Traditional and Nonlinear Heart Rate Variability Are Each Independently Associated with Mortality after Myocardial Infarction

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Traditional and Nonlinear HRV and Mortality. ***Introduction:*** **Decreased heart rate variability (HRV) and abnormal nonlinear HRV shortly after myocardial infarction (MI) are risk factors for mortality. Traditional HRV predicts mortality in patients with a range of times post-MI, but the association of nonlinear HRV and outcome in this population is unknown.**

Methods and Results: **HRV was determined from 740 tapes recorded before antiarrhythmic therapy in Cardiac Arrhythmia Suppression Trial patients with ventricular premature contractions (VPCs) suppressed on the first randomized treatment. Patients were 70 ± 121 days post-MI. Follow up was 362 ± 241 days (70 deaths). The association between traditional time and frequency-domain HRV and mortality and nonlinear HRV and mortality were compared for the entire population (ALL), those without coronary artery bypass graft post-MI (no CABG), and those without CABG or diabetes (no CABG, no DIAB) using univariate and multivariate Cox regression analysis. Strength of association was compared by P values and Wald Chi-square values. Nonlinear HRV included short-term fractal scaling exponent, power law slope, and SD12 (Poincaré dimension). For ALL and for no CABG, increased daytime SD12 had the strongest association with mortality ($P = 0.002$ ALL and $P < 0.001$ no CABG). For no CABG, no DIAB increased 24-hour SD12 hours had the strongest association ($P < 0.001$) with mortality. Upon multivariate analysis, increased SD12, decreased ln ULF (ultra low frequency), and history of prior MI and history of congestive heart failure each remained in the model.**

Conclusion: **Nonlinear HRV is associated with mortality post-MI. However, as with traditional HRV, this is diluted by CABG surgery post-MI and by diabetes. Results suggest that decreased long-term HRV and increased randomness of heart rate are each independent risk factors for mortality post-MI.** *(J Cardiovasc Electrophysiol, Vol. 16, pp. 13-20, January 2005)*

heart rate variability, ambulatory ECG, postmyocardial infarction, risk factors

Introduction

Beginning in 1987 with the results of the Multi-Center Post-Infarction Project (MPIP) and numerous subsequent trials, it has been clearly demonstrated that traditional time-domain and frequency-domain indices of heart rate variability (HRV) measured in the peri-infarction period identify post-myocardial infarction (post-MI) patients at increased risk for mortality.[1-13] Recently, techniques from nonlinear dynamics have been applied to peri-infarction patients. The index power law slope was applied to the MPIP data and found to be a better predictor of mortality than any time- or frequency-domain HRV index.[14] In other studies, the short-term fractal scaling exponent was a better predictor of mortality than traditional HRV measures.[15,16] Thus, limited data suggest that nonlinear HRV may provide superior risk stratification to traditional HRV post-MI.

In risk stratification studies, HRV almost always is measured in the peri-infarction period. Time- and frequency-domain HRV are known to increase in many patients during recovery from MI.[17] The predictive value of HRV measured at a later time is less clear. The Cardiac Arrhythmia Pilot Study (CAPS), the pilot study for the Cardiac Arrhythmia Suppression Trial (CAST), reported that HRV measured in the frequency domain 1 year post-MI continues to predict mortality during an approximately 2-year follow-up.[12]

CAST was an historic post-MI study of patients with impaired left ventricular ejection fraction and high-grade ventricular arrhythmias that were suppressed by class IC drugs. Holter recordings were obtained at a large range of times post-MI. We previously reported that time-domain indices of HRV, such as SDNN (standard deviation of all normal-to-normal interbeat intervals), which are strong predictors of mortality in the peri-infarction period, were not associated with mortality when the entire CAST group was taken together.[18] However, after patients with diabetes and/or coronary artery bypass graft (CABG) surgery post-MI were excluded from the analysis, decreased SDNN was strongly associated with mortality ($P = 0.006$). Similarly, in the frequency domain, when patients with diabetes or CABG post-MI were excluded, as was the case with peri-infarction post-MI studies,[2] decreased ln total power ($P < 0.001$) and decreased ln ultra low frequency power ($P < 0.001$) had the strongest associations with mortality.

