The Ability of Several Short-term Measures of RR Variability to Predict Mortality After Myocardial Infarction

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Background. **We studied 715 patients 2 weeks after myocardial infarction to test the hypothesis that short-term power spectral measures of RR variability (calculated from 2 to 15 minutes of normal RR interval data) will predict all-cause mortality or arrhythmic death.**

Methods and Results. **We performed power spectral analyses on the entire 24-hour RR interval time series. To compare with the 24-hour analyses, we selected short segments of ECG recordings from two time periods for analysis: 8 AM to 4 PM and midnight to 5 AM. The former corresponds to the time interval during which short-term measures of RR variability would most likely be obtained. The latter, during sleep, represents a period of increased vagal tone, which may simulate the conditions that exist when patients have a signal-averaged ECG recorded, ie, lying quietly in the laboratory. Four 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 three frequency bands: (1) 0.0033 to <0.04 Hz, very low frequency power, (2) 0.04 to <0.15 Hz, low frequency power, and (3) 0.15 to 0.40 Hz, high frequency power. In addition, we calculated the ratio of low to high frequency power. These measures were calculated for 15-, 10-, 5-, and 2-minute segments during the day and at night. Mean power spectral values from short periods during the day and night were similar to 24-hour values, and the correlations between short segment values and 24-hour values were strong (many correlations were ≥0.75). Using the optimal cutpoints determined previously for the 24-hour power spectral values, we compared the survival experience of patients with low values for RR variability in short segments of ECG recordings to those with high values. We found that power spectral measures of RR variability were excellent predictors of all-cause, cardiac, and arrhythmic mortality and sudden death. Patients with low values were 2 to 4 times as likely to die over an average follow-up of 31 months as were patients with high values. The power spectral measures of RR variability did not predict arrhythmic or sudden deaths substantially better than all-cause mortality.**

Conclusions. **Power spectral measures of RR variability calculated from short (2 to 15 minutes) ECG recordings are remarkably similar to those calculated over 24 hours. The power spectral measures of RR variability are excellent predictors of all-cause mortality and sudden cardiac death. (*Circulation.* 1993;88:927-934.)**

KEY WORDS • **myocardial infarction** • **RR interval**

Both time and frequency domain measures of RR variability calculated for a 24-hour period predict time to death after myocardial infarction.[1-6] Previous studies showed that RR variability, which is attributable to the activity of the sympathetic and parasympathetic nervous systems, can be characterized adequately in periods as short as 2 to 5 minutes.[7-9] However, it is not known whether short-term measures of RR variability can predict time to death after myocardial infarction. This study tested the hypotheses that short-term measures of RR variability (ie, over 2 to 15 minutes) will predict all-cause mortality or arrhythmic death. If this hypothesis is true, then short-term measures of RR variability can be incorporated into ECG or signal-averaged ECG machines to simplify identification of patients at high risk for sudden cardiac death.

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Methods

Population

For this study, we analyzed 24-hour continuous ECG recordings from 715 participants in the Multicenter Post Infarction Program (MPIP), a natural history study. The recruitment procedures, baseline characteristics, quality control procedures, and follow-up for MPIP have been described previously.[10,11] We selected the MPIP sample of patients for the present study because MPIP was a longitudinal natural history study designed to relate measures of left ventricular function, arrhythmia, and residual ischemia soon after myocardial infarction to mortality during follow-up. The 715 patients we studied had adequate 24-hour ECG recordings; these patients did not differ from patients with inadequate recordings with respect to important predictors of death (age, New York Heart Association class, rales in the

coronary care unit [CCU], left ventricular ejection fraction, frequency of ventricular premature complexes, and ventricular tachycardia) or mortality rates.

Processing of 24-Hour ECG Recordings

Twenty-four-hour recordings were made 11±3 days after myocardial infarction, a time when patients were still in hospital and sedentary except for short walks in hospital corridors. The 24-hour recordings were digitized by a Marquette 8000 Holter system and submitted to the standard Marquette algorithms for QRS labeling and editing (version 5.7 software). The data files then were transferred via high-speed link from the Marquette scanner to a Sun 4/75 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 measure of RR variability. For a tape to be eligible for this study, we required it to have 12 or more hours of analyzable data and to have at least half of the nighttime (midnight to 5 AM) and daytime (7:30 AM to 9:30 PM) periods analyzable. At least 50% had to be sinus rhythm.[6] The duration of analyzable ECG recordings was 22±1.9 hours, and 96% of the recordings had ≥18 hours of data.

