Power Spectrum Analysis of Heart Rate Variability in Human Cardiac Transplant Recipients

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Beat-to-beat heart rate variability was studied by power spectral analysis in 17 orthotopic cardiac transplant patients. Heart rate power spectra were calculated from eighty-four 256-second recordings and compared with those taken from six normal subjects. The power spectra from the control subjects resolved into discrete peaks at 0.04–0.12 Hz and 0.2–0.3 Hz, whereas those of heart transplant recipients resembled broad-band noise without peaks. Log total power in the 0.02–1.0 Hz range was greater in the control subjects (0.982±0.084 [0.206], mean±SEM [SD]) than in the transplanted subjects (−0.766±0.059 [0.541]), (p < 0.0001). Fifty-five electrocardiographic recordings from transplant patients were done within 48 hours of an endomyocardial biopsy. When the power spectra of those patients whose endomyocardial biopsies showed evidence of myocardial rejection were compared with those from patients who were found to be free of rejection, a significant difference was found in log total power (−0.602±0.090 [0.525] vs. −0.909±0.136 [0.577], p < 0.02). We conclude that denervation of the heart significantly reduces heart rate variability and abolishes the discrete spectral peaks seen in untransplanted control subjects and that the development of allograft rejection may significantly increase heart rate variability. (Circulation 1989;79: 76–82)

Spontaneous beat-to-beat fluctuations in heart rate reflect ongoing modulation of sinus node activity through several cardiovascular control mechanisms.1 In addition to the respiratory sinus arrhythmia (0.2–0.3 Hz), the heart rate typically oscillates at specific lower frequencies, most commonly at 0.04–0.12 Hz.2,3–4 Heart rate fluctuations can be quantified by the technique of power spectrum analysis, which calculates the frequency content of time-varying signals.

The purpose of this study was to characterize heart rate variability patterns in the orthotopic cardiac transplant recipient, a clinical model of the denervated heart. Using power spectrum analysis, we compared the heart rate variability patterns of transplant recipients with patterns of normal subjects, and in addition, we compared heart rate variability patterns to the degree of myocardial rejection as determined by endomyocardial biopsy.

Subjects and Methods

Patient Population

The study population consisted of 17 patients who had undergone orthotopic cardiac transplantation between 1984 and 1986 at the Brigham and Women’s Hospital, Boston, Massachusetts, and a control group of six healthy volunteers. The characteristics of the transplant recipients are summarized in Table 1. All cardiac transplant recipients were maintained on cyclosporine A and prednisone immunosuppressive therapy. Six normal subjects included four men and two women without known cardiovascular disease (age, 25–40).

Data Collection

Data were collected at the time of initial hospitalization and during routine prescheduled follow-
up visits. Recordings were done 1–807 days after cardiac transplantation (mean, 142 days). A total of 84 electrocardiographic (ECG) recordings were analyzed, and the number of recordings per patient ranged from one to 18, with an average of five. One recording was done for each of the six healthy volunteers. While subjects were resting comfortably in the supine position, the surface ECG was monitored for 15-minute periods by skin electrodes. A 256-second segment of ECG was then used for power spectrum analysis. The ECG segments chosen for analysis had the fewest sudden jumps or spikes in measured heart rate due to artifacts (such as electrical noise or arm or chest muscle contractions). Preliminary tests demonstrated that there were no significant differences in heart rate power spectra within a period of a few hours.

