Sympathetic Rhythmicity in Cardiac Transplant Recipients
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Background—Variability of R-R interval and muscle sympathetic nerve activity (MSNA) occurs predominantly at a low frequency (LF, ±0.1 Hz) and a high frequency (HF, ±0.25 Hz) in normal humans. Increased sympathetic drive in normal humans is associated with an increased LF component of the R-R interval and MSNA. Patients with severe heart failure have high sympathetic activity but decreased or absent LF power of both R-R and MSNA. We tested the hypothesis that this dysfunction in autonomic modulation in heart failure can be reversed by heart transplantation.

Methods and Results—We performed spectral analysis of resting MSNA, R-R interval, and respiration in 9 patients with heart transplants, 9 chronic heart failure patients, and 9 normal control subjects, all closely matched for age, sex, and body mass index. MSNA (bursts per minute) was higher in patients with heart transplants (74 ±3) than either patients with heart failure (56 ±6) or normal subjects (40 ±4) (P<0.001). LF variability in the R-R interval was reduced in both heart transplant recipients and heart failure patients compared with the control subjects (P<0.01). The LF variability in MSNA was also nearly absent in the heart failure patients (P<0.01). However, the LF and HF oscillations in MSNA in patients with heart transplants were comparable to those evident in the control subjects.

Conclusions—Cardiac transplantation does not reduce MSNA. However, LF oscillations in sympathetic activity are restored after transplantation such that the MSNA oscillatory profile is similar to that observed in normal subjects.

Key Words: nervous system ■ transplantation ■ heart failure

In normal subjects, R-R interval and muscle sympathetic nerve activity (MSNA) contain oscillatory components at a low frequency (LF, 0.03 to 0.14 Hz) and a high frequency (HF, synchronous with the respiratory frequency). The relative power of the LF to the HF variability of MSNA increases when sympathetic activity rises. Sympathetic activation is a key component of the pathophysiology of chronic heart failure. This heightened sympathetic drive may result from enhanced excitatory mechanisms, such as excessive stimulation of cardiac and pulmonary afferent fibers, due to the elevated filling pressure.

Despite tachycardia and high levels of MSNA, the variability of R-R interval and MSNA in heart failure shows a decreased or absent LF component. This may result from a dysfunction in central mechanisms governing autonomic modulation, saturation of LF oscillatory systems due to the high sympathetic drive, or from an excessive stimulation of cardiac sympathetic afferents, disrupting normal oscillatory properties. There is anec-dotal evidence that implantation of a left ventricular assist device may restore the LF oscillations of the native heart. Whether heart transplantation can reverse abnormalities in MSNA variability is unknown. There is conflicting evidence regarding the effect of cardiac transplantation on sympathetic nerve traffic. There are no data regarding the oscillatory characteristics of sympathetic outflow in patients after cardiac transplantation. Spectral analysis of blood pressure oscillations in heart transplant recipients reveals both HF and LF components, suggesting a preservation of sympathetic vascular modulation.

We tested the hypothesis that heart transplantation would normalize the altered pattern of sympathetic nerve activity present in patients with severe heart failure. We therefore performed spectral analysis of simultaneous recordings of MSNA, R-R interval, and respiration in heart transplant patients, in patients with severe heart failure, and in normal control subjects, all closely matched for age, sex, and body mass index.
R-R Interval and MSNA and Their Variabilities in Normal Control Subjects, Patients With Heart Transplants, and Patients With Chronic Congestive Heart Failure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects</th>
<th>Mean</th>
<th>Variance</th>
<th>LF Component</th>
<th>HF Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>Control</td>
<td>919±58 ms</td>
<td>3842±2273 ms²</td>
<td>0.10±0.08</td>
<td>0.28±0.02</td>
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<tr>
<td></td>
<td>HTX</td>
<td>657±16 ms</td>
<td>31±13 ms²</td>
<td>0.07±0.02 (n=5)</td>
<td>0.29±0.03</td>
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<tr>
<td></td>
<td>CHF</td>
<td>784±47 ms</td>
<td>1080±394 ms²</td>
<td>0.13 (n=1)</td>
<td>0.35±0.02</td>
</tr>
<tr>
<td>MSNA</td>
<td>Control</td>
<td>40±4 bursts/min</td>
<td>818±540 au²</td>
<td>0.08±0.01</td>
<td>0.28±0.02</td>
</tr>
<tr>
<td></td>
<td>HTX</td>
<td>74±3 bursts/min</td>
<td>692±129 au²</td>
<td>0.09±0.01</td>
<td>0.30±0.03</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>56±6 bursts/min</td>
<td>1118±921 au²</td>
<td>0.11±0.01 (n=2)</td>
<td>0.34±0.02</td>
</tr>
</tbody>
</table>

