Frequency Domain Measures of Heart Period Variability and Mortality After Myocardial Infarction

J. Thomas Bigger Jr., MD; Joseph L. Fleiss, PhD; Richard C. Steinman, AB; Linda M. Rolnitzky, AB, MS; Robert E. Kleiger, MD; and Jeffrey N. Rottman, MD

Background. We studied 715 patients 2 weeks after myocardial infarction to establish the associations between six frequency domain measures of heart period variability (HPV) and mortality during 4 years of follow-up.

Methods and Results. Each measure of HPV had a significant and at least moderately strong univariate association with all-cause mortality, cardiac death, and arrhythmic death. Power in the lower-frequency bands—ultra low frequency (ULF) and very low frequency (VLF) power—had stronger associations with all three mortality end points than power in the higher-frequency bands—low frequency (LF) and high frequency (HF) power. The 24-hour total power also had a significant and strong association with all three mortality end points. VLF power was the only variable that was more strongly associated with arrhythmic death than with cardiac death or all-cause mortality. In multivariate Cox regression models using a step-up approach to evaluate the independent associations between frequency domain measures of heart period variability and death of all causes, ULF power was selected first (i.e., was the single component with the strongest association). Adding VLF or LF power to the Cox regression model significantly improved the prediction of outcome. With both ULF and VLF power in the Cox regression model, the addition of the other two components, LF and HF power, singly or together, did not significantly improve the prediction of all-cause mortality. We explored the relation between the heart period variability measures and all-cause mortality, cardiac death, and arrhythmic death before and after adjusting for five previously established postinfarction risk predictors: age, New York Heart Association functional class, rales in the coronary care unit, left ventricular ejection fraction, and ventricular arrhythmias detected in a 24-hour Holter ECG recording.

Conclusions. After adjustment for the five risk predictors, the association between mortality and total, ULF, and VLF power remained significant and strong, whereas LF and HF power were only moderately strongly associated with mortality. The tendency for VLF power to be more strongly associated with arrhythmic death than with all-cause or cardiac death was still evident after adjusting for the five covariates. Adding measures of HPV to previously known predictors of risk after myocardial infarction identifies small subgroups with a 2.5-year mortality risk of approximately 50%. (Circulation 1992;85:164–171)

We showed previously that the standard deviation of normal RR intervals (SDNN) computed over 24 hours predicts all-cause mortality after myocardial infarction independently of the major risk factors identified by the Multicenter Post-Infarction Program (MPIP) (i.e., New York Heart Association functional class, pulmonary rales in the coronary care unit phase of the infarction, radionuclide left ventricular ejection fraction, and frequency of ventricular arrhythmias).1

From the Division of Cardiology (J.T.B. Jr., J.L.F., R.C.S., L.M.R.), Department of Medicine, and the Division of Biostatistics, School of Public Health, Columbia University, New York, N.Y.; and the Jewish Hospital of St. Louis (R.E.K., J.N.R.), Washington University School of Medicine, St. Louis, Mo.

Supported in part by National Institutes of Health grants HL-41552 and HL-70204 from the National Heart, Lung, and Blood Institute, Bethesda, Md., and RR-00645 from the Research Resources Administration; and by funds from The Milstein Family Foundation, The Dover Foundation, George and Abby O'Neil, Robert Winthrop, and the Shirley and Henry Bench Foundation, New York, N.Y.

Address for reprints: J. Thomas Bigger Jr., MD, Columbia University, P85 9-445, 630 West 168th Street, New York, N.Y. 10032.

Received February 22, 1991; revision accepted August 27, 1991.
Other measures of heart period variability have been studied as predictors of mortality, but none has been validated in a large study.\textsuperscript{2–4} Measures derived from power spectral analysis of heart period variability are especially attractive candidates for predictors of mortality after myocardial infarction because certain frequency bands of the heart period power spectrum have been associated with autonomic nervous system control of sinus node period.\textsuperscript{5,6} These measures therefore have the potential to provide insight into the mechanisms of death as well as to predict mortality.