In the current investigation, we compared the association with all-cause mortality in the CAST of 24-hour, daytime,

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and nighttime nonlinear HRV indices: power law slope, SD12 (sometimes called the Poincaré dimension), and short-term fractal scaling exponent, with previously computed associations for standard time- and frequency-domain HRV. Because of the confounding effect of including patients with CABG post-MI and diabetes on the association of traditional HRV and mortality, these associations were again determined for the entire dataset, excluding CABG post-MI and excluding both CABG and diabetes. Finally, the independent association of traditional and nonlinear HRV with mortality was determined.

Methods

Patient Population

The primary goal of CAST was to determine the effects of suppression of ventricular premature beats on mortality after myocardial infarction.[19] Enrollment required an acute MI within the preceding 2 years and ≥6 ventricular premature contractions (VPCs) per hour on the pretreatment (qualifying) Holter recording. Those who enrolled within 90 days of the index MI were required to have ejection fractions ≤55%, whereas those enrolled after the 90-day window were required to have an ejection fraction ≤40%. After qualification, patients were randomly assigned to encainide, moricizine, or flecainide, with flecainide omitted in the subgroup with the lowest ejection fraction. Patients who had significant suppression of ventricular premature beats with a particular agent were continued on that agent or placebo. More complete information on study design can be found in the primary endpoint reports.[20-22] In April 1989, the Data and Safety Monitoring Board of CAST recommended that the encainide and flecainide arms of the study be discontinued, and CAST II was begun. Patients in CAST I who were taking moricizine were continued on that agent, and additional patients were selected who were believed to be at higher risk than those in CAST I. CAST II required an ejection fraction ≤40% and required patients to be ≤90 days post-MI.

Baseline, pretreatment (qualifying), and on-therapy (suppression) tapes from participants in CAST I and CAST II were obtained from the CAST data coordinating center. CAST enrolled 3,549 patients. Patients (N = 830) were selected from the CAST database based on their being coded as having usable qualifying and suppression tapes. The patients had their arrhythmias successfully suppressed on their first, randomly assigned antiarrhythmic treatment, and they were continued on that agent. However, only pretreatment recordings were analyzed in the current study. Tapes with atrial fibrillation (N = 27) or paced rhythm (N = 9) were eliminated from this analysis. Some tapes proved to be missing. For 24-hour analyses, tapes with <12 hours of 5-minute segments with adequate data, or other technical problems, were excluded. For daytime (08:00–20:00) or nighttime (00:00–06:00) analyses, tapes with <50% of daytime or nighttime periods with acceptable 5-minutes segments were excluded. For the time-domain analyses, at least 50% of intervals in each usable 5-minute segment had to consist of normal-to-normal (N-N) intervals. For the frequency-domain and nonlinear analyses, which are more sensitive to missing data, the acceptance threshold for a usable segment was 80% N-N intervals. After tapes that were not usable for any of the analyses were excluded, 740 (70 deaths) remained. Also, 263 patients with usable tapes subsequently were randomized to encainide, 207 to flecainide, and 270 to moricizine.

Clinical and Demographic Data

Clinical and demographic data for each patient were provided by the CAST coordinating center. Characteristics of the CAST patient population and the procedures for data validation have been previously reported.[20-22]

Subgroup Analyses

Associations with mortality from the baseline recordings were determined for the entire CAST population, for those without CABG surgery post-MI, and for those who were both nondiabetic and without CABG surgery post-MI.

Analysis of HRV

All tapes were scanned on a Marquette SXP Laser Holter scanner (Milwaukee, WI, software version 5.8) by an experienced research Holter technician using standard Holter analysis procedures. Specifically, attention was paid to accurate and consistent detection of beat onsets. Misdetected beats were excluded from the analysis. Also, the longest and shortest true normal-to-normal intervals were identified for each recording in order to exclude all beats outside this range from the HRV analysis. Intervals within this range were carefully edited. Beat-stream files, representing the time and classification of each QRS complex, were transferred to a Sun Sparcstation computer (Sun Microsystems, Santa Clara, CA) where secondary editing and HRV analysis were performed using previously reported and validated techniques.[23,24]

Calculations of time- and frequency-domain HRV were performed according to standard methods that were previously described.[25] Indices were grouped as longer-term, i.e., quantifying variations in heart rate over >5-minute period (primarily circadian rhythms); intermediate-term, i.e., quantifying variations in heart rate over <5-minute periods; and short-term, i.e., quantifying beat-to-beat changes in heart rate. Definitions for these time- and frequency-domain indices are given in Table 1.

