Sympathetic Reinnervation of the Sinus Node and Exercise Hemodynamics After Cardiac Transplantation

Robert F. Wilson, MD; Thomas H. Johnson, MD; George C. Haidet,† MD; Spencer H. Kubo, MD; Marcus Mianuelli, MS

Background—Sympathetic cardiac reinnervation occurs variably after cardiac transplantation (CT) in humans. We hypothesized that sinus node reinnervation would partially restore normal chronotropic response to exercise.

Methods and Results—Thirteen recent CT recipients, 28 late CT recipients (>1 year after CT), and 20 control subjects were studied. Sinus node sympathetic reinnervation was determined by heart rate (HR) change after tyramine injection into the artery that perfused the sinus node. HR changes of >5 and ≥15 bpm were defined, respectively, as denervation and marked reinnervation. During treadmill exercise, HR, blood pressure, and expired O₂ and CO₂ were measured. All early transplant recipients exhibited features typical of denervation (basal HR, 88 ± 2 bpm; peak HR, 132 ± 4 bpm, peaking 1.8 ± 0.3 minutes after exercise cessation and slowly declining after exercise). A similar pattern was found in the 12 late transplant recipients with persistent sinus node denervation. However, in patients with marked reinnervation, exercise HR rose more (peak HR, 142 ± 4 and 141 ± 2 bpm), peaked earlier after cessation of exercise (0.7 ± 0.4 and 0.3 ± 0.1 minute), and fell more rapidly. Exercise duration and maximal oxygen consumption were not related significantly to reinnervation status, but a trend existed for longer exercise time in markedly reinnervated patients.

Conclusions—The present studies suggest that sympathetic reinnervation of the sinus node is accompanied by partial restoration of normal HR response to exercise. Both maximal oxygen consumption and exercise duration were markedly shorter in CT patients than in control subjects, and most of the difference was not related to innervation status. (Circulation. 2000;101:2727-2733.)

Key Words: surgery • transplantation • tests • nervous system, sympathetic • exercise • cardiovascular diseases • reflex

The sinus node is innervated richly by the parasympathetic and sympathetic nervous systems, both of which modulate heart rate during exercise. In normal individuals, heart rate increases abruptly at onset of exercise because of vagal parasympathetic withdrawal, rises progressively during exercise because of a combination of sympathetic neural and humoral drive, and falls rapidly after cessation of exercise because of withdrawal of neural sympathetic discharge.

Cardiac transplantation results in total denervation of the donor heart, including the donor sinus node, which usually controls heart rate after transplantation. Denervation causes an increase in basal heart rate due to parasympathetic sectioning. Further increases in heart rate during exercise are dependent primarily on increases in plasma catecholamine concentration (eg, from adrenal secretion). This results in a slow, lumbering, and submaximal increase in heart rate during exercise. Typically, heart rate continues to rise after cessation of exercise as a result of delayed humoral catecholamine release. In recovery, heart rate falls slowly as plasma catecholamines are metabolized.

We and others have shown previously that left ventricular norepinephrine stores are absent early after orthotopic human cardiac transplantation but return gradually toward normal levels late after surgery. Reemergence of cardiac norepinephrine stores implies sympathetic reinnervation, because surgical interruption of the postganglionic sympathetic nerve axon invariably causes rapid depletion of norepinephrine within the nerve terminal. The return of norepinephrine stores can occur only if continuity exists between sympathetic ganglia that lie outside the transplanted tissue and cardiac nerve terminals. We also showed previously that ventricular reinnervation was accompanied by partial return of normal sympathetic neuronal effects on ventricular function (increase in inotropic state with neural stimulation) and by sympathetically mediated coronary vasoconstriction.