The purpose of the present study was to establish the associations between mortality and several frequency domain measures of heart period variability present in a 24-hour ECG recording 2 weeks after myocardial infarction. We explored the relation between the heart period variability measures and all-cause mortality, cardiac death, and arrhythmic death before and after adjusting for previously established postinfarction risk predictors. We selected frequency domain variables for our analyses because these variables comprise a mutually exclusive, all-inclusive categorization of heart period variability and because they provide insight into pathophysiology.

**Methods**

**Study Design**

To measure heart period variability after myocardial infarction, we reanalyzed the 24-hour continuous ECG recordings from the MPIP, a multicenter, natural history study.\textsuperscript{7} The details of enrollment, measurement of baseline variables, quality control procedures, and follow-up have been described previously.\textsuperscript{7,8} We selected the MPIP sample of patients for the present study because it was evaluated in a longitudinal epidemiological study designed to relate measures of left ventricular function, arrhythmia, and residual ischemia soon after myocardial infarction to mortality during follow-up. MPIP enrolled its 867 patients from diverse geographies and categories of hospital. All patients with recent myocardial infarction who were less than 70 years old were eligible (i.e., the study did not suffer from the enrollment restrictions that render the placebo-treated groups in intervention trials biased samples of the general population of patients after myocardial infarction). The MPIP sample is representative of the general population of patients with recent infarction in the United States at the time the sample was collected.

**Processing of 24-Hour Holter Recordings**

We retrieved the tape or cassette recordings from the MPIP Data Coordinating Center and attempted to reprocess all of these recordings using recently described methods.\textsuperscript{9,10} Briefly, the 24-hour recordings were digitized by a Marquette 8000 scanner and submitted to the standard Marquette algorithms for QRS labeling and editing (version 5.7 software). Then, the data files were transferred via high-speed link from the Marquette scanner to a Sun workstation where a second stage of editing was done, using algorithms developed at Columbia University, to find and correct any remaining errors in QRS labeling that adversely affect measurement of heart period variability. For a tape to be eligible for the present study, we required it to have 12 hours or more of analyzable data and to have at least half of the night-time (12:00 midnight through 5:00 AM) and daytime (7:30 AM through 11:30 PM) periods analyzable. At least 50% had to be sinus rhythm. We excluded 152 patients from the analysis of heart period variability because of missing or inadequate Holter recordings or because the tapes had deteriorated after 10 years of storage.

**Time Series Analysis of Normal RR Intervals**

After the second stage of editing and review of the results by a cardiologist, the heart period power spectrum was computed over a 24-hour interval using a method first described by Albrecht et al.\textsuperscript{9} Our adaptation of the method was described by Rottman et al.\textsuperscript{10} First, a regularly spaced time series was derived from the RR intervals by sampling the irregularly spaced series defined by the succession of normal RR intervals. For each 24-hour ECG recording, \textsuperscript{218} points were sampled at an interval of 329 msec. A "boxcar" low-pass filter with a window twice the sampling interval was then applied. Gaps in the time series resulting from noise or ectopic beats were filled in with linear splines. A fast Fourier transform was computed, and the resulting power spectrum was corrected for the attenuating effects of both the filter and the sampling.\textsuperscript{9} The effective frequency range for this method is from \(1.1574\times10^{-5}\) Hz to \(>0.40\) Hz (periods of seconds to hours) if the recording is 24 hours long. Finally, frequency domain measures of heart period variability were computed by integrating over their frequency intervals (e.g., \(0.04–0.15\) Hz for low- and \(0.15–0.40\) Hz for high-frequency [LF and HF] power). In addition, we computed LF and HF power for all 715 recordings using our 5-minute method and obtained results virtually identical to the 24-hour in toto method.\textsuperscript{10}