Nonlinear HRV Indices

Whereas time- and frequency-domain measures of HRV capture the amount of HRV at various time scales, nonlinear HRV measures attempt to capture the structure or complexity of the heart rate time series. For example, a random series of heart beats, a normal series of heart beats, and a totally periodic series of heart beats might have the exact same standard deviation (SDNN), but their underlying organization would be completely different.

Power law slope

In normal sinus rhythm, spectral power, when measured over 24 hours, shows a progressive, virtually exponential increase in amplitude with decreasing frequency. This also can be plotted as the log of power versus the log of frequency, which transforms the exponential curve to a line whose slope can be measured.[14] The power law slope is the slope of this line, measured between 10^{-2} and 10^{-4} Hz, and is a negative number. It is believe to reflect the degree to which the patterns of the heart rate time series are self-similar over a scale of minutes to hours.[14] Decreased power law slope has

TABLE 1
Definitions for Time- and Frequency-Domain HRV Indices Calculated in This Study

Long-Term Time Domain	
SDNN	Standard deviation of N-N intervals in ms
SDANN	Standard deviation of the 5-minute average of N-N intervals in ms
Intermediate-Term Time Domain	
SDNNIDX	Average of the standard deviations of N-N intervals over 5 minutes in msec
Long-Term Frequency Domain	
Total power (TP)	Total spectral power (1.15 × 10-5-0.5 Hz) in msec^2
Ultra low frequency (ULF)	Ultra low frequency power (1.15 × 10-5-0.003 Hz) in msec^2
Intermediate-Term Frequency Domain	
Very low frequency (VLF)	Very low frequency spectral power (0.0033–0.04 Hz) in msec^2
Low frequency (LF)	Low frequency spectral power (0.04–0.15 Hz) in msec^2
Normalized LF (NLF)	Low frequency power divided by (TP – VLF) in percent
Short-Term Time Domain	
pNN50	Percent of N-N intervals >50 msec different from the prior interval
Short-Term Frequency Domain	
High frequency (HF)	High frequency spectral power (0.15–0.4 Hz) in msec^2
Normalized HF (NHF)	High frequency power divided by (TP – VLF) in percent
Ratio	
LF/HF ratio	Low to high frequency power ratio averaged for every 5 minutes

Definitions for nonlinear indices are given in the Methods section.

been shown to be a marker for increased risk of mortality post-MI.[14]

SD12

The nonlinear index SD12 quantifies the shape of the Poincaré plot, a figure in which each R-R interval is plotted against the previous one. As shown in Figure 1, the Poincaré plot is a graphic representation of the underlying patterns in the heart rate time series. SD12 is the ratio of the lengths of the axes of an imaginary ellipse that has its center at the average R-R interval of the time series and is fitted to the Poincaré plot. The long axis of this ellipse is along a line beginning at the origin and with a slope of 1 and has a length called SD2. SD2 reflects intermediate-term variability. The length of the transverse axis of the ellipse is SD1 and reflects short-term variability. SD12 is the ratio of these measures and can be considered an intermediate-term nonlinear measure. For this analysis, SD12 was calculated for 1,000 beat segments and averaged.[26] Points where the change in the difference in N-N between adjacent pairs of N-N intervals was >30% were excluded.

Increased SD12 often reflects a more scattered, abnormal Poincaré plot. The insets in Figure 1 show examples of abnormal and normal SD12 and their associated 1-hour Poincaré plots taken from the CAST dataset. Figure 1a and 1b are abnormal plots, with high values of SD12 from nonsurvivors