Power Spectral Analysis

We selected ECG recordings from two time periods for analysis: 8 AM to 4 PM and midnight to 5 AM. The former corresponds to the time interval during which short-term measures of RR variability would most likely be performed. The latter, during sleep, was selected to represent a period of increased vagal tone to simulate the conditions that may exist when patients have signal-averaged ECG recorded, ie, lying quietly in the laboratory. For the day period, we selected a random 15-minute sample to analyze. For the night period, we selected the 15-minute period with the greatest average RR interval. Shorter segments (10, 5, or 2 minutes) were selected at random from within the 15-minute segments.

After editing was completed, the heart period power spectrum was computed over a 24-hour interval using a method first described by Albrecht and Cohen.[12] Our adaptation of the method was described by Rottman et al.[13] 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 24-hour ECG recordings, 2^{18} points were sampled; for 15-minute and 10-minute intervals, 2048 points were sampled; for 5-minute intervals, 1024 points were sampled; and for 2-minute intervals, 512 points were sampled. 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 by linear splining. A fast Fourier transform was computed, and the resulting power spectrum was corrected for the attenuating effects of both the filter and the sampling.[12] The effective lower end of the frequency range for this method was 1.16×10^{-5} for 24 hours; 1.11×10^{-2} Hz for 15 minutes; and 8.33×10^{-2} Hz for 2 minutes. For all time intervals, the upper end of the frequency range was 0.40 Hz. Frequency domain measures of RR variability were computed by integrating over their frequency intervals, eg, 0.04 to 0.15 Hz for low and 0.15 to 0.40 Hz for high frequency power and were expressed in units of milliseconds squared.

Frequency Domain Measures of RR Variability

Four frequency domain measures were calculated from spectral analysis of RR interval data for five time intervals: 24 hours and 15, 10, 5, and 2 minutes. We computed the 24-hour power spectral density and calculated the power (units of milliseconds squared) within three frequency bands: (1) 0.0033 to <0.04 Hz, very low frequency (VLF) power, (2) 0.04 to <0.15 Hz, low frequency (LF) power, and (3) 0.15 to 0.40 Hz, high frequency (HF) power.[5,13] In addition, we calculated the ratio of low to high frequency power.[5,9]

Statistical Procedures

The power spectral measures of RR variability were log transformed because their distributions were positively skewed. The data were summarized as the mean±SD of the log-transformed data. Differences between short-term and 24-hour data were evaluated using the paired t test on the log-transformed data. Product-moment correlations and linear regression equations were calculated between log-transformed values for 24-hour measures of RR variability and values based on shorter segments (15 minutes or less) selected at random during the day and deliberately during the night when normal RR intervals are long.

Mortality End Points

We estimated the association between the four measures of RR variability and four mortality end points: death from all causes, cardiac death, arrhythmic death as defined by Hinkle and Thaler,[14] and sudden cardiac death (<1 hour).

Survival Analytic Methods

We calculated Kaplan-Meier survival functions[15] in order to display graphically the survival experience of the MPIP sample of patients over a 3-year interval of time. Greenwood's formula for the standard error was used to construct confidence intervals for cumulative Kaplan-Meier mortality rates.[16]

We performed Cox proportional hazards analyses[17] when testing hypotheses about the association between one or more risk predictors and mortality. The Cox analysis also provides a measure of association, the relative risk, 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, ie, 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 in the model constant.

Dichotomizing the Measures of RR Variability

For ease of communication and analysis, we dichotomized the four measures of RR variability when estimating their association with mortality. For each measure, we used the dichotomization point previously determined to maximize the hazard ratio from a Cox regression model relating measures of RR variability calculated from 24 hours of RR interval data to all-cause mortality.[5] We compared the survival experience of patients below the cutpoint (expected to be at high risk) with that of patients at or above it (expected to be at low risk).

Association Between Measures of RR Variability and Mortality

Graphs of the Kaplan-Meier survival rates were drawn out 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 four measures of RR 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 at the time they died.

The jackknife. The jackknife procedure[19] was used to estimate the standard error of the difference, L, between two correlated log hazard ratios, L=ln(RR1)−ln(RR2), where RR1 and RR2 are the two relative risks being compared and where ln denotes natural logarithm. Under the hypothesis of equal population relative risks, L is expected to be 0. The reason that a nonstandard procedure such as the jackknife had to be used to estimate the standard error is that the hazard ratios were calculated on the same data set (that is, on the same sample of 715 patients) and therefore were correlated. No statistical package we are aware of estimates the standard error under such circumstances.

The jackknife procedure produces an estimate of the standard error of L by calculating L 715 times (in general, as many times as there are subjects in the sample). Each time, one of the 715 individuals is excluded from the analysis and the quantity L is calculated on the remaining 714 individuals. The 715 resulting values of L are combined with the original overall value to produce what are referred to as "pseudovalues," and the variability of the pseudovalues, finally, is used to estimate the standard error that permits a comparison of RR1 and RR2. Similarly, the jackknife was used to test for differences among correlation coefficients calculated on the same data set.