Data Processing

The heart rate power spectrum was computed from the ECG signal as summarized in Figure 1. Two different systems were used for analysis of the ECG signal; one allowed real-time analysis by a bedside computer, and the other allowed the signal to be recorded on magnetic tape for later analysis in the laboratory. The bedside computer consisted of a 6809E based microprocessor and printer, with designated programming for heart rate power spectrum analysis. The Hewlett-Packard 78341 monitor (Palo Alto, California) attached to the patient sent a signal to the computer whenever it detected an R wave. When analyzed in the laboratory, the ECG signal was recorded with a clock signal, by a Cardio-Data Holter System. The signal was sampled by a Masscomp 500 computer using a phase-locked loop to eliminate distortion due to variations in tape speed and low-pass filters to eliminate aliasing. Both systems recorded R wave activation times to within a 2-msec accuracy. A feature detection program was then used to determine R wave locations. Both systems then created a 1,024-point smoothed heart rate tachogram, calculated from the reciprocal of each RR interval over 256 seconds. Heart rate power spectra were calculated by computing the magnitude squared of the fast Fourier transform of the 1,024 data points of tachometer signal. The total power was obtained by integrating the power spectrum from 0.02 to 1.0 Hz. Power at frequencies below 0.02 Hz was not considered because it may not be reliably measured in data records 256 seconds long. In all cases, power in the range of 1.0–2.0 Hz was negligible. The total power can be viewed as the variance in heart rate during the 256-second period and, therefore, has units of beats per minute squared (beats²/min²). Log total power was calculated by taking the common logarithm of the total power. The log total power is reported in dimensionless units with the additive constant (log [beats²/min²]) being implicit. Some subjects were monitored simultaneously with both systems, and the two systems yielded indistinguishable results.

### Table 1. Clinical Data on Experimental Subjects

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Times monitored</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>50</td>
<td>Postoperative mitral valve replacement</td>
<td>1</td>
</tr>
<tr>
<td>M</td>
<td>48</td>
<td>Idiopathic dilated cardiomyopathy</td>
<td>10</td>
</tr>
<tr>
<td>M</td>
<td>34</td>
<td>Idiopathic dilated cardiomyopathy</td>
<td>18</td>
</tr>
<tr>
<td>M</td>
<td>43</td>
<td>Coronary heart disease</td>
<td>2</td>
</tr>
<tr>
<td>F</td>
<td>57</td>
<td>Idiopathic dilated cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>M</td>
<td>45</td>
<td>Idiopathic dilated cardiomyopathy</td>
<td>8</td>
</tr>
<tr>
<td>M</td>
<td>41</td>
<td>Coronary heart disease</td>
<td>1</td>
</tr>
<tr>
<td>M</td>
<td>54</td>
<td>Idiopathic dilated cardiomyopathy</td>
<td>1</td>
</tr>
<tr>
<td>M</td>
<td>55</td>
<td>Postoperative mitral valve replacement</td>
<td>13</td>
</tr>
<tr>
<td>M</td>
<td>48</td>
<td>Coronary heart disease</td>
<td>3</td>
</tr>
<tr>
<td>M</td>
<td>17</td>
<td>Idiopathic dilated cardiomyopathy</td>
<td>6</td>
</tr>
<tr>
<td>F</td>
<td>50</td>
<td>Idiopathic dilated cardiomyopathy</td>
<td>9</td>
</tr>
<tr>
<td>M</td>
<td>41</td>
<td>Aortic valve disease</td>
<td>1</td>
</tr>
<tr>
<td>M</td>
<td>51</td>
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<td>1</td>
</tr>
<tr>
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<tr>
<td>F</td>
<td>24</td>
<td>Postoperative mitral valve replacement</td>
<td>6</td>
</tr>
<tr>
<td>M</td>
<td>35</td>
<td>Idiopathic dilated cardiomyopathy</td>
<td>1</td>
</tr>
</tbody>
</table>

M, male; F, female.
Correlation With Endomyocardial Biopsy

Recordings taken within 48 hours of an endomyocardial biopsy were analyzed and compared with biopsy results. Although most recordings occurred several hours before biopsy, the relative timing of biopsy and recording was not uniform. As a result, some recordings occurred after biopsy and some occurred more than a few hours before biopsy. A total of 55 biopsies were obtained within 48 hours of an ECG power spectrum recording, representing data from 14 subjects. Severity of rejection in biopsy specimens was graded histologically according to a widely used classification scheme. Early or mild acute rejection was characterized by a light perivascular or endocardial lymphocytic infiltrate or both. In moderate acute rejection, the mononuclear infiltrate was morphologically similar to that in mild rejection but was increased perivascularly and spread into the interstitium. When definite myocyte injury was associated with the inflammatory infiltrate, the diagnosis of moderate rejection with necrosis was rendered. In severe rejection, the increased inflammatory infiltrate often included neutrophils or eosinophils, and there was usually patchy interstitial hemorrhage or vasculitis. Widespread myocyte necrosis and often edema were particularly evident in these cases in areas of maximum infiltrate. After treatment for acute rejection with necrosis, the inflammatory infiltrate was usually reduced (resolving) or disappeared (resolved) within 2 weeks. Power spectra results based on biopsy were then grouped into those that showed no rejection and those that showed mild, moderate, severe, or resolving rejection. Three biopsies taken 5–12 days postoperatively showed evidence of perioperative ischemic damage, and thus, the corresponding power spectra were eliminated from the analysis.

