensed. By analogy, other diseases that cause denervation (for example, diabetes) might also proceed in a patchy manner. The traditional method for assessing cardiac denervation, measurement of the response of the sinus node to various maneuvers, might not reflect accurately the innervation of the heart outside of the sinus node.

The third implication of regional differences in reinnervation is that reinnervation may occur through multiple pathways. Sinus node reinnervation might occur over the right atrial anastomosis, whereas ventricular reinnervation might proceed from the aortic or left atrial connections to the recipient. Further morphological studies should be done to define the regional origins of cardiac reinnervation.

**Acknowledgments**

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**References**


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