Results

Comparison of Mean Values for Power Spectral Measures of RR Variability Calculated for 24 Hours and for 2- to 15-Minute Segments of ECG Recordings

Table 1 lists the means and standard deviations for the log-transformed values for the four power spectral measures of RR variability. The mean logarithms for LF and HF power calculated from the nighttime segments were larger than the 24-hour values, and the values calculated from daytime segments were smaller. Conversely, the values for LF/HF ratio calculated from nighttime segments were smaller than the 24-hour values, and values calculated from the daytime segments were larger. VLF power did not show either of these daytime/nighttime patterns. The precision of the measures, as indicated by the standard deviations, was inversely proportional to the length of the segment from which the calculation was made. The mean logarithms of VLF, LF, HF, and LF/HF ratio for short segments were not meaningfully different from those calculated over 24 hours.

TABLE 1. Mean Values and Standard Deviations for Measures of RR Variability (n=715)

Record length	Power spectral measures in units of ln (milliseconds squared)			
	ln(VLF)	ln(LF)	ln(HF)	ln(LF/HF)
24-Hour	6.36±1.03	5.08±1.22	4.33±1.09	0.75±0.78
Night				
15 Min	6.26±1.40	5.14±1.43	4.55±1.29	0.59±1.07
10 Min	6.17±1.45	5.13±1.47	4.54±1.32	0.59±1.10
5 Min	6.08±1.52	5.11±1.48	4.56±1.33	0.56±1.13
2 Min	...	5.14±1.47	4.51±1.32	0.63±1.17
Day				
15 Min	6.22±1.24	4.87±1.37	4.06±1.19	0.81±0.96
10 Min	6.10±1.30	4.87±1.38	4.05±1.21	0.82±0.98
5 Min	6.09±1.44	4.84±1.42	4.03±1.21	0.81±1.05
2 Min	...	4.82±1.47	4.01±1.28	0.81±1.11

VLF indicates very low frequency power; LF, low frequency power; and HF, high frequency power.

Values were log transformed because the data were positively skewed.

Geometric means in the original scale of measure (milliseconds squared) can be determined by exp(mean of the logarithmically transformed values).

A 95% confidence interval for the geometric mean of a measure of variability can be determined as follows. Let L and SD represent the mean logarithm and the corresponding standard deviation. The 95% confidence limits are $\exp(L \pm 1.96[SD/\sqrt{715}])$.

Correlations Between Power Spectral Measures of RR Variability Calculated for 24 Hours and for 2- to 15-Minute Segments of ECG Recordings

Table 2 gives the Pearson correlation coefficients for log-transformed values. All of the correlation coefficients were statistically significant, and many were very strong ($r>.75$). Values calculated from 2-minute segments correlated nearly as strongly with 24-hour values, as did values calculated from 15-minute segments. A 2-minute segment is too short to calculate VLF power.

Fig 1 plots the covariation of the 24-hour values with the 5-minute values for the four power spectral measures of RR variability for a daytime segment selected by random sampling. This plot makes it apparent that the correlations were very strong. Furthermore, the best fit regression lines (solid lines) show that the 5-minute values predict the 24-hour values very well. The slopes of the regression lines are not as steep as the lines of identity (dotted lines), most likely because of random measure error. The difference between the line of identity and the fitted regression line was greatest for

TABLE 2. Correlations Between Values for RR Variability in Short ECG Recordings and 24-Hour Recordings (n=715)

Record length	ln(VLF)	ln(LF)	ln(HF)	ln(LF/HF)
Night				
15 Min	0.685	0.834	0.873	0.737
10 Min	0.676	0.823	0.870	0.712
5 Min	0.621	0.789	0.855	0.665
2 Min	...	0.730	0.836	0.588
Day				
15 Min	0.776	0.882	0.846	0.763
10 Min	0.763	0.871	0.835	0.743
5 Min	0.674	0.840	0.818	0.694
2 Min	...	0.803	0.787	0.622

VLF indicates very low frequency power; LF, low frequency power; and HF, high frequency power. All values are Pearson product moment correlations on log-transformed measurements.

VLF power because for this measure of RR variability there were the fewest cycles for estimating the mean value.

The Association of Measures of RR Variability Calculated From Short Segments of ECG Recordings With Mortality During 2 to 4 Years of Follow-up

Table 3 lists, for the four measures of RR variability, the *Z* scores and relative risks for the four mortality end points: all-cause mortality, cardiac death, arrhythmic death, and sudden death for values calculated over 24 hours and the four shorter segments. The *Z* scores (measures of statistical significance) and the relative risks were determined using Cox regression analysis unadjusted for any covariates. The dichotomizing cut-points were those previously found to provide the greatest difference in mortality rates between the group with low values for RR variability measures calculated on 24 hours of RR intervals and the group with high values: VLF, <180 milliseconds squared; LF, <35 milliseconds squared; HF, <20 milliseconds squared; LF/HF, <0.95.[5] The reader will notice that the four relative risks for the 15-minute daytime segments for cardiac death and for arrhythmic death are equal. This is not an error; the values diverge when the results in the second decimal place are examined.