nu indicates normalized units; RR, R-R interval; HTX, heart transplant patients; CHF, congestive heart failure patients; and au, arbitrary units.

Pairwise contrasts (if ANOVA P<0.05): *P<0.05, †P<0.001, ‡P<0.0001 HTX vs Control and HTX vs CHF, n=9 unless otherwise specified. Distribution of variance of RR and MSNA were normalized with a log transformation.

Methods

Subjects

Heart Transplant Recipients

Heart transplant patients were studied 51±9 months after transplantation. We studied 9 patients (7 men, 2 women) 53±3 years old. Body mass index was 31±2 kg/m² (mean±SEM). Indication for heart transplantation was severe heart failure due to either ischemic heart disease (n=6), valvular heart disease (n=1), or idiopathic cardiomyopathy (n=2). Immunosuppression was achieved by combination therapy with cyclosporine, azathioprine (n=7), and prednisolone (n=5). Cyclosporine doses averaged 317±52 mg/d. All patients were free of heart failure postoperatively, and left ventricular ejection fraction determined by radionuclide ventriculogram was 53±2%. All patients were also free of moderate or severe rejection, as shown by histological evaluation. All were receiving antihypertensive medications at the time of the study, specifically ACE inhibitors (n=7), diuretics (n=4), calcium antagonists (n=2), hydralazine (n=2), β-blockers (n=1), and a clonidine patch (n=1).

Chronic Heart Failure Patients

Nine chronic heart failure patients (7 men, 2 women) 53±3 years old were studied. Body mass index was 31±2 kg/m². All patients had supporting clinical, chest radiographic, and echocardiographic evidence of impaired ventricular function and were in NYHA functional class III and IV. The cause of heart failure was ischemic heart disease (n=5) or idiopathic cardiomyopathy (n=4). Left ventricular ejection fraction determined by a resting radionuclide ventriculogram was 25±3% (mean±SEM). All patients were in sinus rhythm and were receiving a combination of diuretics, nitrates, ACE inhibitors, and digitalis.

Normal Control Subjects

We also studied 9 healthy control subjects matched for age, sex and body mass index (mean age, 53±6 years; 7 men, 2 women; body mass index, 31±3 kg/m²). None was receiving any medications.

Medications for transplant and heart failure patients were not withheld for the purposes of this study. Informed written consent was obtained from all patients and control subjects. The study was approved by the Institutional Human Subjects Review Committee.

Measurements

Sympathetic nerve activity to muscle circulation was recorded continuously by multunit recordings of postganglionic sympathetic activity to muscle, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head as described previously.1,3,8 All subjects were studied during free breathing, without any controlled respiration. ECG, respiration (thoracic belt; Preu

Data Analysis

Sympathetic bursts were identified by a single observer (P.v.d.B.) and calculated as bursts per minute. Stationary segments devoid of arrhythmias (150 to 300 R-R intervals) were analyzed with autoregressive algorithms, which provided the number, center frequency, and power of the oscillatory components. Log transformation was used to normalize the distribution of variance of R-R and MSNA. The LF and HF components were expressed in normalized units, obtained by calculating the percentage LF and HF variability with respect to the total power after subtracting the power of the very-low-frequency component (frequencies <0.03 Hz).3,16

Statistical Analysis

Results are expressed as mean±SEM. Statistical analysis consisted of an ANOVA. The significance of pairwise contrasts was estimated by Fisher’s test. Significance was assumed at P<0.05.