**Frequency Domain Measures of Heart Period Variability**

Six frequency domain measures were calculated from spectral analysis of heart period data over a 24-hour interval. We computed the 24-hour power spectral density and calculated the power within four frequency bands: 1) \(<0.0033\) Hz, ultra low frequency (ULF) power; 2) \(0.0033\) to \(<0.04\) Hz, very low frequency (VLF) power, which shows a relative increase in patients with congestive heart failure\textsuperscript{11} and is the lowest-frequency band that can be estimated by our 5-minute method\textsuperscript{10}; 3) \(0.04\) to \(<0.15\) Hz, LF power, which reflects modulation of sympathetic or parasympathetic tone by baroreflex activity\textsuperscript{12}; and 4) \(0.15–0.40\) Hz, HF power, which reflects modulation of vagal tone, primarily by breathing.\textsuperscript{13,14} In addition, we calculated total power (power in the band, \(\leq 0.40\)
Hz) and the ratio of LF to HF power, a measure that has been used as an indicator of sympathovagal balance.6 High values for the ratio suggest predominance of sympathetic nervous activity. The 24-hour ECG recordings were digitized without benefit of phase lock loop; therefore, flutter and wow could cause small (<4%) increases in HF power (0.15–0.40 Hz).

Mortality End Points
We estimated the association between the six measures of heart period variability and three mortality end points: death from all causes, cardiac death, and arrhythmic death by the Hinkle-Thaler definition.15

Survival Analytic Methods
We calculated Kaplan-Meier survival functions16 to display graphically the survival experience of the MPIP sample of patients over a 3-year interval of time and to tabulate survival rates up to a prespecified time, 2.5 years. We performed Cox proportional hazards analyses17 when testing hypotheses about the association between one or more risk predictors and mortality. The Cox analysis also provides a measure of association, the hazard ratio, that is not linked to a single time point. The P2L BMDP computer program was used to carry out the Cox survival analyses.18 This program permits categorical and continuous predictor variables to be analyzed together. The Cox proportional hazards model produces estimates of the independent effects of each of several predictor variables on survival.17 The hazard function (i.e., the instantaneous probability of dying at any point in time) is assumed in the Cox model to be proportional to the exponential function \( \exp(\Sigma B_i X_i) \), where the \( B_i \)s are the regression coefficients and the \( X_i \)s are the values of the predictor variables. The values of the regression coefficients are assumed to remain constant over time, and each \( \exp(B_i) \) is interpretable as a relative risk for variable \( i \): \( \exp(B_i) \) is the ratio of instantaneous probabilities of dying for patients with values of \( X_i \) 1 unit apart, holding all other variables constant.

Dichotomizing the Measures of Heart Period Variability
For ease of communication as well as for eventual clinical use, we dichotomized the six measures of heart period variability when estimating their association with mortality. For each, we sought the dichotomization point that maximized the hazard ratio from a Cox regression model17 for comparing patients below the cutpoint (expected to be at high risk) with those at or above it (expected to be at low risk). Given our knowledge of optimal cutpoint for other measures and given the need for adequate numbers of patients for testing hypotheses, we restricted our search to dichotomizations in the interval between 10% low–90% high and 35% low–65% high. We calculated the hazard ratio for each possible dichotomization point within this interval (unadjusted for any covariates), identified the point at which the hazard ratio attained its maximum, and then rounded to the nearest multiple of 5, 10, or 100.

Univariate Association Between Measures of Heart Period Variability and Mortality
For tabulating Kaplan-Meier mortality rates, we specified mortality at 2.5 years of follow-up, a time when about 20 patients were still at risk in the smallest subgroup. Graphs of the Kaplan-Meier survival rates were drawn up to 3 years of follow-up. For Cox regression analyses and for analyses of hazard ratios, we used all of the follow-up experience. To determine whether each of the six measures of heart period variability was significantly associated with mortality and to estimate the relative strengths of association, we evaluated each measure separately, after dichotomization, in a Cox proportional hazards survival model.17 When mortality of all causes was the end point, patients were included in the analysis as long as their survival status was known. In analyses of cause-specific mortality, patients who died of other causes were censored when they died.

Multivariate Association Between Frequency Domain Measures of Heart Period Variability and Mortality
Four frequency domain measures—ULF, VLF, LF, and HF power—provide an all-inclusive and mutually exclusive description of heart period variability. The multivariate association between these four measures and mortality was evaluated in a step-up Cox regression analysis. The variable with the strongest association with mortality entered the model first. Then, each of the remaining three variables was evaluated to determine whether it significantly improved the fit. If so, it was added to the model. This process was continued until additional variables did not improve the fit of the model at a significance level of 0.05.