Many measures had a highly significant ($P<.001$) and strong (relative risk ≥2) association with all-cause mortality. The power spectral values for LF and HF power calculated from the short segments were nearly as strongly associated with mortality as were values calculated from a full 24-hour period. Also, the confidence intervals around the relative risks were narrow (see the footnote to Table 3). For example, the relative risk for LF power calculated from a daytime 5-minute interval was 2.9 (95% confidence interval, 2.0 to 4.3); the relative risk for HF power calculated from a daytime 5-minute interval was 2.5 (95% confidence interval, 2.0 to 3.1). There was a tendency for the daytime segments (selected at random) to have stronger associations with all-cause mortality than the nighttime segments (selected for the maximum average RR interval). The weaker associations for sudden death are probably related to the smaller number of occurrences for this end point (38 compared with 119 for all-cause mortality; see Table 3). Fig 2 shows survival over 3 years for

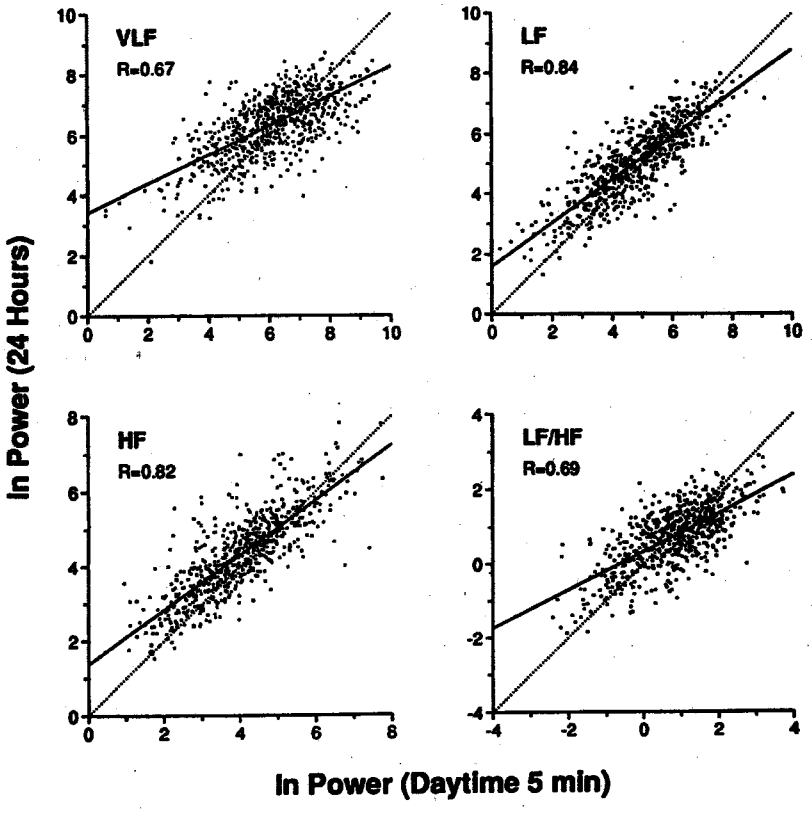

FIG 1. *Plots show prediction of 24-hour values for frequency domain measures of RR variability from values calculated from a random 5-minute daytime segment of the 24-hour ECG recording. The ECG recordings were made 11±3 days after acute myocardial infarction. The 5-minute values are excellent predictors of the 24-hour values. VLF indicates very low frequency power; LF, low frequency power; and HF, high frequency power.*

TABLE 3. Results of Cox Models Evaluating the Predictive Value of Measures of RR Variability Calculated From Short ECG Recordings

