Prognostic Value and Physiological Correlates of Heart Rate Variability in Chronic Severe Mitral Regurgitation

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Background. A variety of measures of heart rate variability have been devised to measure high-frequency (0.15–0.40 Hz), low-frequency (0.04–0.15 Hz), or ultralow-frequency (<0.0033 Hz) fluctuations in sinus cycle length. Although measures of low-frequency and ultralow-frequency heart rate variability have been shown to correlate with prognosis in several populations with ischemic heart disease, their relevance to patients with primary valvular heart disease remains to be determined.

Methods and Results. Thirty-eight patients with nonischemic causes of chronic severe mitral regurgitation who were in sinus rhythm underwent 24-hour ambulatory electrocardiography as part of a prospective study of the natural history of regurgitant valvular heart disease. Patients were followed for as long as 9.2 years, and end points of mortality, progression to mitral valve surgery, and development of chronic atrial fibrillation were tabulated. Time- and frequency-domain measurements of high-frequency, low-frequency, and ultralow-frequency heart rate variability were computed and compared with resting ventricular function by radionuclide cineangiography and outcome. The standard deviation of the 5-minute mean RR intervals (SDANN), a measure of ultralow-frequency heart rate variability, was correlated with left ventricular ejection fraction \( r=0.49, p=0.002 \) and right ventricular ejection fraction \( r=0.43, p=0.007 \), whereas low-frequency and high-frequency heart rate variabilities were not.

Conclusions. Ultralow-frequency heart rate variability, as measured by SDANN, correlates with right and left ventricular performance and predicts development of atrial fibrillation, mortality, and progression to valve surgery in patients with chronic severe mitral regurgitation. (Circulation 1993;88:127-135)

Key Words • electrocardiography • valvular disease • heart rate • mitral regurgitation

Abnormalities in the beat-to-beat variability of the heart rate in sinus rhythm have been associated with an adverse prognosis in patients with ischemic heart disease with\(^1\) and without\(^2,3\) recent myocardial infarction. A variety of individual measures of heart rate variability have been devised\(^4,5\) to measure high-frequency (0.15–0.40 Hz), low-frequency (0.04–0.15 Hz), and ultralow-frequency (<0.0033 Hz) fluctuations in sinus cycle length. These measures have yet to be applied systematically to patients with primary valvular heart disease. Accordingly, we examined the patterns, physiological correlates, and prognostic significance of measures of sinus cycle length variability among patients with severe mitral regurgitation.

Methods

We examined ambulatory ECGs and resting and right ventricular ejection fractions from radionuclide cineangiograms in 38 patients with hemodynamically important chronic mitral regurgitation who were studied at entry into our prospective assessment of the prognostic value of noninvasive testing in regurgitant valvular disease. Detailed enrollment criteria for the study have been published previously.\(^6,7\) For the present analysis, we used a subset of our patients with 1) severe isolated mitral regurgitation (3+ or 4+ by contrast angiography or Doppler echocardiography or, in pa-
tients who were studied before the routine availability of Doppler echocardiography, abnormal left ventricular or left atrial dimensions and a physical examination consistent with severe mitral regurgitation) at the time of the index Holter monitoring, 2) a 24-hour ambulatory ECG demonstrating normal sinus rhythm obtained more than 1 day before any end-point events, and 3) radionuclide cineangiography performed within 12 cal-

month's ambulatory ECG recording without an intercurrent clinical event. No other criteria were used to exclude patients from this subset.

The mean age was 51 years (range, 20–75 years); 17 patients were women, and 21 were men. The cause of mitral regurgitation was primary mitral valve prolapse in 24 patients (63%), rheumatic heart disease in four patients (11%), calcific degeneration in three patients (8%), ruptured chordae tendineae in two patients (5%), infective endocarditis in two patients (5%), and mitral valve prolapse resulting from the Marfan syndrome in one patient (3%). The cause was unknown in one patient (3%), and there was one patient (3%) with infective endocarditis, possible ruptured chordae tendineae, and possible rheumatic heart disease in whom the primary cause of mitral regurgitation could not be determined. The study population comprises patients with chronic nonischemic mitral regurgitation; however, three patients with clinically apparent coro-

nary artery disease are included: two patients who underwent coronary artery bypass grafting at the time of mitral valve surgery and one patient with a reported myocardial infarction during the follow-up period. The primary results of the study were not changed by exclusion of these patients.