Univariate Association Between Measures of Heart Period Variability and Mortality Adjusting for Previously Reported Postinfarction Risk Predictors
We used the Cox proportional hazards survival model to determine whether any of the various measures of heart period variability predicted mortality independently of five important postinfarction risk predictors that we previously found to be strongly associated with mortality. The measures of heart period variability were dichotomized to provide ease of interpretation, but the covariates were coded to provide the best-fitting model to predict mortality.8,19 Age was divided into three categories: <50, 50–59, ≥60 years. New York Heart Association functional class was dichotomized at class I or II versus III or IV. Rales were dichotomized at none or basilar versus greater than basilar. Left ventricular ejection fraction was coded on a four-interval scale in accordance with the relation between ejection fraction and mortality: <0.20, 0.20–0.29, 0.30–0.39, and ≥0.40. The average frequency of ventricular premature complexes also was coded on a four-interval
TABLE 1. Frequency Domain Measures of Heart Period Variability: Cutoff Points Used for Analysis of All-Cause Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cutpoint</th>
<th>Percent below cutpoint</th>
<th>Below cutpoint</th>
<th>At or above cutpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>Kaplan-Meier 2.5 year mortality rate (%)</td>
</tr>
<tr>
<td>Ultra low frequency power</td>
<td>1,600</td>
<td>10.1</td>
<td>72</td>
<td>42.5</td>
</tr>
<tr>
<td>Very low frequency power</td>
<td>180</td>
<td>11.9</td>
<td>85</td>
<td>41.0</td>
</tr>
<tr>
<td>Low frequency power</td>
<td>35</td>
<td>12.2</td>
<td>87</td>
<td>34.8</td>
</tr>
<tr>
<td>High frequency power</td>
<td>20</td>
<td>11.7</td>
<td>84</td>
<td>30.4</td>
</tr>
<tr>
<td>Total power</td>
<td>2,000</td>
<td>10.9</td>
<td>78</td>
<td>41.2</td>
</tr>
<tr>
<td>Low-to-high frequency ratio</td>
<td>0.95</td>
<td>15.4</td>
<td>110</td>
<td>32.1</td>
</tr>
</tbody>
</table>

n=715.

scale: none, more than none but less than three per hour, three or more but less than 10 per hour, and 10 or more per hour.

We ran the Cox model twice for each of the six measures of heart period variability, once with the measure of heart period variability alone and then together with the full set of covariates. Statistical significance was assessed by referring Z, the estimated regression coefficient Bi, divided by its standard error, to the standard normal distribution. The strength of association between measures of heart period variability and the mortality end points was evaluated using \( \exp(B_i) \), which can be interpreted as a relative risk for variable \( i \).

Results

Risk Based on Dichotomized Measures of Heart Period Variability

Table 1 lists the six variables we evaluated, their optimum cutoff points, the numbers of patients in the groups categorized as having low or high values for the variable, and the Kaplan-Meier 2.5-year all-cause mortality rates for the two groups. The fractions of total power contributed by the components were ULF power, 82±8%; VLF power, 12±6%; LF power, 4±3%; and HF power, 2±2%. Figure 1 shows Kaplan-Meier cumulative 3-year survival curves for each of the four mutually exclusive frequency domain measures using death of all-causes as the end point.

Univariate Association Between Measures of Heart Period Variability and All-Cause or Cause-Specific Mortality

Table 2 lists, for each measure of heart period variability, the Z scores and relative risks for three mortality end points determined using Cox regression analysis unadjusted for any covariates: death from all causes, cardiac death, and arrhythmic death. The measures of heart period variability were dichotomized as shown in Table 1. Each measure had a significant \( p<0.05 \) and strong (hazard ratio \( \geq 2 \)) univariate association with each of the mortality end points. Power in the lower-frequency bands (ULF and VLF power) had stronger associations with all three mortality end points than power in the higher-frequency bands (LF and HF power). The 24-hour total power also had a significant and strong association with all three mortality end points. Interestingly, VLF power showed a gradient of association with the classification of mortality (i.e., it was most strongly associated with arrhythmic death, slightly less so with cardiac death, and least with all-cause mortality).