In addition to ventricular reinnervation, sympathetic reinnervation of the sinus node was shown specifically by measurement of the change in heart rate that occurs after injection of tyramine into the artery that perfuses the sinus node. Although patients studied within 4 months of trans-
plantation had no change in heart rate in response to tyramine (consistent with denervation), by 1 year after surgery, a majority of transplanted hearts exhibited an increase in heart rate with tyramine stimulation, which was indicative of limited sympathetic reinnervation.12

The physiological effects of reinnervation on sinus node function are not well defined. Limited studies performed soon after the advent of human cardiac transplantation suggested that the average heart rate response to exercise within the first 2 years after transplantation was typical of denervation.5 More recently, a fraction of transplant recipients have been shown to develop increased heart rate variability and enhanced heart rate falls after exercise, which suggests sinus node reinnervation.13,14 Because the occurrence and magnitude of sinus node sympathetic reinnervation varies greatly between patients and some patients develop concurrent sinus node dysfunction, effects of reinnervation have been difficult to delineate.15

Once we developed tools to assess sympathetic reinnervation of the sinus node in humans, we undertook the present studies to determine the physiological effects of sympathetic reinnervation on exercise hemodynamics, particularly on heart rate response during exercise. We hypothesized that sympathetic reinnervation would partially normalize heart rate response to exercise and improve exercise duration.

Methods

Patient Selection

The University of Minnesota Institutional Review Board approved all studies, and each patient was studied after informed consent was provided.

Three groups of patients were studied. All patients underwent uncomplicated orthotopic transplantation and were studied at the time of routine, scheduled baseline angiography. The first group was composed of 13 patients studied within 6 months of cardiac transplantation (mean, 3.8±0.4 months; range, 2 to 6 months). A second group was comprised of 28 patients who were studied ≥1 years after transplantation (mean, 30±4 months; range, 12 to 60 months). All patients were treated with immunosuppressive therapy similar to that described previously.16 A third group was composed of 20 healthy control subjects in whom normal cardiac innervation was presumed. An effort was made to match the age range of transplant recipients. None of these subjects took medications or had known medical illnesses.

Patients were excluded if they had diabetes mellitus, amyloidosis, or other diseases that could impair peripheral neural function. Additionally, patients with a resting heart rate >105 bpm and those unable to exercise for >5 minutes were excluded because further increases in heart rate might be limited, regardless of neural input.

Assessment of Sinus Node Reinnervation

Cardiac transplant recipients were brought to the cardiac catheterization laboratory in a fasting state after they were premedicated with diazepam (5 to 10 mg orally). After the diagnostic procedure, sympathetic reinnervation of the sinus node was assessed by injection of tyramine sequentially into left and right coronary arteries and measurement of consequent change in heart rate. Tyramine 4 μg/kg (Sigma F+D Division) were 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 marked cardiac norepinephrine release (~2-fold that elicited by 55 μg/kg of intravenously administered tyramine). The dose was adjusted to 1 μg/kg for nondominant right coronary arteries. Heart rate was recorded continuously for 1 minute before and 2 minutes after each tyramine injection (until heart rate returned to basal levels).

To assess the effect of tyramine on sinus node rate, maximal heart rate within the first 2 minutes after tyramine injection (averaged over 3 heart periods) was subtracted from the heart rate measured during the 1-minute period preceding tyramine injection. To assess normal variability in heart rate measurement, we previously measured basal heart rate twice over a 3-minute period in 17 late transplant recipients.12 Maximal change in heart rate without intervention was +2±1 bpm (mean±SD; range, −3 to +4 bpm). Consequently, a change in heart rate of +5 bpm was considered a measurable response to tyramine (ie, outside 99% confidence limits of normal variability). For purposes of analysis, change in heart rate after tyramine administration in transplant recipients was defined as none if heart rate rose ≤5 bpm, small-moderate if heart rate rose 5 to 14 bpm, and marked if heart rate increased ≥15 bpm.

Chronotropic Response to Exercise

To assess chronotropic response to exercise, each study participant underwent treadmill exercise testing in an environmentally controlled laboratory. All medications known to affect chronotropic response to exercise were withdrawn at least 5 drug half-lives before exercise testing (2 to 7 days for long-acting β-adrenoceptor antagonists), and subjects were studied in a 3-hour postprandial state. A modified Bruce (Sheffield) treadmill exercise protocol with standard 12-lead ECG monitoring (Quinton model Q5000) and on-line, computerized expired breath-by-breath CO2 and O2 monitoring (Medgraphics Inc, model CPX-D) was used.17,18

Before exercise, an ECG was taken and arterial blood pressure (arm cuff), expired O2, and CO2 concentrations were measured. ECG and blood pressure measurements were obtained at 1-minute intervals from beginning of exercise until the patient was unable to exercise further (eg, due to fatigue or dyspnea). An ECG was recorded 30 seconds and 1 minute after exercise and every minute thereafter in the recovery period until heart rate returned to within 10% of basal levels or until 20 minutes had passed.