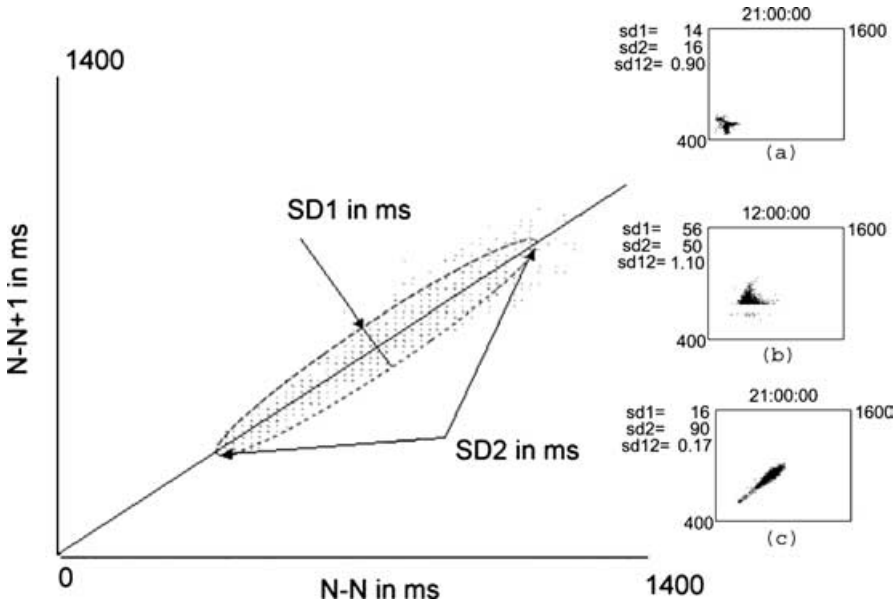

Figure 1. *Calculation of SD1, SD2, and SD12 from an ellipse fitted around the Poincaré plot. Insets: (a) 1-hour Poincaré plot in a CAST nonsurvivor with high SD12 and depressed HRV; (b) 1-hour Poincaré plot in a CAST nonsurvivor with high SD12 without depressed HRV; (c) 1-hour Poincaré plot in a CAST survivor with normal SD12.*

TABLE 2
Clinical and Demographic Characteristics of Study Subjects with Qualifying Recordings

Age (years)	61 ± 10
Male gender	82%
Left ventricular ejection fraction	37 ± 10%
Coronary artery bypass graft surgery post-MI	19%
Diabetes	22%
History of MI prior to qualifying MI	41%
History of congestive heart failure prior to qualifying MI	12%
New York Heart Association functional class I	84%
Thrombolysis at MI	32%
Percutaneous transluminal coronary angioplasty	18%

N = 749; 70 deaths.
MI = myocardial infarction.

in the CAST. SD12 is 0.90 in Figure 1a and 1.10 in Figure 1b. In contrast, Figure 1c shows a normal plot from a CAST survivor. SD12 is 0.017.

DFA1

Detrended fluctuation analysis provides a quantitative method for determining the degree to which a time series is random at the one extreme and correlated at the other. DFA1 ranges in value from 0.5 (random) to 1.5 (correlated), with normal values of just over 1.0. Decreased DFA1 (also called alpha 1) has been associated with adverse outcomes in cardiac patient populations.[16] The details of this method have been described elsewhere.[27–29] Only N-N intervals were used for this calculation. DFA1 can be considered a short-term nonlinear measure.

Statistical Analyses

Indices of HRV were tested for normality and natural log transformation applied, when necessary, to provide a normal distribution appropriate for parametric statistical comparisons. Univariate prediction of all-cause mortality for each potential predictor variable was evaluated using Cox proportional hazards regression. A stepwise Cox proportional hazards regression analysis was used to determine the independent clinical and HRV predictors of mortality.

Results

Demographics

Table 2 lists the clinical and demographic characteristics of the population studied.

Comparison of the Association of Nonlinear and Standard Indices of HRV with Mortality for the Entire CAST Group

Table 3 lists the HRV indices most strongly associated with mortality ($P < 0.01$) in the CAST group taken as a whole. Using the Wald Chi-square (essentially the square of the *t*-statistic) and the P value as surrogates for the strength of association with mortality, it can be seen that among HRV indices calculated over 24 hours, the nonlinear indices SD12 and power law slope (both $P = 0.002$) had the strongest association with mortality. Surprisingly, when HRV was computed during the daytime only, the association of HRV with mortality sharply increased for SD12 ($P < 0.001$). Thus, increased daytime values of SD12 had the strongest association with mortality in the CAST. Also, as previously reported, the frequency-domain index increased normalized high frequency (HF) was a similarly strong predictor of mortality ($P = 0.001$) when calculated during the daytime.[17]