Multivariate Association Between Frequency Domain Measures of Heart Period Variability and Mortality

In multivariate Cox regression models using a step-up approach to evaluate the independent association of the four mutually exclusive frequency domain measures of heart period variability with death of all causes, ULF power was selected first (i.e., was the single component with the strongest association). Adding VLF or LF power to the Cox

![Figure 1. Kaplan-Meier survival curves for 715 patients in the high or low category for the four mutually exclusive frequency domain measures of heart period variability—ultra low frequency (ULF), very low frequency (VLF), low frequency (LF), and high frequency (HF) powers—using all-cause mortality as the end point. The number of patients at the start of follow-up and the patients known to be alive and being followed after 1, 2, and 3 years were high ULF, 643, 388, 542, 244; low ULF, 72, 54, 44, 24; high VLF, 630, 584, 538, 240; low VLF, 85, 58, 48, 22; high LF, 628, 579, 533, 244; low LF, 87, 63, 53, 18; high HF, 631, 573, 525, 243; and low HF, 84, 69, 61, 19.](image-url)
TABLE 2. Frequency Domain Measures of Heart Period Variability: Unadjusted Association With All-Cause, Cardiac, and Arrhythmic Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>All causes (119 deaths)</th>
<th>Cardiac (88 deaths)</th>
<th>Arrhythmic (68 deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z*  Relative risk†</td>
<td>Z*  Relative risk†</td>
<td>Z*  Relative risk†</td>
</tr>
<tr>
<td>Ultra low frequency power</td>
<td>6.95  4.4</td>
<td>5.84  4.3</td>
<td>4.93  4.2</td>
</tr>
<tr>
<td>Very low frequency power</td>
<td>7.14  4.3</td>
<td>6.57  4.7</td>
<td>5.81  4.8</td>
</tr>
<tr>
<td>Low frequency power</td>
<td>5.61  3.3</td>
<td>4.73  3.3</td>
<td>4.51  3.6</td>
</tr>
<tr>
<td>High frequency power</td>
<td>4.06  2.5</td>
<td>3.62  2.6</td>
<td>2.86  2.4</td>
</tr>
<tr>
<td>Total power</td>
<td>6.79  4.1</td>
<td>5.47  3.9</td>
<td>4.54  3.7</td>
</tr>
<tr>
<td>Low-to-high frequency ratio</td>
<td>5.35  3.1</td>
<td>4.67  3.1</td>
<td>4.29  3.3</td>
</tr>
</tbody>
</table>

n=715.
*Z≥1.96, p<0.05; Z≥2.58, p<0.01; Z≥3.30, p<0.001.
†Relative risk, probability of dying if below the cutpoint/probability of dying if above the cutpoint.

regression model with ULF power already in significantly improved the prediction of outcome. With both ULF and VLF power in the Cox regression model, the addition of the other two components, LF and HF power, singly or together, did not significantly improve the prediction of all-cause mortality.

Univariate Association Between Measures of Heart Period Variability and Mortality Adjusting for Previously Reported Postinfarction Risk Predictors

Figure 2 shows survival curves for the four mutually exclusive frequency domain components of total power calculated using the Cox regression method before and after adjusting for the five covariates. The 673 patients who had an adequate Holter recording and measurements on all five covariates were included in these analyses. Table 3 lists, for each measure of heart period variability, the Z scores and relative risks for the three mortality end points, determined using Cox regression analysis to adjust for the five risk predictor covariates. Measures of heart period variability were dichotomized as shown in Table 1. After adjustment, some of the variables were no longer significantly associated with mortality. The association between mortality and total, ULF, and VLF power remained significant and strong, whereas LF and HF power were only moderately strongly associated with mortality after adjustment. The tendency for VLF power to be more strongly associated with arrhythmic death than with all-cause or cardiac death was still evident after adjusting for the five covariates.