Radionuclide cineangiography was performed in the supine position at rest.6 Red blood cells were labeled in vivo by intravenous administration of stannous pyrophosphate followed by intravenous injection of 10–20 mCi of 99mTc. Resting left ventricular ejection fraction was determined according to a procedure analogous to our standard count-based method.8–10 Resting right ventricular ejection fraction was determined by the method of Maddahi et al.,11 previously validated in our laboratory by comparison with contrast-based videodensitometry.12

Ambulatory ECG recordings of bipolar leads CM1 and CM4 were scanned by a computer-based system (Marquette Laser XP, Marquette Electronics Inc., Mil-

waukee, Wis) with total visual verification and correction of beat morphology and timing by one of the authors (K.M.S.). All patients included in this study were in sinus rhythm throughout the index recording period. Arrhythmias were classified as simple when the entire 24-hour recording was free of ventricular cou-

ples, triplets, and tachycardia and were classified as complex when one or more of these repetitive forms was present.13

For statistical evaluation, ventricular premature contraction (VPC) density was adjusted for its skewed distribution by log transformation as follows:

\[ \text{Adjusted VPC density} = \log_2[1 + (1000 \times \text{VPC total/QRS total})] \]

Indexes of heart rate variability can be defined in the time and frequency domains. In addition to the mean heart rate, the following time-domain indexes of heart rate variability were determined: 1) the standard devi-

ation of the mean RR intervals during the 288 five-

minute periods that constitute the 24-hour day (SDANN)13,14 and 2) the root mean square of successive differences (RMSSD) in RR intervals among consec-

utive normal beats. In the frequency domain, we deter-

mined 3) total-frequency amplitude, the square root of the total power from 0.01 to 1.00 Hz expressed in millisecond, 4) high-frequency amplitude, the square root of the total power from 0.15 to 0.40 Hz, and 5) low-frequency amplitude, the square root of the total power from 0.04 to 0.15 Hz.

The power spectra were calculated by converting the tabulation of RR intervals into a tachogram relating instantaneous heart rate to time (corrected for ventricular or supraventricular ecto-

dy by interpolation), resampling at 2 Hz, calculating nonoverlapping 2-minute power spectra based on a 256-point fast Fourier transform, and then computing the mean RR interval power spectrum using software provided by Marquette Electronics. According to Parse-

val’s theorem, the total power of a signal, integrated over all frequencies, is equal to the variance of the entire signal. The total power of the RR interval spectrum within a given frequency band is therefore a measure of the amount of total RR interval variance contributed by fluctuations within that frequency range. Thus, the amplitudes derived from the heart rate power spectrum are measures (in millisecond) of the SD of the RR interval within the specified frequency ranges.

To examine the effects of the sleep–wake cycle on heart rate variability in mitral regurgitation, we sepa-

rately computed the same time- and frequency-domain measures of heart rate variability for a 4-hour daytime period (8 AM to 12 noon) and a 4-hour nighttime period (12 midnight to 4 AM). Most, but not all, Holter recordings were initiated in the early afternoon; thus, there were 25 patients who had continuous ambulatory recordings through both of these comparison periods. Note that the daytime and nighttime SDANN values do not measure heart rate fluctuations that occur over a period of >4 hours and therefore are not strictly comparable to the 24-hour SDANN.

The many possible measures of heart rate variability can be divided into measures of high-frequency heart rate variability (0.15–0.40 Hz), measures of low-

frequency heart rate variability (0.04–0.15 Hz), and measures of ultralow-frequency heart rate variability (<0.0033 Hz).13 According to these definitions, RMSSD and high-frequency amplitude are measures of high-

frequency heart rate variability, and low-frequency amplitude is a measure of low-frequency heart rate vari-

ability. SDANN behaves as a low-pass filter with a cutoff frequency of approximately 0.006 Hz,16 and as a result, the vast majority of “power” within SDANN is contained in the ultralow-frequency heart rate variabil-

ity range. Total frequency amplitude is a measure of combined low-frequency and high-frequency heart rate variability. However, because 2-minute segments of data were used to calculate the power spectra, this measure of “total” frequency amplitude does not include any ultralow-frequency heart rate variability. These theoretical relations among measurements of heart rate variability are displayed in Figure 1.
The median time between radionuclide cineangiography and ambulatory ECG recording was 0 days (89% within 7 days; range, 0–387 days). Patients were instructed to continue diuretic therapy during the ambulatory ECG recording. The population thus includes 11 patients on diuretics (nine furosemide, two Dyazide). Patients were requested to discontinue other cardiovascular medications 5 half-lives before evaluation, but this was left to the discretion of the referring physician. As a result, 15 patients were receiving digoxin, four patients β-blockers (two propranolol, two nadolol), one patient a calcium channel blocker (nifedipine), six patients vasodilating agents (one captopril, one prazosin, and four hydralazine), and four patients type Ia antiarrhythmic drugs (one quinidine, one procainamide, two disopyramide) at the time of the ambulatory ECG recording.