Comparison of the Association of Nonlinear and Standard Indices of HRV with Mortality When Patients with CABG Surgery after the Qualifying MI Were Excluded

We previously reported that standard HRV indices were depressed in patients with CABG surgery after their MI.[30] Comparison of nonlinear HRV indices for those with and without CABG showed a similar phenomenon, with more abnormal values in those with CABG surgery. These included significant increases in SD12 ($P < 0.001$), decreases in DFA1 ($P < 0.001$), and decreases in power law slope ($P = 0.020$). Comparison of Tables 3 and 4 shows the increased association

TABLE 3
Significant Univariate Associations with Mortality of Traditional and Nonlinear HRV for the Entire Group ($P < 0.01$)

24 Hours	Wald Chi-Square	Hazard Ratio	95% CI	P Value
Nonlinear (N = 625, 59 deaths)				
DFA1	7.2	0.251	0.091–0.690	0.007
SD12	9.7	6.200	1.196–19.581	0.002
Slope	9.8	0.853	0.772–0.942	0.002
Daytime				
Time Domain (N = 679, 63 deaths)				
pNN50	5.9	1.026	1.005–1.048	0.007
Frequency Domain (N = 541, 51 deaths)				
NHF	11.9	1.041	1.018–1.066	0.001
Nonlinear (N = 541, 51 deaths)				
DFA1	6.7	0.243	0.083–0.711	0.010
SD1	6.6	1.030	1.01–1.05	0.010
SD12	12.3	6.288	2.254–17.547	<0.001
Slope	6.9	0.180	0.050–0.647	0.009

N = 735 recordings, 69 deaths eligible for 24-hour time domain analysis, no significant 24-hour time domain predictors of mortality, $P < 0.05$.
For time- and frequency-domain HRV, see Table 1.
DFA1 = short-term fractal scaling exponent; SD1 = short axis of ellipse fitted around a Poincaré plot of N-N intervals; SD2 = long axis of an ellipse fitted around a Poincaré plot of N-N intervals; SD12 = SD1/SD2; Slope = power law slope.

of standard and nonlinear HRV with mortality when patients with CABG surgery post-MI were excluded from the analysis. Because the total number of subjects and deaths was smaller in this subset, all things being equal, the association of HRV and mortality would be expected to decrease. However, this association became stronger for every index. Among indices calculated over 24 hours, the nonlinear HRV indices SD12 and power law slope (both $P < 0.001$) continued to have the strongest association with mortality. The stronger association of *daytime* HRV and mortality persisted, with increased daytime values for SD12 and decreased values for DFA1 each (despite the smaller number of qualifying recordings and deaths) more strongly associated with mortality than 24-hour values.

As we previously reported, 24-hour and daytime longer and intermediate-term frequency-domain HRV became significantly associated with mortality once CABG patients were excluded.[17] Whereas decreased 24-hour SDNN, SDANN, and ln SDNNIDX were each significantly associated with mortality ($n = 596$, 63 deaths, $P < 0.05$), P values were >0.01 and results were not included in Table 4. As shown in Table 4, frequency-domain HRV indices had a far stronger association with mortality than time-domain indices, even though they were based on a smaller sample size. Decreased ln ULF (ultra low frequency) over 24 hours was strongly associated with mortality ($P < 0.001$), and increased normalized HF power during the daytime had the second strongest association with mortality of all the HRV indices. Also, after patients with CABG post-MI were excluded, HRV calculated during the nighttime became significantly associated with mortality, although this association was relatively weak.

Comparison of the Association of Nonlinear and Standard Indices of HRV with Mortality for the Group Without Diabetes or CABG Surgery after the Qualifying MI

We previously showed that standard HRV indices were decreased in CAST patients with diabetes.[30] When nonlinear HRV was compared between diabetics and nondiabetics, they too were more adverse in diabetics. SD12 was significantly higher and DFA1 and power law slope significantly lower among diabetics (all $P < 0.001$). However, neither standard nor nonlinear HRV indices were associated with mortality among diabetic patients in the CAST. Table 5 compares the association of different HRV indices with mortality when both CABG patients and diabetics were excluded from the analysis. Among 24-hour HRV indices, after diabetic patients were excluded, increased SD12 had the strongest association with mortality, and the association with mortality of power law slope weakened. Daytime nonlinear HRV (DFA1 and SD12) remained strongly associated with mortality, but this association was not stronger than for those indices calculated over 24 hours.