Combining Risk Predictors to Identify High-Risk Groups

ULF and VLF powers were strongly associated with mortality after adjustment for important covariates, suggesting that these two variables would improve predictive accuracy when combined with other risk predictors. Table 4 shows that low ULF or low VLF power individually had better positive predictive accuracy (measured as a 2.5-year Kaplan-Meier mortality rate) (i.e., each about 40%) than low left ventricular ejection fraction (dichotomized at 0.40) or high rate of ventricular premature complexes (dichotomized at three per hour) (i.e., each about 25%). In fact, either low ULF or low VLF power alone had better positive predictive accuracy than low left ventricular ejection fraction.
TABLE 3. Frequency Domain Measures of Heart Period Variability: Association With All-Cause, Cardiac, and Arrhythmic Mortality, Adjusted for Age, New York Heart Association Class, Rales in Coronary Care Unit, Left Ventricular Ejection Fraction, and Ventricular Arrhythmias

<table>
<thead>
<tr>
<th>Variable</th>
<th>All causes (112 deaths)</th>
<th>Cardiac (84 deaths)</th>
<th>Arrhythmic (64 deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z*</td>
<td>Relative risk†</td>
<td>Z*</td>
</tr>
<tr>
<td>Ultra low frequency power</td>
<td>3.49</td>
<td>2.3</td>
<td>2.98</td>
</tr>
<tr>
<td>Very low frequency power</td>
<td>3.23</td>
<td>2.1</td>
<td>3.00</td>
</tr>
<tr>
<td>Low frequency power</td>
<td>1.89</td>
<td>1.6</td>
<td>1.51</td>
</tr>
<tr>
<td>High frequency power</td>
<td>2.14</td>
<td>1.7</td>
<td>1.92</td>
</tr>
<tr>
<td>Total power</td>
<td>3.16</td>
<td>2.1</td>
<td>2.36</td>
</tr>
<tr>
<td>Low–to–high frequency ratio</td>
<td>2.41</td>
<td>1.7</td>
<td>2.21</td>
</tr>
</tbody>
</table>

n=673.

*Z≥1.96, p<0.05; Z≥2.58, p<0.01; Z≥3.30, p<0.001.

†Relative risk, instantaneous probability of dying if below the cutoff point/instantaneous probability of dying if above the cutoff point.

fraction and high ventricular premature complexes together. Together, low ULF and low VLF power (power <0.04 Hz) had a positive predictive accuracy of almost 50%; combined with low left ventricular ejection fraction, high ventricular premature complexes, or both, they had a positive predictive accuracy of more than 50%. It should be noted that the 95% confidence intervals around the point estimates for positive predictive accuracy are relatively wide. The sensitivity, specificity, and positive predictive accuracy columns in Table 4 all pertain to deaths of all causes within 2.5 years of follow-up. These values would change if the follow-up interval were different.

**Discussion**

*Measures of Heart Period Variability as Risk Predictors After Myocardial Infarction*

A previous analysis of this data set using SDNN as the only measure of heart period variability found that it was significantly associated with mortality of all causes, independently of other postinfarction risk predictors. Because SDNN is virtually identical to the square root of total power in a 24-hour heart period power spectrum, the association of total power with death was expected. Previous studies (all relatively small) suggested that other measures of heart period variability, such as HF power or the SDRR index, might predict sudden cardiac death better than SDNN. Myers et al compared the 24-hour ECG recordings of six patients who survived cardiac arrest and were inducible by programmed ventricular stimulation with 12 control patients and suggested that power in the 0.15–0.50-Hz range separated the two groups substantially better than power in the 0.0167–0.15-Hz range. Cripps et al studied a series of 177 consecutive patients with myocardial infarction and found that SDRR index

TABLE 4. Sensitivity, Specificity, Positive Predictive Accuracy* Using Measures of Heart Period Variability Alone or Combined With Other Risk Predictors