	24 Hours		Night segment (min) 15		10		5		2		Day segment (min) 15		10		5		2	
	Z*	RR†	Z*	RR†	Z*	RR†	Z*	RR†	Z*	RR†	Z*	RR†	Z*	RR†	Z*	RR†	Z*	RR†
Death of all causes (n=119)																		
VLF	6.63	3.8	4.41	2.3	3.91	2.1	3.28	1.9	...	...	4.46	2.4	4.28	2.3	4.04	2.1	...	...
LF	5.18	3.1	5.98	3.3	5.75	3.2	4.97	2.8	4.31	2.5	6.49	3.5	5.70	3.0	5.45	2.9	6.35	3.4
HF	3.42	2.2	3.08	2.0	2.49	1.8	2.83	1.9	3.82	2.3	4.14	2.3	4.40	2.5	4.58	2.5	3.04	1.9
LF/HF	4.67	2.7	1.86	1.4	1.76	1.4	1.78	1.4	0.63	1.1	3.90	2.2	4.36	2.4	4.55	2.5	2.78	1.8
Cardiac death (n=88)																		
VLF	6.11	4.1	3.32	2.1	3.13	2.0	3.16	2.0	...	...	4.61	2.8	4.05	2.5	4.12	2.4	...	...
LF	5.11	3.6	5.43	3.5	5.36	3.5	4.64	3.0	4.14	2.8	6.88	4.6	5.65	3.6	5.43	3.3	6.01	3.8
HF	3.56	2.6	2.73	2.1	2.22	1.8	3.13	2.3	3.85	2.6	4.08	2.7	4.27	2.8	4.56	2.9	3.67	2.4
LF/HF	3.51	2.4	1.26	1.3	1.49	1.4	1.17	1.3	0.22	1.1	3.40	2.3	3.92	2.5	4.20	2.6	2.21	1.7
Arrhythmic death (n=68)																		
VLF	5.57	4.3	3.25	2.3	3.00	2.1	2.98	2.1	...	...	4.09	2.8	3.45	2.4	3.28	2.3	...	...
LF	4.55	3.6	4.93	3.6	4.61	3.4	3.42	2.6	3.37	2.6	6.08	4.6	5.03	3.6	4.93	3.5	5.57	4.0
HF	2.80	2.4	2.41	2.1	1.82	1.8	2.53	2.1	3.33	2.6	3.68	2.7	3.91	2.8	4.28	3.1	3.78	2.7
LF/HF	3.63	2.8	1.18	1.4	0.93	1.3	0.80	1.2	0.42	1.1	3.12	2.3	3.32	2.5	3.64	2.6	2.08	1.8
Sudden death (n=38)																		
VLF	4.39	4.7	1.02	1.5	0.85	1.4	0.98	1.4	...	...	2.85	2.7	2.36	2.3	2.79	2.5	...	...
LF	4.26	4.7	3.22	3.2	3.47	3.5	2.94	2.9	2.55	2.7	4.51	4.6	3.80	3.7	4.55	4.6	4.32	4.3
HF	2.56	2.7	1.14	1.6	0.49	1.3	1.45	1.8	2.10	2.3	3.14	3.0	3.19	3.1	2.74	2.6	3.15	3.0
LF/HF	3.02	3.1	0.58	1.2	0.19	1.1	0.32	1.1	−0.38	0.9	2.59	2.5	3.20	3.2	2.54	2.5	1.42	1.7

VLF indicates very low frequency power; LF, low frequency power; and HF, high frequency power.
*$Z \geq 1.96$, $P<.05$; $Z \geq 2.58$, $P<.01$; $Z \geq 3.30$, $P<.001$.
†Relative risk (RR), probability of dying if below the cutpoint/probability of dying if above the cutpoint. The 95% confidence intervals for the relative risk can be computed by $\exp(\ln RR \pm 1.96 \times [\ln RR/Z])$.

patients in low and high categories of the four frequency domain measures.

We hypothesized that the nighttime values for RR variability would have stronger associations with mortality than daytime values. We tested this hypothesis by comparing relative risks for daytime and nighttime 15-minute segments for cardiac death. The differences were not significant ($P>.05$). Thus, we failed to confirm this hypothesis. Additional comparisons among the relative risks in Table 3 were exploratory analyses done after inspection of the data. For each of the four predictors of outcome (HF, LF, and VLF power, plus the LF/HF ratio), there were eight comparisons possible between relative risks calculated for 24 hours and relative risks calculated for 15-minute periods: daytime plus nighttime for each of the four end point events. The 15-minute to 24-hour comparisons were made using the jackknife procedure.

For LF and HF power, there were no statistically significant differences between the 15-minute and 24-hour relative risks. For VLF power, five of the eight comparisons showed that the relative risks calculated for 15-minute segments were significantly weaker than the relative risks calculated for 24 hours ($P<.05$). For the LF/HF ratio, each of the four relative risks calculated from 15-minute nighttime segments was significantly poorer than the corresponding relative risk calculated for 24 hours, but none of the four relative risks calculated from 15-minute daytime segments was significantly different from the corresponding 24-hour relative risk.

Short-term Measures of RR Variability Improve Prediction of Mortality

Having demonstrated in univariate analyses that measures of RR variability calculated from short segments of ECG recording predict mortality, we used multivariate analyses to determine whether these measures improve the prediction of all-cause mortality. We used Cox regression analysis to determine whether power spectral measures of RR variability computed from 5-minute random samples of ECG recordings added significantly to the prediction of all-cause mortality. First, one of the three established risk predictors—New York Heart Association functional class before the index myocardial infarction, rales in the CCU, and left ventricular ejection fraction—was entered into the Cox regression model. Then, a power spectral measure of RR variability was added to the model. When evaluated in this way, VLF, LF, HF, and LF/HF all added significantly to the prediction of risk ($P<.01$ in each case).