Statistical Analysis

All 84 observations of logarithm of the total power in transplant recipients were compared with the observations in six normal subjects. Observations within 48 hours of biopsies revealing no rejection were pooled and compared with those classified as mild, moderate, severe, or resolving rejection. When comparing two populations, the total pool of data was ranked from highest to lowest values of the log power. The ranks were then grouped by population. Finally, the unpaired Student’s t test was used to test whether the ranks of the two populations were significantly different.
Results

Transplant Recipients Compared With Healthy Volunteers

Figures 2A and 2B show representative heart rate tachograms and corresponding power spectra for a healthy volunteer and a transplant recipient with no clinical or histological signs of rejection. In the tachogram from the healthy volunteer, an oscillatory pattern of heart rate fluctuations is evident, whereas the corresponding power spectrum illustrates that these fluctuations are concentrated mainly in two frequency bands: one at 0.10 Hz and the other, corresponding to the respiratory frequency, at 0.30 Hz. The tachogram from the cardiac transplant recipient, however, shows nearly no heart rate variability, which is exemplified in the power spectrum as a flat tracing without spectral peaks. Pooled values for all recordings in normal subjects compared with transplant recipients are shown in Figure 3. The values (mean±SEM [SD]) for log total power ranging from 0.02 to 1.0 Hz was 0.98±0.084 (0.206) for normal subjects and -0.766±0.059 (0.541) for all observations in transplant recipients (p<0.0001).

Transplant Recipients With and Without Evidence of Rejection

Of the 55 biopsies corresponding to analyzed power spectra, 18 were classified as no rejection, three were classified as resolved rejection, and 34 were classified as mild, moderate, severe, or resolving rejection. Figure 2C shows the heart rate tachogram and corresponding power spectrum in the same transplant recipient as in Figure 2B but during an episode of moderate rejection. In the heart rate tachogram, a slightly greater degree of heart rate variability during the episode of moderate rejection is detectable. However, the increase is more clearly evident in the heart rate power spectrum. The corresponding power spectrum, however, differs from that from the normal subject in that it does not show peaks at specific frequencies but rather a more random, or “broad-band,” pattern of heart rate variability. Serial results of endomyocardial biopsies and heart rate power spectra for this patient are shown in Figure 4. It illustrates that the patient, after an initial rejection episode before the measurements of this study, remained stable for several months until endomyocardial biopsy indicated moderate rejection. Correspondingly, heart rate power spectrum values were low until suddenly increasing 50-fold at the time of the latter rejection episode. In two additional patients with multiple measurements allowing serial comparisons, the onset of acute rejection was accompanied by a dramatic increase in total heart rate power. In two other patients, however, total power did not change significantly with the onset of rejection.

Values for log total power were pooled into the no rejection (n=18) versus rejection (n=34) groups defined above, and the results are graphed in Figure 5. The values were -0.909±0.136 (0.577) for the group showing no rejection and -0.602±0.090 (0.525) in the group with evidence of rejection (p<0.02). Although the total power in the two groups is statistically different, these values represent differences in beat-to-beat heart rate variance of 0.176 beats²/min² or, equivalently, a standard deviation difference of less than 0.45 beats/min. Assuming a mean heart rate of 90 beats/min, this significant difference in heart rate standard deviation is less than 0.5% of the mean, corresponding to fluctuation differences on the order of 5 msec for each RR interval.