<table>
<thead>
<tr>
<th>Predictors defining risk group</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive accuracy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>227</td>
<td>0.58</td>
<td>0.71</td>
<td>0.26 (0.20, 0.32)</td>
</tr>
<tr>
<td>VPC</td>
<td>201</td>
<td>0.48</td>
<td>0.73</td>
<td>0.24 (0.18, 0.30)</td>
</tr>
<tr>
<td>ULF</td>
<td>69</td>
<td>0.28</td>
<td>0.93</td>
<td>0.41 (0.29, 0.53)</td>
</tr>
<tr>
<td>VLF</td>
<td>78</td>
<td>0.30</td>
<td>0.92</td>
<td>0.39 (0.28, 0.51)</td>
</tr>
<tr>
<td>EF, VPC</td>
<td>94</td>
<td>0.32</td>
<td>0.89</td>
<td>0.34 (0.24, 0.44)</td>
</tr>
<tr>
<td>VPC, ULF</td>
<td>28</td>
<td>0.11</td>
<td>0.97</td>
<td>0.40 (0.22, 0.58)</td>
</tr>
<tr>
<td>VPC, VLF</td>
<td>30</td>
<td>0.13</td>
<td>0.97</td>
<td>0.44 (0.26, 0.62)</td>
</tr>
<tr>
<td>EF, ULF</td>
<td>41</td>
<td>0.20</td>
<td>0.96</td>
<td>0.48 (0.32, 0.64)</td>
</tr>
<tr>
<td>EF, VLF</td>
<td>45</td>
<td>0.22</td>
<td>0.96</td>
<td>0.49 (0.34, 0.65)</td>
</tr>
<tr>
<td>ULF, VLF</td>
<td>41</td>
<td>0.20</td>
<td>0.96</td>
<td>0.48 (0.32, 0.64)</td>
</tr>
<tr>
<td>VPC, ULF, VLF</td>
<td>15</td>
<td>0.08</td>
<td>0.98</td>
<td>0.53 (0.28, 0.79)</td>
</tr>
<tr>
<td>EF, VPC, ULF</td>
<td>20</td>
<td>0.08</td>
<td>0.98</td>
<td>0.41 (0.19, 0.63)</td>
</tr>
<tr>
<td>EF, VPC, VLF</td>
<td>22</td>
<td>0.10</td>
<td>0.98</td>
<td>0.46 (0.25, 0.67)</td>
</tr>
<tr>
<td>EF, ULF, VLF</td>
<td>26</td>
<td>0.14</td>
<td>0.98</td>
<td>0.56 (0.36, 0.75)</td>
</tr>
<tr>
<td>EF, VPC, ULF, VLF</td>
<td>12</td>
<td>0.06</td>
<td>0.99</td>
<td>0.50 (0.22, 0.78)</td>
</tr>
</tbody>
</table>

EF, left ventricular ejection fraction <0.40; VPC, ventricular premature complexes of three or more per hour; VLF, very low frequency power (0.0033–0.04 Hz) <180 msec; ULF, ultra low frequency power (<0.0033 Hz) <1,600 msec. *Kaplan-Meier estimate of all-cause mortality at 2.5 years of follow-up (numbers in parentheses are 95% confidence intervals).
predicted arrhythmic events (sudden cardiac death or nonfatal sustained ventricular tachycardia) better than SDNN. In this study, we explored the capability of various measures of heart period variability to predict not only mortality from all causes but also cardiac and arrhythmic death. We found that ULF and VLF power were excellent univariate predictors of mortality and also predicted mortality independently of five important postinfarction risk predictors: age, New York Heart Association functional class, rales in the coronary care unit, left ventricular ejection fraction, and ventricular arrhythmias detected in a 24-hour Holter ECG recording. LF and HF power were good univariate predictors of mortality but did not add much to the risk prediction of the five covariates. The ratio of LF to HF power was a good univariate predictor of mortality but was only a modest predictor after adjusting for the five covariates used in this study. Thus, in contrast to Myers et al, we found that VLF information (<0.04 Hz) predicted death after myocardial infarction better than higher-frequency information (≥0.04 Hz).