For purposes of life-table analysis, observation was begun on the date of the patient’s earliest analyzable ambulatory ECG recording. Follow-up generally was performed annually and included both clinical evaluation and objective testing. In cases in which direct assessment was precluded, determination of clinical status was made by phone contact with the patient, the patient’s immediate family, or the patient’s primary physician. Conversion from sinus rhythm to sustained atrial fibrillation, death (from any cause), and progression to valve surgery were defined as end points for this analysis. Deaths were classified as witnessed sudden cardiac death, probable sudden cardiac death, nonfatal cardiac death, or noncardiac death, according to criteria described elsewhere,\textsuperscript{13} by physicians who were unaware of the results of the heart rate variability calculations. Follow-up ranged from 3.2 to 9.2 years (mean, 6.7 years) for event-free survivors; events occurred after 0.01–8.5 years (mean, 3.3 years).

Survival and event rates were calculated by the product-limit method, with survival data censored at the time of mitral valve surgery. Survival analysis for discrete and continuous variables and multiple variables was performed with a Cox proportional hazards model. For all comparisons, a value of \( p<0.05 \) was required for rejection of the null hypothesis.

**Results**

At study entry, mean left ventricular ejection fraction was 52% (range, 18–65%), and mean right ventricular ejection fraction was 40% (range, 21–53%). Mean VPC density was 22 per 1000 total beats (range, 0–156); 22 (58%) of the patients had complex ventricular ectopy (VPC couplets, salvos, or nonsustained ventricular tachycardia) during the monitoring period. Correlations among the measures of heart rate variability are shown in Table 1, and correlations between these measures and other clinical and laboratory findings are shown in Table 2. Many of the heart rate variability measurements exhibited strong covariability, with close relations between low-frequency amplitude and total-frequency amplitude (\( r=0.97, p<0.0001 \)) and between RMSSD and high-frequency amplitude (\( r=0.95, p<0.0001 \)), consistent with theoretical predictions (Figure 1). All measurements of heart rate variability were covariate with mean RR interval. SDANN, the measure of ultralow-frequency variation, was weakly correlated with both right ventricular ejection fraction (\( r=0.43, p=0.007 \)) and left ventricular ejection fraction (\( r=0.49, p=0.002 \)). In contrast, measures of low-frequency and high-frequency heart rate variability were not significantly correlated with the indexes of resting ventricular performance. These relations were not affected by adjustment for the interval between radionuclide cineangiography and ambulatory electrocardiography.

Patients who were taking vasodilating agents at the time of evaluation (\( n=6 \)) had significantly lower SDANN (65 versus 127 msec, \( p=0.002 \), low-frequency
amplitude (14 versus 24 msec, \( p = 0.04 \)), and total-frequency amplitude (25 versus 40 msec, \( p = 0.04 \)) than patients who were not on vasodilators (\( n = 32 \)). In addition, patients on vasodilators had significantly lower left ventricular ejection fraction than patients not on vasodilators (44\% versus 54\%, \( p = 0.02 \)), although there was no significant difference in right ventricular ejection fraction between the two groups. Patients who were on diuretics at the time of evaluation (\( n = 11 \)) also had significantly lower SDANN (75 versus 135 msec, \( p = 0.0001 \), low-frequency amplitude (15 versus 25 msec, \( p = 0.009 \)), and total-frequency amplitude (27 versus 42 msec, \( p = 0.01 \)) than patients who were not on diuretics (\( n = 27 \)). There were no significant differences in left or right ventricular ejection fractions between these groups. There were no significant interactions between any of the other classes of medications and measures of heart rate variability in this population.