Measurement of Exercise Hemodynamic Parameters

Exercise heart rate response was characterized by the following parameters: basal heart rate before exercise, heart rate at each minute of exercise, heart rate at anaerobic threshold, peak heart rate, and heart rate in recovery at 5 minutes after exercise cessation. Additionally, heart rate was indexed to the predicted heart rate on the basis of the age of the donor heart (from standard tables; see Reference 17).

Assessment of Metabolic Parameters

Peak oxygen uptake (maximal oxygen consumption; VO2max) was defined as the average value obtained during the last 30 seconds of exercise. Anaerobic threshold was determined noninvasively by 2 independent investigators.18 Values for anaerobic threshold determined by each observer varied by <10% in any patient. Anaerobic threshold and exercise time at which anaerobic threshold occurred were assessed by an average of determinations from 2 observers.

Assessment of Humoral Catecholamine Response to Exercise

In a subgroup of patients from each group, plasma norepinephrine and epinephrine concentrations in a peripheral arm vein were measured before exercise and at peak exercise.19

Statistical Analysis

All data are presented as mean±SEM. Differences between group means were assessed with ANOVA (Statview 4). A value of P≤0.05 was considered significant.
Results

Sympathetic Reinnervation of Sinus Node

None of the 13 early transplant recipients had a significant increase in heart rate after tyramine injection (mean change, 1.6±0.3 bpm; range, 0 to 4 bpm), which indicated denervation (Figure 1). Average increase in heart rate in late transplant survivors was 12.5±2.0 bpm (range, −3 to 52 bpm). No significant heart rate response to tyramine (<5-bpm heart rate change) was found in 12 late transplant recipients, a small-moderate response (5- to 14-bpm increase) was found in 5, and a marked (≥15 bpm) increase was found in 11.

Exercise Hemodynamics and Effects of Reinnervation

Heart Rate

Basal heart rate was higher in early and late transplant recipients than in normal control subjects (Table 1). During exercise, heart rate in normal subjects rose from 76±3 to 90±3 bpm within the first 2 minutes of exercise. Thereafter, heart rate rose progressively, to 151±3 bpm at anaerobic threshold and 178±4 bpm at the end of exercise. After cessation of exercise, heart rate fell immediately in all patients and was 64±3% of the peak heart rate by 5 minutes into the recovery period.

In early transplant recipients, heart rate failed to rise significantly in the first 2 minutes of exercise (88±3 bpm at rest and 92±3 bpm at 2 minutes), rose slowly to 109±4 bpm at anaerobic threshold, and peaked at a lower heart rate at end of exercise (129±3 bpm; Table 1). In 13 of 13 patients, heart rate continued to rise after exercise, peaking an average of 1.8±0.3 minutes into the recovery period. Unlike normal subjects, heart rate 5 minutes after exercise was still 94±1% of the peak heart rate.

In persistently denervated late transplant recipients, heart rate also was elevated at rest, failed to rise significantly in the first 2 minutes of exercise (85±3 bpm at rest and 90±3 bpm at 2 minutes; Figure 2) and peaked at a lower heart rate at end of exercise (126±5 bpm; Figure 3). In 10 of 12 patients, heart rate continued to rise after exercise and peaked an average of 0.9±0.2 minutes into the recovery period. Heart rate 5 minutes into recovery period was still 91±4% of peak heart rate.

In patients with mild-moderate sympathetic reinnervation of the sinus node, basal heart rate was elevated compared with normally innervated subjects (Table 1) and also rose little within the first 2 minutes of exercise (94±4 bpm at rest and 101±6 bpm at 2 minutes). However, heart rates at anaerobic threshold (121±9 bpm; Figures 4 and 5) and at peak exercise (142±7 bpm) were significantly higher than observed in early or persistently denervated late transplant recipients. Heart rate peaked at end of exercise in 3 of 5
patients, and mean time of peak heart rate was 0.7±0.4 minutes after cessation of exercise. Heart rate 5 minutes into the recovery period (87±3% of peak heart rate) was significantly lower than that found in early and denervated late transplant recipients but higher than in normal subjects (Figure 6).