Fig 3 shows how much power spectral measures of RR variability add to the prediction of risk of patients

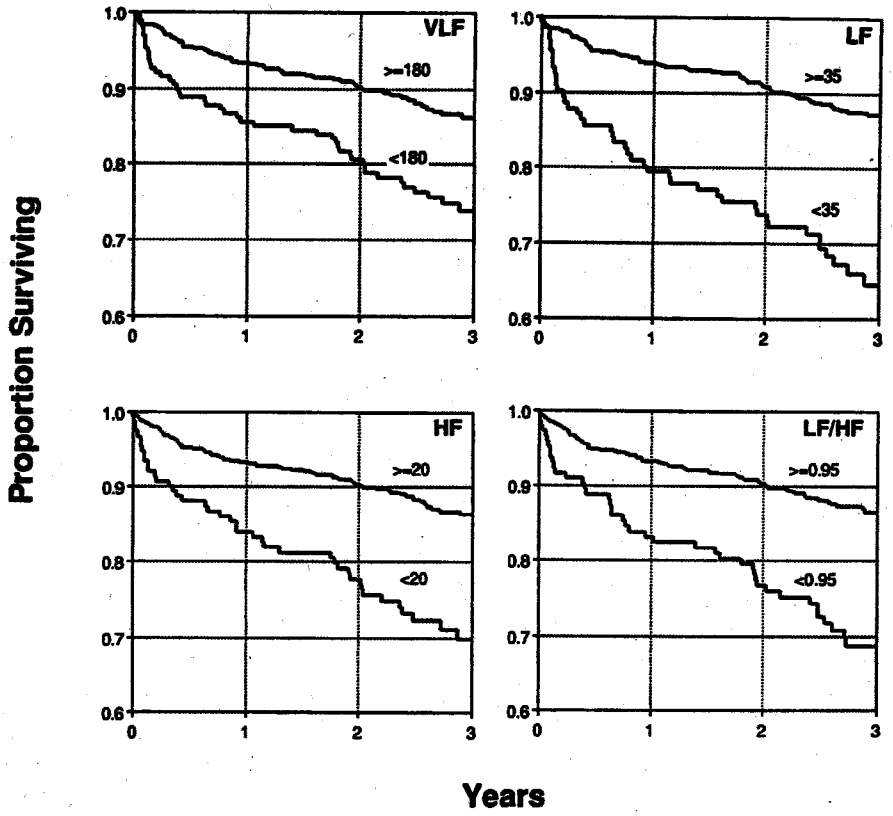

FIG 2. *Curves show prediction of long-term mortality after myocardial infarction by frequency domain measures of RR variability calculated from a random 5-minute daytime segment of the 24-hour ECG recording. The values for frequency domain measures of RR variability calculated from 5-minute segments are excellent predictors of long-term mortality of all causes. The number of patients at the start of follow-up and the number known to be alive and being followed up after 1, 2, and 3 years were as follows: high VLF (very low frequency power), 526, 484, 445, 191; low VLF, 189, 158, 141, 71; high LF (low frequency power), 583, 539, 495, 223; low LF, 132, 103, 91, 39; high HF (high frequency power), 564, 518, 478, 217; low HF, 151, 124, 108, 45; high LF/HF ratio, 570, 525, 481, 208; low LF/HF ratio, 145, 117, 105, 54.*

classified as high risk because of low left ventricular ejection fraction.[10,11] Fig 3 shows Kaplan-Meier survival curves for the group of 227 patients who are at high risk because they have a left ventricular ejection fraction <0.40. This group is divided into two subgroups based on frequency domain measures of RR variability calculated from a randomly selected 5-minute daytime ECG recording. For each measure of RR variability, VLF, LF, and HF, survival is significantly poorer in the group with low values. The LF/HF ratio also improves prediction of survival in patients with low ejection fraction.

Table 4 shows how much measures of RR variability improve the predictive accuracy for all-cause mortality 2.5 years after myocardial infarction when these measures are added to previously established risk predictors. The established risk predictors evaluated in Table 4 are those previously shown to be independent predictors of all-cause mortality in this sample of postinfarction patients: New York Heart Association functional class before the index myocardial infarction, rales in the CCU, and left ventricular ejection fraction measured about 10 days after the index myocardial infarction. The other independent predictor, ventricular arrhythmias, is not included because this variable requires 24 hours of data to calculate a reasonable estimate of the average hourly frequency of ventricular premature complexes. If a 24-hour ECG recording is done to evaluate the frequency of ventricular premature complexes, then long-term measures of RR variability should be calculated because they are better predictors. The data in Table 4 show that measures of RR variability calculated from a randomly selected 5-minute daytime segment do improve the predictive accuracy for each of the three established risk predictors. In each comparison, the measure of RR variability significantly improved the predictive accuracy when added to one of the three previously established risk predictors. Similar results were obtained using the data from the 5-minute nighttime segment.