There was a significant diurnal variation (Table 3) in mean RR interval (daytime, 770 msec; nighttime, 904 msec; \( p < 0.0001 \)). The magnitude of the difference from day to night was linearly correlated with the 24-hour SDANN (\( r = 0.58, p = 0.003 \)) but not with age, measures of left or right ventricular performance, or any measures of 24-hour heart rate variability. The only frequency-domain measure of heart rate variability that displayed significant day/night variation was high-frequency amplitude (mean daytime high-frequency amplitude, 11.2 msec; mean nighttime high-frequency amplitude, 14.4 msec; \( p = 0.03 \)). The magnitude of this variation, expressed as the difference between nighttime and daytime values, was not significantly correlated with age, left ventricular ejection fraction, or right ventricular ejection fraction and did not correlate with mean RR interval or 24-hour SDANN. There were no significant group differences between the 25 patients who were included in and the 13 who were excluded from the analysis of circadian rhythmicity of heart rate variability in age, sex, frequency or complexity of ventricular ectopy, left or right ventricular ejection fraction, or any of the 24-hour measures of heart rate variability or frequency of endpoint events.

Among the 38 patients, six developed sustained atrial fibrillation (16\%). The median time to the onset of atrial fibrillation was 2.6 years (range, 1.9–9.1 years). Among the variables that we studied, including age, measures of right and left ventricular performance, VPC density, VPC complexity, and several measures of heart rate variability (mean heart rate, SDANN, RMSSD, low-frequency amplitude, high-frequency amplitude, and total-frequency amplitude), only SDANN

### Table 1. Correlations Among Measures of Heart Rate Variability

<table>
<thead>
<tr>
<th></th>
<th>Low-frequency power amplitude</th>
<th>Total-frequency power amplitude</th>
<th>High-frequency power amplitude</th>
<th>RMSSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDANN</td>
<td>( r = 0.63 )</td>
<td>0.61</td>
<td>0.33</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.0001 )</td>
<td>( p &lt; 0.0001 )</td>
<td>( p = 0.04 )</td>
<td></td>
</tr>
<tr>
<td>Low-frequency</td>
<td>( r = 0.97 )</td>
<td>0.77</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>power amplitude</td>
<td>( p &lt; 0.0001 )</td>
<td>( p &lt; 0.0001 )</td>
<td>( p &lt; 0.0001 )</td>
<td></td>
</tr>
<tr>
<td>Total-frequency</td>
<td>( r = 0.87 )</td>
<td>0.75</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>power amplitude</td>
<td>( p &lt; 0.0001 )</td>
<td>( p &lt; 0.0001 )</td>
<td>( p &lt; 0.0001 )</td>
<td></td>
</tr>
<tr>
<td>High-frequency</td>
<td>( r = 0.95 )</td>
<td>( p &lt; 0.0001 )</td>
<td>( p &lt; 0.0001 )</td>
<td></td>
</tr>
<tr>
<td>power amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSSD</td>
<td></td>
<td></td>
<td></td>
<td>( p &lt; 0.0001 )</td>
</tr>
</tbody>
</table>

SDANN, SD of the 5-minute mean RR interval; RMSSD, root-mean-square successive difference of the RR interval.

### Table 2. Correlations Between Measures of Heart Rate Variability and Other Variables

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>VPC density</th>
<th>Left ventricular ejection fraction (%)</th>
<th>Right ventricular ejection fraction (%)</th>
<th>Mean RR interval (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDANN</td>
<td>( r = -0.13 )</td>
<td>0.12</td>
<td>0.49</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>( p = 0.43 )</td>
<td>( p = 0.47 )</td>
<td>( p = 0.002 )</td>
<td>( p = 0.007 )</td>
</tr>
<tr>
<td>Low-frequency power amplitude</td>
<td>( r = -0.31 )</td>
<td>0.10</td>
<td>0.27</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>( p = 0.06 )</td>
<td>( p = 0.54 )</td>
<td>( p = 0.11 )</td>
<td>( p = 0.14 )</td>
</tr>
<tr>
<td>Total-frequency power amplitude</td>
<td>( r = -0.25 )</td>
<td>0.14</td>
<td>0.27</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>( p = 0.13 )</td>
<td>( p = 0.41 )</td>
<td>( p = 0.10 )</td>
<td>( p = 0.15 )</td>
</tr>
<tr>
<td>High-frequency power amplitude</td>
<td>( r = -0.05 )</td>
<td>0.23</td>
<td>0.16</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>( p = 0.75 )</td>
<td>( p = 0.17 )</td>
<td>( p = 0.34 )</td>
<td>( p = 0.47 )</td>
</tr>
<tr>
<td>RMSSD</td>
<td>( r = 0.03 )</td>
<td>0.32</td>
<td>0.06</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>( p = 0.86 )</td>
<td>( p = 0.05 )</td>
<td>( p = 0.73 )</td>
<td>( p = 0.81 )</td>
</tr>
</tbody>
</table>

VPC, ventricular premature contraction; SDANN, SD of the 5-minute mean RR interval; RMSSD, root-mean-square successive difference of the RR interval.
was significantly associated with the subsequent development of atrial fibrillation (relative risk, 3.1; \( p = 0.03 \)).