Also, as previously reported, despite the smaller number of patients and events, removing diabetics also *increased* the association with mortality of most longer-term time- and frequency-domain HRV.[17] Among 24-hour indices, ln TP and ln ULF had the strongest association with mortality of the standard HRV indices ($P < 0.001$ for each). Increased normalized HF during the daytime remained strongly associated with mortality ($P = 0.001$). HRV calculated during the nighttime had a stronger association with mortality when diabetic patients also were excluded but remained weaker than either daytime or 24-hour indices.

TABLE 4

Significant Univariate Associations of Traditional and Nonlinear HRV with Mortality with CABG Post-MI Excluded ($P < 0.01$)

24 Hours	Wald Chi-Square	Hazard Ratio	95% CI	P Value
Frequency Domain (N = 504, 53 deaths)				
ln TP	12.0	0.577	0.423–0.788	0.001
ln ULF	12.2	0.574	0.420–0.784	<0.001
ln VLF	8.8	0.685	0.533–0.879	0.003
ln LF	10.4	0.691	0.552–0.865	0.001
NLF	9.1	0.964	0.942–0.987	0.003
NHF	7.90	1.040	1.012–1.070	0.005
Nonlinear (N = 504, 53 deaths)				
DFA1	11.8	0.136	0.044–0.426	0.001
ln SD2	8.9	0.443	0.259–0.756	0.003
SD12	16.3	14.20	3.915–51.489	<0.001
Slope	13.4	0.810	0.724–0.907	<0.001
Daytime				
Frequency Domain (N = 438, 36 deaths)				
ln TP	8.7	0.578	0.401–0.831	0.003
ln ULF	8.5	0.584	0.407–0.839	0.004
ln VLF	10.0	0.640	0.485–0.843	0.002
lF/HF	6.6	0.799	0.673–0.949	0.010
NLF	5.7	0.961	0.937–0.987	0.003
NHF	15.0	1.058	1.028–1.089	<0.001
Nonlinear (N = 438, 36 deaths)				
DFA1	12.2	0.122	0.036–0.398	<0.001
ln SD2	6.9	0.448	0.246–0.817	0.009
SD12	19.7	9.20	3.46–24.49	<0.001
Nighttime				
Frequency Domain (N = 520, 54 deaths)				
ln LF	7.5	0.752	0.613–0.922	0.006

Abbreviations as in Table 3.

TABLE 5

Significant Univariate Associations with Mortality of Traditional and Nonlinear HRV with CABG Post-MI and Diabetes Excluded (P < 0.01)

24 Hours	Wald Chi-Square	Hazard Ratio	95% CI	P Value
Time Domain (N = 468, 38 deaths)				
SDNN	7.6	0.986	0.976–0.996	0.006
SDANN	7.6	0.984	0.974–0.995	0.006
Frequency Domain (N = 391, 32 deaths)				
ln TP	18.4	0.385	0.248–0.587	<0.001
ln ULF	18.8	0.378	0.244–0.587	<0.001
ln VLF	11.9	0.540	0.381–0.766	0.001
ln LF	11.3	0.596	0.440–0.806	0.001
NLF	7.0	0.960	0.931–0.990	0.008
Nonlinear (N = 391, 32 deaths)				
DFA1	15.4	0.054	0.012–0.232	<0.001
SD12	20.5	25.9	6.344–105.910	<0.001
Slope	9.5	0.810	0.709–0.927	0.002
Daytime				
Frequency Domain (N = 334, 26 deaths)				
ln TP	8.7	0.578	0.401–0.831	0.003
ln ULF	8.5	0.584	0.407–0.839	0.004
ln VLF	10.0	0.640	0.485–0.843	0.002
NHF	10.3	1.063	1.024–1.103	0.001
Nonlinear (N = 334, 26 deaths)				
DFA1	11.6	0.069	0.015–0.321	0.001
ln SD2	5.8	0.352	0.150–0.823	0.006
SD12	18.3	10.586	3.558–31.231	<0.001
Nighttime				
Frequency Domain (N = 407, 33 deaths)				
ln LF	9.0	0.655	0.497–0.864	0.003
Nonlinear (N = 407, 33 deaths)				
DFA1	6.9	0.166	0.043–0.636	0.009
ln SD2	6.7	0.690	0.224–0.813	0.010
SD12	6.9	11.690	1.876–72.833	0.008

Abbreviations as in Table 3.