Results

MSNA was markedly higher in patients with heart transplants (74±3 bursts/min) than in normal subjects (40±4 bursts/min) and the patients with heart failure (56±6 bursts/min) (ANOVA P=0.0002; Table, Figure 1). Heart transplantation was also accompanied by a shorter R-R interval and a marked reduction in the variance of R-R interval compared with control subjects and patients with trace, Gould Electronics), and MSNA were recorded during 10 minutes on a Gould 2800 S recorder and an IBM 433DX/T computer. Blood pressure was measured each minute with a Physio-Control Lifestat 200 automated sphygmomanometer.

Figure 1. ECG, MSNA, and respiration in a control subject (left), a patient with severe heart failure (CHF, middle), and a heart transplant recipient (HTX, right). MSNA is markedly elevated in patient with heart failure and in heart transplant recipient. Spectral analysis recordings from these subjects are shown in Figure 2. HR indicates heart rate.
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heart failure (ANOVA P<0.01; Table). Blood pressure averaged 125±2/78±1 mm Hg in the control subjects, 125±9/77±7 mm Hg in the heart failure patients, and 140±4/94±3 mm Hg in the transplant patients (ANOVA P=NS for systolic blood pressure and P<0.01 for diastolic blood pressure. Transplant versus control and transplant versus heart failure for diastolic pressures were both P<0.01).

Comparisons between heart failure and control subjects showed that heart failure patients had faster heart rates (P=0.04) and heightened MSNA (P=0.03) (Table). In addition, respiratory rate was also increased in heart failure patients (0.35±0.02 Hz) versus control subjects (0.28±0.02 Hz; P=0.05).

Clear LF and HF components were evident in MSNA recordings of all patients with heart transplants and all control subjects (Figures 1 and 2). Both LF and HF components of R-R interval variability were present in all control subjects and in 5 of 9 cardiac transplant recipients. In contrast, only 1 of the 9 R-R interval recordings and 2 of the 9 muscle sympathetic nerve recordings of the heart failure patients disclosed any LF component (Table; Figures 1 and 2). All 9 heart failure patients had HF components in both R-R interval and MSNA variabilities.

R-R interval variability in heart transplant patients, although reduced, consisted mainly of HF oscillations (Table; Figure 2). Consequently, the normalized HF power of R-R interval was greater and the normalized LF power of R-R interval was markedly reduced in the heart transplant patients compared with the control subjects (ANOVA P<0.01; Table; Figure 2). Normalized LF and HF powers in the R-R interval did not differ significantly between patients with heart failure and patients with heart transplants (Table).

By contrast, the normalized LF and HF powers in MSNA in patients with heart transplants were comparable to those of the control subjects, whereas the LF variability in MSNA was reduced or absent in the heart failure patients (Table). Thus, sympathetic activation, confirmed by direct intraneural recordings using microneurography, was accompanied by clear LF and HF oscillatory components of MSNA variability in transplant recipients but by a drastic reduction of LF in heart failure patients. None of the subjects demonstrated LF components in respiration that might have accounted for the presence of LF oscillations in R-R and MSNA.

Discussion

Patients with heart failure have heightened MSNA and tachycardia but demonstrate a marked reduction in the LF components of MSNA and R-R variability. The novel finding of this study is that heart transplant recipients, who also have high MSNA, have clear LF and HF components in MSNA variability. Thus, although cardiac transplantation does not lower the high levels of MSNA evident in heart failure patients, abnormalities in modulation of sympathetic activity in patients with heart failure are reversible after cardiac transplantation. The restoration of LF of MSNA is evident despite the absence of any similar LF in R-R variability in the transplanted heart. Hence, there is an uncoupling of variability characteristics of the R-R interval of the transplanted heart and variability characteristics of MSNA.