In markedly reinnervated transplant recipients, basal heart rate also was elevated and rose little in the first 2 minutes of exercise (87±3 bpm at rest and 96±3 bpm at 2 minutes). However, heart rates at anaerobic threshold (120±3 bpm) and peak exercise (141±2) were significantly higher than in early transplant recipients and late, persistently denervated transplanted patients. In only 3 of 11 patients did heart rate continue to rise after cessation of exercise and the mean time of peak heart rate was only 0.3±0.1 minutes after stopping exercise. Five minutes after exercise was stopped, heart rate had fallen to 80±2% of the peak rate (P<0.01 versus early and late denervated transplant recipients).

Blood Pressure
Diastolic blood pressure during basal conditions was slightly higher in transplant recipients (all groups) than in normal control patients (Table 2). In all groups, diastolic blood pressure fell during exercise. Systolic blood pressure at anaerobic threshold and peak exercise increased more in normally innervated control patients and in those with marked transplant reinnervation than in early and late denervated transplant recipients.

Exercise Duration, Anaerobic Threshold, and Maximal Oxygen Consumption
Basal oxygen consumption was similar in all groups (Table 3). Compared with healthy normal subjects, transplantation was associated with a marked reduction in exercise duration and VO\textsubscript{2} max, and this was dependent on neither time elapsed since transplantation nor indices of sinus node reinnervation (Figure 7). Similarly, anaerobic threshold was reduced in both early and late transplant recipients, without respect to indices of reinnervation (although a trend occurred for greater VO\textsubscript{2} max in the markedly reinnervated group).

Humoral Catecholamine Response to Exercise
Venous plasma norepinephrine and epinephrine concentration at rest and peak exercise were similar in all groups. Norepinephrine concentrations in early transplant recipients and persistently denervated patients were 669±167 and

<table>
<thead>
<tr>
<th>TABLE 1. Effects of Reinnervation on Heart Rate During Exercise</th>
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<tr>
<td>Heart Rate, bpm</td>
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<tr>
<td>---------------------------------------------------------------</td>
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<tr>
<td><strong>Transplant recipients</strong></td>
</tr>
<tr>
<td>Early (&lt;6 mo)</td>
</tr>
<tr>
<td>Late (&gt;1 y)</td>
</tr>
<tr>
<td>Denervated</td>
</tr>
<tr>
<td>Mild-moderate reinnervation</td>
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<tr>
<td>Marked reinnervation</td>
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<tr>
<td>Normal controls</td>
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<tr>
<td>All data are mean±SEM. AT indicates anaerobic threshold; Rec\textsubscript{5}, heart rate 5 minutes into recovery after exercise cessation (expressed as percentage of peak heart rate); and Peak/Predicted heart rate, peak/predicted heart rate for donor heart (based on age of donor heart).</td>
</tr>
<tr>
<td>*P&lt;0.01 vs early and all late transplant recipients; †P&lt;0.05 vs early and late denervated transplant recipients.</td>
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</tbody>
</table>
648±108 pg/mL and rose at peak exercise by 1846±937 and 1826±391 pg/mL, respectively. In mildly and markedly reinnervated patients, basal norepinephrine concentrations of 850±245 and 590±110 pg/mL rose at peak exercise by 2675±748 and 1972±114 pg/mL, respectively. In normal subjects, basal norepinephrine concentration was 544±44 pg/mL and rose by 2520±484 pg/mL by peak exercise.

Transplant recipients had reduced basal plasma epinephrine concentration (early transplant recipients, 9±8 pg/mL; late denervated patients, 24±15 pg/mL; mild-moderately reinnervated patients, 18±9 pg/mL; and markedly reinnervated patients, 26±8 pg/mL) compared with normal subjects (67±19 pg/mL; P<0.02). At peak exercise, plasma epinephrine concentration rose similarly in all transplant recipient groups (an increase of 61±51 pg/mL in early transplant recipients, 159±29 pg/mL in late denervated patients, 307±161 pg/mL in mild-moderately reinnervated patients, and 101±40 pg/mL in markedly reinnervated patients). In contrast, plasma epinephrine rose more in normal subjects (+504±161 pg/mL) than in late reinnervated transplant patients (P<0.05).