There were three deaths in the group (8%), of which two were witnessed or probable sudden cardiac deaths and one was a non-sudden cardiac death; there were no non-cardiac deaths. Seventeen patients (45%) underwent mitral valve surgery (13 mitral valve replacements and four mitral valve repairs) during the follow-up period. Overall, actuarial 1-year event-free survival was 87% and 2-year event-free survival was 76%. Among the measures of heart rate variability, the significant univariate predictors of mortality were reduced SDANN, reduced total-frequency amplitude, and reduced low-frequency amplitude (Table 4). Neither high-frequency amplitude nor RMSSD correlated with mortality. The three deaths occurred in the three patients in this population with mean RR intervals \( \leq 621 \) msec (mean heart rate, \( \geq 97 \) beats per minute). Among the other variables we studied, reductions in right and left ventricular ejection fractions were both associated with increased mortality. Among the measures of heart rate variability, the significant univariate predictors of the combined risk of mortality or the requirement for mitral valve surgery were reduced SDANN, reduced total-frequency amplitude, and reduced low-frequency amplitude. In addition, reduction in the mean RR interval was a significant univariate predictor of combined risk. There was a nonsignificant trend toward increased risk with reductions in high-frequency amplitude (\( p = 0.06 \)). Among the other variables we studied, reductions in right and left ventricular ejection fractions were both associated with increased risk. Of all the variables, the most potent univariate predictor of mortality and of combined risk was SDANN.

All variables (age, mean heart rate, left and right ventricular ejection fractions, VPC density, VPC complexity, SDANN, RMSSD, low-frequency amplitude, high-frequency amplitude, and total-frequency amplitude) were entered into a multivariate Cox proportional-hazards model in an automated stepwise manner (Table 5). In this multivariate model, SDANN retained independent predictive power for events (\( p = 0.0001 \)). After SDANN was accounted for, only the presence of complex ventricular ectopy during 24-hour ambulatory electrocardiography provided significant additional

### Table 3. Diurnal Differences in Heart Rate Variability

<table>
<thead>
<tr>
<th></th>
<th>Daytime (8 AM–12 noon)</th>
<th>Nighttime (12 midnight–4 AM)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time domain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RR interval</td>
<td>770±128</td>
<td>904±157</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4-Hour SDANN</td>
<td>82±43</td>
<td>43±21</td>
<td>0.0002</td>
</tr>
<tr>
<td>RMSSD</td>
<td>26±11</td>
<td>29±15</td>
<td>0.29</td>
</tr>
<tr>
<td>Frequency domain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-frequency power amplitude</td>
<td>11.2±5.3</td>
<td>14.4±7.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Low-frequency power amplitude</td>
<td>20.4±8.6</td>
<td>21.8±11.4</td>
<td>0.43</td>
</tr>
<tr>
<td>Total-frequency power amplitude</td>
<td>35.0±12.6</td>
<td>37.2±17.5</td>
<td>0.43</td>
</tr>
</tbody>
</table>

SDANN, SD of the 5-minute mean RR interval; RMSSD, root-mean-square successive difference of the RR interval. All data are expressed in milliseconds as mean±SD.