Although patients with no rejection and resolved rejection appear the same histologically, there may be differences in their electrical activity. This study was designed, therefore, to test the null hypothesis that there would be no difference between the rejection and no rejection groups as defined above. An a posteriori comparison between the resolved rejection and no rejection groups revealed that the level of heart rate variability in patients with resolved rejection was in fact not significantly different from the level in patients with no rejection (-1.068±0.200 [0.346], n=3 vs. -0.909±0.136 [0.577], n=18, p=0.3).
FIGURE 5. Bar graph of comparison of total power (0.02–1.0 Hz) in transplant recipients with no rejection and those with mild, moderate, or severe rejection. Data are mean ± SD. Difference between the two groups is statistically significant (p < 0.02).

Discussion

Power spectrum analysis of heart rate variability has been shown to be a quantitative, noninvasive method for assessing cardiovascular control in animals and humans.1,2,4 Spectral analysis, thus, has been used to analyze the mechanisms involved in heart rate variability. For example, studies with pharmacological blockade in the conscious dog indicate that heart rate fluctuations at normal respiratory rates are mediated solely by the vagus, whereas lower frequency oscillations appear to be jointly mediated by the sympathetic and parasympathetic systems.5 Power spectrum analysis of heart rate variability has also been characterized in dogs with surgically denervated hearts,6 in humans during postural changes and pharmacological interventions,9 and in infants at risk for the sudden infant death syndrome.10,11 We chose to study heart rate variability in orthotopic cardiac transplant recipients for two reasons: heart rate variability patterns have not been characterized in the human denervated heart; and we wanted to determine if any relation exists between heart rate variability patterns and evidence of myocardial rejection in cardiac transplant recipients receiving cyclosporine A therapy. We found that when compared with normal volunteers, transplant recipients overall showed a 96% reduction in heart rate variability in the 0.02–1.0-Hz frequency band. Fluctuations within this range have been shown to be modulated primarily by the autonomic nervous system and are thought to be too rapid to reflect changes in levels of circulating catecholamines. We also found that within 48 hours of endomyocardial biopsy, there was overall a significant increase in heart rate variability in the group showing histological evidence of rejection when compared with those showing no signs of rejection. This increase would not be detectable by visual inspection of ECG, representing beat-to-beat changes in RR interval of under 10 msec. Although there were not enough data points to assess every patient serially, in three patients with multiple measurements and coincident episodes of acute rejection, the onset of rejection was accompanied by a large increase in heart rate total power. Moreover, the pattern of heart rate variability was of random, broad-band fluctuations, quite distinct from the well-characterized oscillations at specific frequencies in normal subjects. Two patients with episodes of moderate rejection within 2 weeks after transplantation did not show an increase in heart rate variability with the onset of rejection. Further study is needed to analyze the time course of increased heart rate variability during rejection and the effect of antirejection therapy on heart rate variability patterns.

The literature contains different accounts of the effects of denervation on heart rate variability. Raeder et al8 demonstrated that surgical denervation of the heart in the anesthetized dog immediately abolished most heart rate fluctuations in the 0.02–0.30-Hz frequency band. In a longer-term study, Thames et al12 observed the recurrence of parasympathetic innervation of the heart after cardiac transplantation in dogs and that most of the reinnervated dogs developed respiratory sinus arrhythmia 2.5–20 months postoperatively. These investigators concluded that vagal reinnervation was necessary, but not sufficient, for respiratory sinus arrhythmia after heart transplantation. However, their interpretation differs from that of Hrushesky et al,13 who reported a normal respiratory sinus arrhythmia in one human cardiac transplant recipient and concluded that respiratory frequency fluctuations are related to pressure-dependent intracardiac effects. In our population of 17 cardiac transplant recipients, heart rate fluctuations at all frequencies between 0.02 and 1.0 Hz were reduced by more than 90%. Furthermore, the prominent peak at the respiratory frequency in control patients was absent or substantially diminished in spectra from heart transplant recipients. A small amount of variability at the respiratory frequency is expected because changes in cardiac axis with respiration will cause changes in the measured RR interval. A very small amount of respiratory sinus arrhythmia may result from local sinoatrial node stretch reflexes.9 We conclude that heart rate fluctuations in humans in the frequency band from 0.02–1.0 Hz are related primarily to autonomic modulation of sinus node activity. Our data are consistent with the widely accepted notion that, unlike the situation in dogs, physiologically significant reinnervation of transplanted human hearts does not occur,14 at least during the period after transplant studied here.