**Discussion**

The present studies show that sympathetic reinnervation of the sinus node after transplantation is accompanied by partial restoration of normal heart rate response to exercise and that degree of the normalization is related to extent of reinnervation (as detected by heart rate response to intracoronary tyramine). In patients with reinnervation, heart rate increased more, peaked near end of exercise, and after exercise fell more rapidly than in denervated patients. Duration of exercise and VO2 max was not affected significantly, although a trend existed for marked reinnervation to be accompanied by longer exercise duration and higher VO2 at anaerobic threshold and end of exercise.

**Limitations**

Rate of sinus node depolarization is controlled by a number of factors other than sympathetic innervation. Circulating catecholamines modulate heart rate. However, in the subgroup of patients in whom plasma norepinephrine and epinephrine concentrations during exercise were measured, we found no difference between transplantation groups. Moreover, an excess in humoral catecholamine response should be associated with delayed heart rate peak and fall after exercise, the opposite of the findings in reinnervated transplant recipients.

Within the heart, a small intrinsic nervous system (ie, ganglia and postganglionic fibers) exists that is primarily cholinergic, although it may also contain a small amount of catecholamine transmitters.1,20 Although it is possible that intracoronary tyramine elicited heart rate increases because of...

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### TABLE 2. Blood Pressure Before, During, and After Exercise

<table>
<thead>
<tr>
<th></th>
<th>Before Exercise</th>
<th>Anaerobic Threshold</th>
<th>End of Exercise</th>
<th>Rec&lt;sub&gt;5&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Transplant recipients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (&lt;6 mo)</td>
<td>131±3</td>
<td>86±4</td>
<td>146±5</td>
<td>74±3</td>
</tr>
<tr>
<td>Late (&gt;1 y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>127±4</td>
<td>90±4</td>
<td>156±11</td>
<td>73±4</td>
</tr>
<tr>
<td>Moderate</td>
<td>131±9</td>
<td>92±5</td>
<td>144±7</td>
<td>83±6</td>
</tr>
<tr>
<td>Marked</td>
<td>124±3</td>
<td>88±2</td>
<td>169±6*</td>
<td>80±6</td>
</tr>
<tr>
<td>Normal controls</td>
<td>116±5</td>
<td>77±4</td>
<td>168±10*</td>
<td>66±5</td>
</tr>
</tbody>
</table>

All values are in mm Hg. Rec<sub>5</sub> indicates 5 minutes into recovery after exercise cessation.

*P<0.05 vs early and moderately reinnervated transplant recipients; †P<0.05 vs early transplant recipients; and ‡P<0.05 vs all transplant groups.
intracardiac neuronal release, absence of a tyramine-induced heart rate increase within the first 6 months after transplantation suggests that its effects were minimal. Moreover, in a previous in vivo study of transplanted human hearts, we showed that sustained handgrip by the recipient elicited intracardiac norepinephrine release, a reflex action that required an intact sympathetic connection between at least the spinal cord of the recipient and the donor heart.7

Heart rate response to exercise may also be affected by intrinsic sinus node disease, which can occur in late transplant recipients. Sinus node dysfunction would hide the effects of reinnervation on heart rate because its incidence might increase with time concurrently with reinnervation. However, progressive sympathetic reinnervation could protect somewhat against progressive effects of intrinsic sinus node disease.

In the present study, we did not assess vagal reinnervation of the sinus node, which, if present, might have altered heart rate response to exercise. Several factors argue against significant vagal reinnervation.21,22 Additionally, resting heart rate in the patients presented in the present study was similar in sympathetically reinnervated and persistently denervated patients, and heart rate did not rise importantly in the first 2 minutes of exercise (the usual timing of heart rate increase due to vagal withdrawal) in either group.2,3

The finding that reinnervation was not associated with a significant rise in exercise duration is not surprising, because total exercise time is related to a number of factors not influenced by cardiac reinnervation, such as steroid myopathy, progressive osteopenia, or peripheral vascular disease. Additionally, cardiac output during exercise is influenced profoundly by diastolic ventricular compliance, which can be reduced after transplantation.