Restoration of LF oscillations in cardiovascular variability after cardiac transplantation cannot be determined by measurements of R-R variability alone but rather were unmasked only by microneurographic recordings. Although the reason for the restoration of the LF oscillation of MSNA is not known, it may be secondary to the elimination of abnormal sensory inputs from the heart and lung circulation to central neural control mechanisms. Arterial baroreflexes may also be implicated in the restoration of the LF oscillations in MSNA. The baroreflexes contribute importantly to modulation of the LF component of cardiovascular variability.17,18 Cardiac transplantation is accompanied by marked increases in baroreflex gain.11
Other mechanisms allowing restoration of LF of MSNA after cardiac transplantation may include the reduction in central effects of circulating catecholamines, angiotensin, or vasopressin. It is also conceivable that hypertension and/or antihypertensive medications in the heart transplant recipients may have influenced measurements of MSNA and MSNA variability.

The presence of an LF, albeit markedly reduced, in the R-R oscillation in ≈50% of the cardiac transplant recipients is suggestive of efferent cardiac reinnervation and is consistent with findings reported by Bernardi and colleagues.18,19 These investigators demonstrated that this reinnervation was incomplete and was primarily sympathetic rather than vagal reinnervation. They also showed that bivacal heart transplantation markedly increases the likelihood of autonomic reinnervation compared with standard cardiac transplantation.20 The patients in our study had undergone standard cardiac transplantation.

Our patients with heart failure had a resting tachycardia and high levels of sympathetic nerve activity, confirming the high sympathetic drive characteristic of heart failure.4,5,8 After cardiac transplantation, sympathetic nerve traffic remained elevated. However, oscillatory properties of sympathetic neural discharge were restored to a pattern similar to that present in normal subjects. To interpret this finding, it is important to consider that transplantation leads to efferent and afferent cardiac denervation. Cardiac denervation has been linked to changes in left ventricular function.21 Whereas afferent denervation is responsible for the drastic reduction of R-R variability, the effects of afferent denervation can be inferred from prior studies suggesting that complete cardiac denervation is followed by increased sympathetic efferent activity, as a consequence of a reduction of the tonic restraint of vagal sensory afferents.22 Thus, we speculate that afferent parasympathetic cardiac denervation may contribute to the maintenance of high MSNA after cardiac transplantation.

Immunosuppressive therapy with cyclosporine may also be implicated in the increased MSNA and blood pressures in the cardiac transplant recipients.12,23,24 Nevertheless, microneurographic studies in heart transplant recipients on cyclosporine have not consistently shown increased sympathetic traffic. Kaye et al13 and Elam et al14 compared cyclosporine-treated heart transplant recipients with healthy age-matched control subjects. MSNA was comparable to normal13 or only marginally greater than normal14 in the heart transplant recipients. It is important, however, that the initial study by Scherrer et al15 demonstrating higher sympathetic activity in cyclosporine-treated heart transplant recipients compared MSNA measurements with those of heart transplant recipients not receiving cyclosporine. Increases in MSNA and blood pressure in patients receiving cyclosporine for myasthenia gravis were less marked in the myasthenic patients than in heart transplant recipients, even though cyclosporine doses were similar.12 These findings led to the postulate that cardiac denervation in heart transplant recipients removed inhibitory ventricular afferent restraint on sympathetic outflow, thereby amplifying the hypertensive effects of cyclosporine.12,23

In summary, we have shown that heart transplant recipients have high levels of MSNA, even greater than observed in patients with severe heart failure. In contrast to heart failure patients, patients with heart transplants have clear LF oscillations in sympathetic activity. Thus, disturbances of rhythmic oscillations in autonomic outflow in patients with severe heart failure are reversible. We speculate that impaired cardiovascular variability in heart failure may be a consequence of abnormal sensory inputs from the cardiac and pulmonary receptors.

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References


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