Independent Predictors of Mortality

Using Cox regression analysis, we identified the cutpoint of 24-hour SD12 that best separated nonsurvivors and survivors in the group without CABG or diabetes. At the best cutpoint, SD12 = 0.55, mortality was 53% among the 15 patients with the highest values and 6.7% among the 351 with lower values. Figure 2 shows Kaplan-Meier survival curves for patients above and below the cutpoint for SD12.

Because ln ULF and SD12 each reflect totally different aspects of HRV, we determined if they were independent predictors of mortality by putting them both into the Cox model. Both were retained (SD12: Wald Chi-square = 8.35, P = 0.004; ln ULF: Wald Chi-square = 11.8, P = 0.001). We previously demonstrated that, among the group that excluded CABG and diabetes, decreased 24-hour ln ULF remained in the Cox model when history of prior MI or history of congestive heart failure, the two clinical factors most strongly associated with mortality (P < 0.001), were added. We performed a similar analysis including these clinical factors with both ln ULF and SD12 in the Cox regression analysis. Each factor was retained in the final model, which included ln ULF (Wald Chi-square = 9.67, P = 0.002), SD12 (Wald Chi-square = 6.94, P = 0.008), history of MI (Wald Chi-square = 9.38, P = 0.002), and history of congestive heart failure (Wald Chi-square = 5.27, P = 0.022).

Discussion

Results suggest that traditional and nonlinear HRV indices capture different aspects of increased risk for mortality post-MI. Traditional HRV risk stratifiers (total and ultra low frequency power and SDNN) capture longer-term, primarily circadian trends in HRV. Reduction in these has been clearly associated with increased mortality in the peri-infarction period and in CAST. The nonlinear HRV indices SD12 and DFA1 capture the randomness of R-R dynamics. Both decreased DFA1 and increased SD12 were associated with worse survival in CAST. Consistent with this finding, the other index strongly associated with worse survival was increased daytime normalized HF, i.e., increased relative HF power. Increased HF power can result from either increased vagal control of heart rate or increased beat-to-beat randomness. We speculate that increased normalized HF power represents nonrespiratory sinus arrhythmia rather than increased vagal modulation of heart rate. Thus, the consistent association of *increased* short-term HRV (including time-domain indices) with mortality supports the hypothesis that increased nonrespiratory beat-to-beat HRV indicates a worse prognosis. Furthermore, this explains why increased short-term HRV, usually hypothesized to reflect vagal modulation of heart rate, has not been associated with better survival.

The mechanism for increased short-term randomness of heart rate is unclear. Potentially, it could be due to sinus nodal

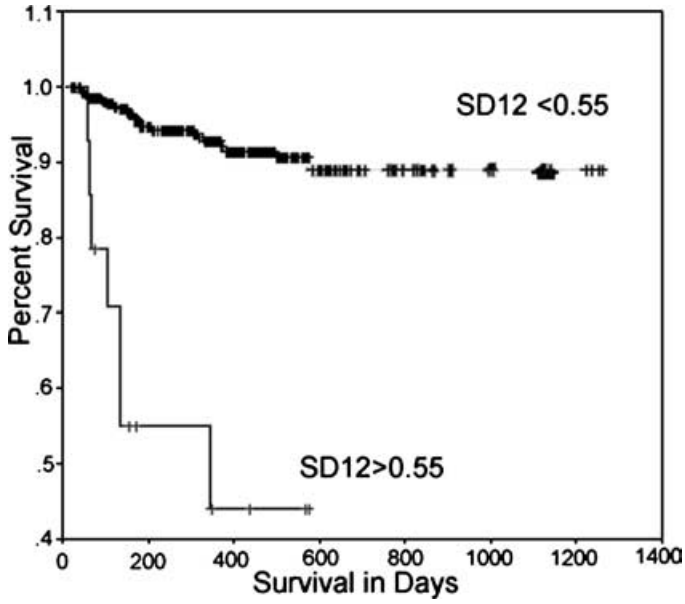

Figure 2. *Survival curve showing markedly decreased survival for patients without CABG or diabetes with SD12 >55%.*