### Table 4. Univariate Cox Proportional Hazards Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison*</th>
<th>Relative risk: mortality</th>
<th>( p )</th>
<th>Relative risk: all events</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDANN</td>
<td>Decrease by 47 msec</td>
<td>107.3</td>
<td>0.0007</td>
<td>2.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Total-frequency power amplitude</td>
<td>Decrease by 16 msec</td>
<td>17.0</td>
<td>0.03</td>
<td>2.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Low-frequency power amplitude</td>
<td>Decrease by 11 msec</td>
<td>15.2</td>
<td>0.03</td>
<td>2.0</td>
<td>0.01</td>
</tr>
<tr>
<td>High-frequency power amplitude</td>
<td>Decrease by 8 msec</td>
<td>5.0</td>
<td>0.22</td>
<td>2.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Right ventricular ejection fraction</td>
<td>Decrease by 7%</td>
<td>16.3</td>
<td>&lt;0.0001</td>
<td>1.9</td>
<td>0.008</td>
</tr>
<tr>
<td>RMSSD</td>
<td>Decrease by 23 msec</td>
<td>1.5</td>
<td>0.64</td>
<td>1.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean RR interval</td>
<td>Decrease by 123 msec</td>
<td>**</td>
<td>**</td>
<td>1.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>Decrease by 10%</td>
<td>17.3</td>
<td>&lt;0.0001</td>
<td>1.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Complex ventricular ectopy</td>
<td>Present</td>
<td>1.6</td>
<td>0.70</td>
<td>1.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Age</td>
<td>Increase by 14 years</td>
<td>0.7</td>
<td>0.55</td>
<td>1.4</td>
<td>0.22</td>
</tr>
<tr>
<td>VPC density</td>
<td>Increase by 0.7 log units</td>
<td>1.9</td>
<td>0.31</td>
<td>1.3</td>
<td>0.21</td>
</tr>
</tbody>
</table>

SDANN, SD of the 5-minute mean RR interval; RMSSD, root-mean-square successive difference of the RR interval; VPC, ventricular premature contractions. Events include death from all causes (\( n = 3 \)) and mitral valve surgery (\( n = 17 \)).  
*Relative risk comparison is present/absent for the dichotomous variable; for the continuous variables, the comparison is between values differing by 1 SD from the mean.  
**Regression coefficient failed to converge. There were three patients with mean RR intervals \( \leq 621 \) msec; they represent all three patients who died during follow-up.

### Table 5. Multivariate Stepwise Cox Proportional-Hazards Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison</th>
<th>Relative risk for all events (with 95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDANN</td>
<td>Decrease by 47 msec</td>
<td>2.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Complex ventricular ectopy</td>
<td>Present</td>
<td>3.0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI, confidence interval; SDANN, SD of the 5-minute mean RR interval. Variables considered but excluded from the model: age, mean heart rate, left ventricular ejection fraction, right ventricular ejection fraction, ventricular premature contraction density, root-mean-square successive difference of the RR interval, low-frequency amplitude, high-frequency amplitude, and total-frequency amplitude. Global \( \chi^2 \) for multivariate model, 17.1; \( p = 0.0002 \). Events include death from all causes (\( n = 3 \)) or mitral valve surgery (\( n = 17 \)).
prognostic information \((p=0.02)\). The relations of heart rate variability and complex ventricular ectopy to adverse outcomes (death or mitral valve surgery) are shown in Figure 2.

By use of partition values for SDANN previously defined by Kleiger et al.\(^14\) the patients were divided into three groups. Group 1 was composed of patients with SDANN > 100 msec (“normal”), group 2 was composed of patients with SDANN between 50 and 100 msec (“reduced”), and group 3 was composed of patients with SDANN < 50 msec (“markedly reduced”). Unadjusted death and total event rates in the three groups are shown in Figure 3. The odds ratio for surgery or death was 6.1 \((p=0.007; 95\% \text{ CI}, 1.3–28.0)\) among patients with reduced or markedly reduced SDANN (groups 2 and 3) compared with the patients with normal SDANN (group 1). The actuarial 1-year event-free survival rate was 71\% among patients in group 2 or group 3 and 96\% among patients in group 1. Life-table curves for survival and event-free survival in the three groups are shown in Figures 4 and 5.

**Discussion**

**Prognostic Value of Heart Rate Variability**

Analysis of beat-to-beat variability in the heart rate during sinus rhythm provides a unique and noninvasive way to assess neurohumoral influences on the cardiovascular system.\(^{17,18}\) In this study of patients with non-ischemic causes of chronic severe mitral regurgitation, we found that measures of ultralow-frequency heart rate variability were moderately correlated with resting right and left ventricular ejection fractions and that the RR interval, ultralow-frequency heart rate variability,
and high-frequency heart rate variability all exhibited significant diurnal variation. Most important, heart rate and measures of ultralow-frequency (SDANN), low-frequency (low-frequency amplitude), and combined low- and high-frequency heart rate variability (total-frequency amplitude) predicted mortality as well as total events. In contrast, pure measures of high-frequency heart rate variability (high-frequency amplitude, RMSSD) did not correlate significantly with outcome. SDANN, a measure of ultralow-frequency heart rate variability, was the most potent prognostic indicator in this patient population and, in addition to predicting mortality and progression to valve surgery, also correlated with subsequent conversion from sinus rhythm to sustained atrial fibrillation.