Discussion

Comparison of RR Variability Measures Computed From Short Segments (2 to 15 Minutes) to Those Computed Using 24 Hours of Data

Previous studies have shown that both time and frequency domain measures of RR variability calculated from 24 hours of data predict death after myocardial infarction.[1-6] Measures of RR variability made at the time of hospital discharge or after recovery to steady-state values both predict death during subsequent follow-up.[1-6,20] This study showed that the mean values for frequency domain measures, computed from short segments (2 to 15 minutes), were not meaningfully different from mean values obtained from a full 24-hour period. This was true for daytime segments chosen by random sampling and for nighttime segments chosen because they had the maximum average RR interval. Also, there were strong and significant correlations between the values computed from short segments and those computed using a full 24-hour period.

Measures of RR Variability Computed From Short Segments of ECG as Risk Predictors After Myocardial Infarction

The measures of RR variability that could be computed from 2 to 15 minutes of ECG data were excellent

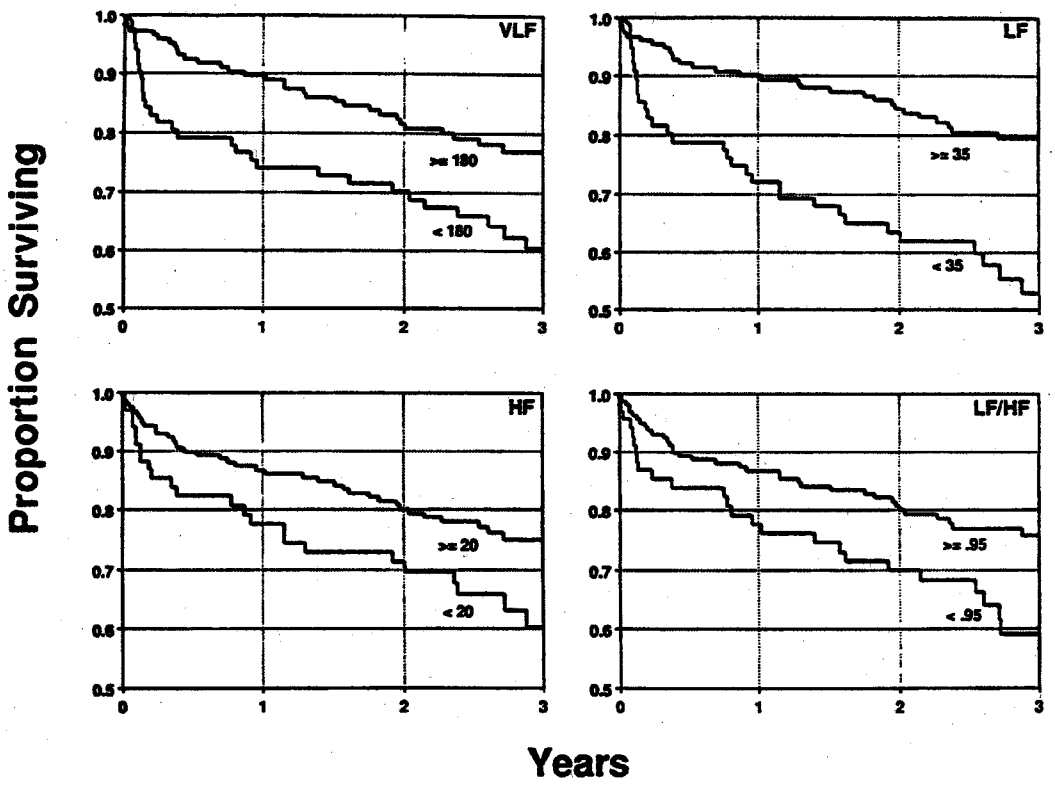

FIG 3. *Curves show prediction of long-term mortality after myocardial infarction by frequency domain measures of RR variability calculated from a random 5-minute daytime segment of the 24-hour ECG recording for patients with left ventricular ejection fraction <0.40. Even in this small group of high risk patients, the values for frequency domain measures of RR variability calculated from 5-minute segments are excellent predictors of long-term mortality of all causes. The number of patients at the start of follow-up and the number known to be alive and being followed up after 1, 2, and 3 years were as follows: high VLF (very low frequency power), 145, 126, 111, 46; low VLF, 82, 58, 51, 26; high LF (low frequency power), 151, 131, 119, 54; low LF, 76, 53, 43, 18; high HF (high frequency power), 159, 134, 119, 52; low HF, 68, 50, 43, 20; high LF/HF ratio, 159, 133, 118, 52; low LF/HF ratio, 68, 51, 44, 20.*