Because the duration of exercise varied between patients, the sympathetic stimulus also could have been different. A variable sympathetic stimulus should make discernment of the effects of reinnervation on heart rate more difficult. We attempted to circumvent this problem by comparing the heart rate at similar relative metabolic activity levels (ie, anaerobic threshold).

Finally, effects of sympathetic reinnervation on exercise-induced heart rate increases may be exaggerated because of synaptic hypersensitivity.23–26 If some form of β-adrenergic hypersensitivity is present, the physiological response to neurotransmitter release from a meager number of reinnervating fibers might be amplified significantly.

### Comparison to Prior Work

After the initial transplantation experience in humans, many investigators concluded that sympathetic reinnervation of the sinus node did not occur.5,27 Additionally, a recent study failed to show differences in chronotropic response to exercise over time in transplant recipients.28 Two factors might account for differences between the present study and those reported previously. First, our patients were studied ∼5 years after transplantation, whereas many previous reports included only patients encountered within the first 2 years of surgery. Because reinnervation is time dependent, our patients may have had greater reinnervation.

A second difference is that the previous inability to distinguish between patients with sinus node reinnervation and those without may have reduced the detection of this phenomenon that does not occur uniformly after transplantation. Concurrent development of sinus node dysfunction further hampers interpretation of chronotropic responses in individual patients. Third, closer examination of heart rate

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**TABLE 3. Effects of Reinnervation on Exercise Duration and Oxygen Consumption**

<table>
<thead>
<tr>
<th>Oxygen Consumption, mL O₂/kg</th>
<th>Exercise Duration, min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transplant recipients</strong></td>
<td></td>
</tr>
<tr>
<td>Early (&lt;6 mo)</td>
<td>3.4±0.3 14.2±0.9 18.9±1.4 60±4 13.8±1.4</td>
</tr>
<tr>
<td>Late (&gt;1 y)</td>
<td></td>
</tr>
<tr>
<td>Denervated</td>
<td>3.4±0.2 13.5±0.5 18.6±1.6 58±5 12.9±1.1</td>
</tr>
<tr>
<td>Mild reinnervation</td>
<td>3.0±0.3 12.7±1.4 16.9±1.6 52±4 11.8±1.4</td>
</tr>
<tr>
<td>Marked reinnervation</td>
<td>4.1±0.3 15.9±1.2 21.2±1.5 67±5 14.5±1.2</td>
</tr>
<tr>
<td>Normal controls</td>
<td>4.1±0.4 23.6±1.4† 35.6±2.2† 109±4† 21.1±1.3†</td>
</tr>
</tbody>
</table>

AT indicates anaerobic threshold.

*Percentage predicted from standard values corrected for age and sex.18
†P<0.05 vs all transplant groups.

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![Figure 7. Modified Bruce protocol treadmill exercise duration in each subject. mod indicates moderate.](http://circ.ahajournals.org/)

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changes during exercise in individual patients reported previously suggests that some patients exhibited heart rate responses more typical of subjects with normal sympathetic innervation (peak heart rate at end of exercise and rapid fall thereafter). Given the results of the present study, it is possible that more-detailed physiological studies in those patients might have confirmed sympathetic reinnervation.

**Implications**

The principal implication of the present study is that reinnervation of the sinus node causes a partial return of the normal physiological response to exercise but the magnitude of the effect is variable. In some patients, near-normalization occurred of the sympathetically mediated heart rate response to exercise, whereas in others, response was meager or nonexistent. Many patients with marked reinnervation described the return of a normal startle response characterized by sudden rapid pounding of their heart immediately after a frightful event (e.g., in response to a car pulling out in front of the patient while he or she was driving).

Finally, studies assessing the effects of the sympathetic nervous system on heart rate should not presume that the sinus node is denervated or that there is uniform reinnervation after transplantation. Compelling evidence now exists for limited sinus node sympathetic reinnervation, and the present study demonstrates that the phenomenon has physiological importance.

**Acknowledgments**

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**References**

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