These findings extend to patients with valvular heart disease observations that link ultralow-frequency heart rate variability to outcome in patients with ischemic heart disease. Previously, Kleiger and colleagues\(^{14}\) found reduced SDANN to be highly predictive of mortality in patients after myocardial infarction. Likewise, Bigger and colleagues\(^{15}\) found that although reductions in all of the frequency-domain measures of heart rate variability were predictive of mortality after myocardial infarction, measures of ultralow-frequency and very-low-frequency heart rate variability were the most strongly predictive. In patients who underwent cardiac catheterization for suspected coronary artery disease but without recent myocardial infarction, valvular heart disease, or nonischemic cardiomyopathy, Rich et al\(^{16}\) found that markedly reduced SDANN was also highly predictive of outcome. When a group of patients with a history of resuscitation from sudden cardiac death was compared with patients with complex ventricular ectopy who were noninducible by programmed ventricular stimulation, Myers et al\(^{16}\) found significant reductions in all measures of heart rate variability, including SDANN, among the sudden death group. In that setting, however, measures of high-frequency heart rate variability were found to have greater discriminatory power than low-frequency or ultralow-frequency measures. The present data also suggest that the presence of complex ventricular ectopy confers significant additional risk in patients with important mitral regurgitation after the effect of SDANN is accounted for. This is consistent with our previous observation of the prognostic importance of complex ventricular arrhythmias in an overlapping population.\(^{13}\)

**Measures of Heart Rate Variability**

Heart rate variability can be studied in the time domain through conventional statistical techniques (e.g., SDANN, RMSSD) or in the frequency domain through the more cumbersome technique of power spectral analysis (e.g., total-frequency amplitude, high-frequency amplitude, low-frequency amplitude). We found a high correlation between power spectral (high-frequency amplitude) and time-domain (RMSSD) measures of high-frequency heart rate variability (\(r=0.95\)). The study of ultralow-frequency fluctuations in the frequency domain is technically difficult because it requires long periods of ectopy-free data and lengthy computations.\(^{17,19}\) SDANN provides a time-domain measure of heart rate fluctuations on an ultralow-frequency scale. SDANN is calculated by taking the SD of the mean heart rates of the 288 five-minute periods that compose 24 hours. Thus, it is relatively insensitive to heart rate fluctuations occurring on time scales shorter than 5 minutes (0.0033 Hz). The mathematical relation between SDANN and the power spectrum is complex, because SDANN is a nonlinear measure. Myers et al\(^{16}\) analyzed this relation by transfer function analysis and found that SDANN behaves as a low-pass filter with a cutoff frequency of approximately 0.006 Hz. Therefore, the vast majority of “power” within SDANN is contained in the frequencies below 0.0033 Hz.

Experiments in human subjects\(^{20}\) and animal models\(^{17}\) have demonstrated that high-frequency heart rate fluctuations (with a center frequency of 0.224–0.28 Hz) reflect respiratory sinus arrhythmia and are mediated predominantly by the parasympathetic nervous system, whereas low-frequency fluctuations (0.042–0.12 Hz) represent a combined interaction of the sympathetic and parasympathetic nervous systems. However, the physiology underlying ultralow-frequency heart rate fluctuations is poorly understood. In view of the correlation between ultralow-frequency heart rate variability and low-frequency heart rate variability, it is likely that neurohumoral factors play a role, but the exact relation has yet to be described.

**Physiological Correlates and Diurnal Variation**

In these patients with severe mitral regurgitation, we found positive correlations between both resting left and right ventricular systolic performance and ultralow-frequency heart rate variability. In contrast, the measures of low-frequency and high-frequency heart rate variability were not significantly associated with ventricular performance. Previously, Saul et al\(^{21}\) described a reduction in heart rate power spectral content at all frequencies in a group of patients with severe symptomatic congestive heart failure caused by ischemic heart disease or idiopathic cardiomyopathy, and Casolo et al\(^{22}\) found patients with severe congestive heart failure to have a marked reduction in the mean hourly SD of the RR interval. These observations are consistent with the prognostic importance of chronic neurohumoral activation in patients with functionally significant chronic impairment of ventricular function\(^{23}\); regardless of cause, sympathetic stimulation may result in reduced heart rate variability.