The diagnosis of allograft rejection is paramount in the long-term postoperative management of heart transplant recipients. Cyclosporine A–treated patients may develop advanced myocardial rejection without clinical symptoms followed by precipitous deterioration of donor heart function. Thus, in patients treated with contemporary immunosuppres-
sive therapy, endomyocardial biopsy is the only reliable means by which acute allograft rejection may be diagnosed at a stage that is reversible in the majority of patients and that has not resulted in massive tissue damage. Several methods for detecting cardiac allograft rejection have been investigated, including electrocardiography,\textsuperscript{15} proton nuclear magnetic resonance spectroscopy,\textsuperscript{16,17} lymphocyte radiolabeling,\textsuperscript{18} echocardiographic measurements of wall motion or organ mass,\textsuperscript{19} and variables of diastolic relaxation.\textsuperscript{20} However, in transplant recipients maintained on cyclosporine A therapy, no noninvasive method has yet proved reliable, and repeated endomyocardial biopsies continue to be necessary.

Therefore, to investigate the performance of total heart rate power in discriminating between groups of patients with different biopsy results is of interest. An ideal clinical test would operate with a sensitivity and specificity of 1. After plotting the receiver operating characteristic curve for the data, the optimal operating point was obtained with a log power of $-0.92$ as the threshold for identifying patients whose biopsies show at least focal moderate rejection with necrosis (approximately the level of rejection used to determine the need for increased immunosuppression). This operating point results in a sensitivity of 0.88 and a specificity of 0.39. The same threshold identifies patients with multifocal moderate rejection and necrosis with a sensitivity of 1.00. Also noteworthy is that the only biopsy specimen classified as severe rejection corresponded to a log total power of 0.744. This is the highest value we observed in any of the transplant patients and is far above the mean ($-0.766$) of all transplant patients we monitored. Although $0.02-1.0$ Hz power distinguishes patients needing treatment from those who do not and also distinguishes nonrejecting patients from those whose biopsies show rejection, the Spearman’s rank correlation coefficient suggests that the correlation between biopsy grade and log heart rate power is not statistically significant ($p = 0.2$). We believe that this paradox is explained by the relative insensitivity of heart rate power to the differences among the less serious levels of rejection. Thus, it seems that the presence of rejection and the presence of necrosis significantly affect heart rate variability, whereas the other morphological sequelae of varying levels of rejection may not. It must be emphasized that biopsy specimens, which represent only a small sample of tissue from the right interventricular septum, are assumed to represent the histology of the entire myocardium. Nevertheless, these results indicate that power spectral analysis could ultimately be a useful noninvasive diagnostic methodology that would aid decisions concerning biopsy timing.

In summary, we have shown that transplant recipients exhibit 96% less heart rate variability than control subjects and that the variability in transplant recipients is broad banded, in contrast to the discrete peaks observed in the power spectra of normal patients. Furthermore, among the subjects in this study, patients with rejection documented by endomyocardial biopsy show significantly more variability in the $0.02-1.0$ Hz range than those with no evidence of rejection. It would be desirable to undertake a larger study with more effort toward controlling variables such as the time since transplant and the relative timing of biopsy and ECG recording to test the hypothesis that heart rate variability can be used as a noninvasive test for monitoring patients for cardiac rejection. Nonetheless, the preliminary results presented here indicate an association between myocardial rejection and increased broad-band heart rate variability, suggestive of an immunologically mediated interference with intracardiac conduction leading to more erratic beat-to-beat conduction through cardiac tissue. Increased beat-to-beat variability in the RR interval would be expected when the morphological sequelae of the rejection process (lymphocytic infiltration, edema, and necrosis) involve the supraventricular conduction system. Our data do not allow the distinction between increased PP interval variability and PR interval variability as the underlying cause of increased RR interval variability during rejection. Although extrasystoles could theoretically also affect heart rate variability, we analyzed data epochs free of arrhythmic events. Future studies are planned to follow patients with frequent serial measurements to define better the time relation between rejection episodes and heart rate variability patterns.

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