predictors of all-cause mortality and of several cause-specific deaths: cardiac death, arrhythmic death, and sudden cardiac death. In fact, the measures of RR variability computed from 2 to 15 minutes of data generally predicted death nearly as well as values for the same measures computed from a full 24-hour period. Measures of RR variability, calculated from a randomly selected daytime segment, significantly improved the prediction of all-cause mortality when added to each of the three best risk predictors for this sample, New York Heart Association functional class before the index myocardial infarction, rales in the CCU, and left ventricular ejection fraction.

Short-term Measures of RR Variability Provide an Efficient Tool for Risk Stratification After Myocardial Infarction

Ultra low frequency (ULF) power, power in the the frequency band <0.0033 Hz, is the best predictor of mortality among the frequency domain measures in this sample[5] but cannot be computed from ≤15 minutes of ECG data. Also, VLF power is estimated somewhat imprecisely from ≤15 minutes of ECG data. Therefore, when 24 hours of data are available, eg, a 24-hour continuous ECG (Holter) recording, it makes sense to use all of the available data to calculate measures of RR variability with the best predictive values. However, the values computed from short daytime segments of RR data are good to excellent predictors of all-cause mortality and cardiac, arrhythmic, and sudden cardiac death. This finding indicates that it will be useful to compute measures of RR variability on the same data being acquired and processed to obtain the signal-averaged ECG. This hypothesis needs to be tested in future studies. However, Farrell et al[4] already showed that combining heart rate variability index, a time domain measure of RR variability dominated by ULF power, with the signal-averaged ECG gave superb prediction of future arrhythmic events after myocardial infarction. Although the positive predictive accuracy of the signal-averaged ECG alone was about 20%, the signal-averaged ECG and heart rate variability index together gave a predictive accuracy of about 50%.[4] Now that we have shown that short ECG segments can provide excellent prediction of time to death, it would be efficient to calculate measures of RR variability in machines that are used to compute the signal-averaged ECG. Using a diagnostic instrument with both capabilities, two important predictors of death and arrhythmic events could be obtained over about 5 minutes. To-

TABLE 4. Positive Predictive Accuracy Using Measures of RR Variability (Calculated Using 5-Minute Daytime Segments) Alone or Combined with Other Risk Predictors

Predictors defining high risk group	Patients in high risk category	Positive predictive accuracy*
Established risk predictors		
LVEF	227	0.26 (0.20, 0.32)
NYHA	142	0.29 (0.22, 0.37)
Rales	102	0.33 (0.24, 0.42)
Measures of RR variability		
VLF	189	0.24 (0.17, 0.30)
LF	132	0.31 (0.23, 0.39)
HF	151	0.28 (0.20, 0.35)
LF/HF	145	0.27 (0.19, 0.34)
Combinations of risk predictors		
LVEF+VLF	82	0.34 (0.24, 0.45)
LVEF+LF	76	0.38 (0.27, 0.49)
LVEF+HF	68	0.34 (0.22, 0.46)
LVEF+LF/HF	68	0.32 (0.21, 0.43)
NYHA+VLF	52	0.41 (0.27, 0.55)
NYHA+LF	43	0.44 (0.28, 0.59)
NYHA+HF	34	0.47 (0.29, 0.64)
NYHA+LF/HF	46	0.39 (0.25, 0.54)
Rales+VLF	47	0.45 (0.31, 0.60)
Rales+LF	41	0.45 (0.29, 0.60)
Rales+HF	33	0.46 (0.29, 0.63)
Rales+LF/HF	30	0.44 (0.26, 0.62)

LVEF indicates left ventricular ejection fraction <0.40; NYHA, New York Heart Association functional class III, IV; rales, rales in the coronary care unit greater than bibasilar; VLF, very low frequency power (0.0033 Hz to 0.04 Hz) <180 milliseconds squared; LF, low frequency power (0.04 Hz to 0.15 Hz) <35 milliseconds squared; HF, high frequency power (0.15 Hz to 0.40 Hz) <20 milliseconds squared; LF/HF, ratio of low frequency power to high frequency power <0.95.

*Kaplan-Meier estimate of all-cause mortality at 2.5 years of follow-up (the numbers in parentheses are 95% confidence intervals calculated using the Greenwood formula for the standard error).

gether, the two variables should have a positive predictive accuracy approaching 50%. Such a diagnostic instrument would provide a rapid, flexible, effective, and inexpensive tool for risk assessment in coronary heart disease. We hope that additional studies will validate this approach.

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