Previous studies of normal subjects have described significant circadian variations in overall heart rate variability and in low-frequency and high-frequency heart rate variability. Huikuri et al\(^{24}\) noted that the SD of the RR interval is greatest in the early morning hours and falls abruptly after waking. Saposnikov et al\(^{25}\) reported a significant daytime decrease in a low-frequency spectral peak occurring between 0.003 and 0.05 Hz and a high-frequency spectral peak occurring between 0.20 and 0.35 Hz as well as a significant daytime increase in a “midfrequency” spectral peak occurring between 0.05 and 0.20 Hz. Casolo et al\(^{26}\) observed no circadian variation in low-frequency heart rate variability among normal volunteers but did find a significant daytime increase in a high-frequency spectral peak occurring between 0.22 and 0.32 Hz. These authors found no diurnal variation in any measure of heart rate variability in a group of patients with coronary artery disease and symptomatic congestive heart failure. We
also found significant diurnal variation in high-frequency heart rate variability. However, the magnitude of this variation was not related to ventricular performance. The magnitude of the day-night variation in high-frequency heart rate variability that we observed in patients with chronic severe nonischemic mitral regurgitation was similar to that previously reported for normal subjects (=1:2 in power units, corresponding to =1:1.4 in amplitude units25-26). Since high-frequency heart rate variability can be considered to be a measure of cardiac parasympathetic tone, this suggests that the ability to modulate vagal tone dynamically is preserved in the setting of chronic mitral regurgitation.

We are not aware of any previous analyses of the diurnal variability of ultralow-frequency heart rate variability. When we analyzed 4-hour SDANN measurements, we observed a dramatic increase from nighttime to daytime in the 4-hour SDANN values. Furthermore, these 4-hour SDANN measurements were considerably lower than the 24-hour SDANN, and the 24-hour SDANN was significantly correlated with the magnitude of diurnal variability in the RR interval. The first observation suggests that SDANN in part reflects variations in the heart rate present during daily activity but absent during sleep, and the second suggests that, in addition, SDANN is influenced by circadian variability in the RR interval.

Several explanations may thus account for the observed inverse association between ultralow-frequency heart rate variability and prognosis in chronic severe mitral regurgitation. First, as the 4-hour SDANN measurements suggest, reduced ultralow-frequency heart rate variability over 24 hours may reflect an interaction between reduced daytime physical activity associated with severe symptoms and advanced disease and persistent neurohumoral stimulation of the heart rate at night. Second, as suggested by the observed relation between SDANN and ejection fraction, reductions in ultralow-frequency heart rate variability may serve to identify those patients with functionally significant impairment of ventricular performance. Alternatively, both SDANN and ventricular performance might vary with other factors. Although chronic sympathetic activation25 might represent such an additional factor, the relation between SDANN and neurohumoral tone has yet to be firmly established. Finally, the associations between the use of vasodilator drugs, diuretics, ultralow-frequency and low-frequency heart rate variability, and ventricular performance suggest that SDANN could be directly affected by drugs in this population. However, these associations might reflect more severe mitral regurgitation in patients receiving these agents.

Limitations

The present study has several limitations. First, the sample size is relatively small, and validation in a larger set is required. Second, although measurement of the variability of the ventricular response in patients with atrial fibrillation is feasible, this would measure function of the atrioventricular node rather than the sinoatrial node, and results would not be directly analogous to results in patients with sinus rhythm. This led to the exclusion of patients with mitral regurgitation and atrial fibrillation from this study, patients who compose a large subset of the population with severe mitral regurgitation and who are at high risk in comparison with patients with sinus rhythm. Third, although SDANN, the measure of ultralow-frequency heart rate variability, was the most potent prognostic indicator in this population, other measures of heart rate variability were also significantly related to prognosis; the study does not have sufficient power to test for statistically significant differences in performance among the different variables. Furthermore, although SDANN performed better than the other variables that we measured, it is only one of many possible measures of ultralow-frequency heart rate variability, and we cannot conclude from this study that SDANN is the best of all possible measures of ultralow-frequency heart rate variability. Last, the study does not enable us to define the mechanisms that link heart rate variability and outcome in mitral regurgitation. Despite these limitations, the findings suggest that analysis of heart rate variability may improve our understanding of the neurohumoral changes that accompany chronic nonischemic mitral regurgitation and that measures of ultralow-frequency heart rate variability may provide significant prognostic information for these patients.

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