VLF power had an interesting relation with arrhythmic death both before and after adjustment (i.e., stronger associations with arrhythmic death than with all-cause mortality or cardiac death), relations that the other measures of heart period variability did not have. This is a potentially important finding because variables that specifically predict arrhythmic death have not been identified previously. Accordingly, this pattern should be validated in other data sets.

Effects of Dichotomizing Measures of Heart Period Variability

The Z values for all-cause mortality in Table 2 are slightly inflated and the corresponding significance levels are slightly overstated because the cutoff points were chosen to maximize the relative risks for mortality of all causes. The rank orderings of the relative risks are minimally affected by the procedure, however, as are the Z values and associated p values for death due to cardiac and arrhythmic causes. Furthermore, the use of cutoff points that were optimal made our identification of the weak risk predictors almost certainly correct. As dichotomized, LF power, HF power, and LF-to-HF ratio were only modestly strong risk predictors after adjustment for the five covariates. They would have been found to be even weaker risk predictors had other, suboptimal, cutoff points been used.

Mechanistic Implications of the Associations Between Measures of Heart Period Variability and Mortality After Myocardial Infarction

HF power is a pure measure of the modulation of vagal tone by respiratory frequency and depth. LF power is a measure of the modulation of vagal and sympathetic tone by baroreflex activity. Together, HF and LF powers account for only about 6% of the total power in a 24-hour heart period power spectrum. There is good evidence from animal experiments that individuals with greater baroreflex sensitivity after myocardial infarction have a lower prevalence of ventricular fibrillation during ischemia induced during exercise. The association of HF power with death is concordant with these findings. However, in a preliminary study, we showed that the strength of the correlation between baroreflex sensitivity and measures of vagal tone was only moderate. Thus, it is possible that HF power and baroreflex sensitivity will have independent predictive power after myocardial infarction.

Although ULF and VLF power together account for more than 90% of the total power in a 24-hour heart period power spectrum, the physiological mechanisms for these two components have not been identified. The large fraction of a 24-hour power spectrum comprised by frequencies below 0.04 Hz was previously reported. These researchers pointed out that spectral density increased logarithmically as frequency decreased, accounting for the large fraction of a 24-hour power spectrum contributed by LF components. Hypotheses about the processes modulating ULF and VLF powers of the heart period power spectrum include temperature regulation and fluctuations in activity of the renin-angiotensin system. It will be interesting and important to determine the source of ULF and VLF power because these components of the heart period power spectrum are such powerful, independent predictors of mortality. A better understanding of the origin of changes in these components could lead to hypotheses about interventions aimed at improving survival.

Combining Risk Predictors to Identify High-Risk Groups After Myocardial Infarction

When measures of heart period variability are used together with other predictors of risk after myocardial infarction (e.g., left ventricular ejection fraction and ventricular arrhythmias detected by Holter recordings), small groups can be identified with risk approaching 50% mortality in 2½ years. Such high-risk groups are candidates for aggressive treatment in an attempt to improve survival. The signal-averaged ECG is another important risk predictor in patients with recent myocardial infarction. Preliminary evidence suggests that the signal-averaged ECG predicts mortality independently of left ventricular ejection fraction and of the frequency of ventricular premature complexes detected in 24-hour ECG recordings. Unfortunately, there have been no large-scale, longitudinal studies to determine whether the signal-averaged ECG and one or more components of heart period variability provide independent prediction of arrhythmic events. Such studies are strongly indicated given the results of the present study. Also, the small, high-risk subgroups identified in this sample should be validated in another postinfarction sample before the findings are assumed to be generalizable.

Acknowledgments

The authors gratefully acknowledge the expert technical assistance of Bernard Glembocki, Paul
Gonzalez, Michael Fosina, Thomas Suarez, and Reidar Bornholdt.

References

KEY WORDS • nervous system, autonomic • electrocardiography • vagus nerves
Frequency domain measures of heart period variability and mortality after myocardial infarction.

J T Bigger, Jr, J L Fleiss, R C Steinman, L M Rolnitzky, R E Kleiger and J N Rottman

Circulation. 1992;85:164-171
doi: 10.1161/01.CIR.85.1.164

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/85/1/164