dysfunction resulting in abrupt, random prolongations of sinus intervals. Alternatively, a study of normal volunteers has shown that increasing doses of norepinephrine result in a similar R-R interval behavior, such as abrupt prolongations in R-R intervals that are not related to respiration and result in increased SD12 and altered short-term fractal HR behavior (decreased DFA1).[31,32] Similarly, Woo et al.[33] showed that elevated levels of circulating norepinephrine are associated with complex Poincaré plots among heart failure patients. Although SD12 was not calculated in that study, complex Poincaré plots, as shown, for example, in Figures 1a and b, have a relative increase in SD1 and often a decrease in SD2 that results in markedly increased SD12 values. Together, these findings support the hypothesis that increased random beat-to-beat HR dynamics is a marker for sympathoexcitation and thereby is associated with an increased risk for mortality.

For both traditional and now nonlinear HRV, however, the association with mortality appears to be weakened by the inclusion of patients with CABG surgery post-MI or with diabetes. Longer-term HRV is markedly reduced (by 69% of no CABG in CAST) in patient with recent CABG surgery.[30] It has become clear that this reduction persists for many months.[34] We now have shown that adverse changes in HRV among CABG patients also are seen in nonlinear indices. Thus, the variables most strongly associated with mortality post-MI are markedly decreased (or, in the case of SD12, increased) in a population (19% in CAST) that has better, rather than worse, short-term survival. Results are consistent with a study of patients immediately before and after CABG surgery in which similar changes in nonlinear HRV were observed.[26] Furthermore, increased SD12 on postoperative day 1 was the most powerful independent predictor of postoperative ischemia.[35] Similarly, both traditional and nonlinear HRV are adversely affected in diabetics, but this may be a result of the diabetes and is not, at least in the CAST, associated with risk of mortality post-MI. Thus, exclusion of these two confounding groups may improve the potential for HRV to aid in risk stratification of a post-MI clinical population.

This is the first study we are aware of that used SD12 for risk stratification in a large patient sample. Concurrent with present findings, a previous study showed that an increase in SD12 specifically precedes the onset of life-threatening arrhythmias in post-MI patients.[36] In the CAST population, SD12 proved to have a stronger association with mortality than either DFA1 or power law slope, the two nonlinear indices previously associated with mortality post-MI.[14,16] Moreover, rather than examining the shapes of 24-hour R-R interval plots, we have calculated averaged SD12 for each 1,000 beats from *normal-to-normal* interbeat intervals only. A benefit of this index in risk stratification is that it combines two obvious abnormalities in HR behavior, i.e., decreased intermediate-term variability and increased short-term beat-to-beat variability, although, importantly, the combination of decreased ln ULF and increased SD12 was more powerful than SD12 alone for predicting mortality. Another benefit of this method is that calculation of SD12 is relatively easy.

Although it is unclear whether the reduced number of subjects and events for those recordings eligible for daytime analysis (26 daytime vs 32 for 24 hours) explains why the stronger association with mortality of daytime nonlinear HRV indices compared to 24-hour indices was no longer seen when diabetics also were excluded from the analysis, our results suggest that 24-hour HRV may not always be the best measure for risk stratification purposes. It could be that daytime HRV, which is influenced by both autonomic function and activity,[37] is a better reflection of certain aspects of patient status, much as exercise-based values for many cardiovascular parameters are more useful than resting values. The effect on HRV of increased randomness on the heart rate signal may be more prominent during the daytime when vagal modulation of HR is normally low, and there may be more bursts of sympathetic activation resulting in an increase in random HR behavior. Also, HRV during the nighttime may be exaggerated by conditions such as sleep apnea and other sleep disturbances that could confound the association with mortality.

Limitations to the generalizability of the present study must be noted. First, post-MI therapy has changed since the time of the CAST trial. Although 31% of CAST patients had thrombolytic therapy and 18% underwent percutaneous transluminal coronary angioplasty, specific results must be validated in a population receiving current therapy. However, it must be noted that traditional and nonlinear HRV have continued to predict mortality post-MI even in the modern era.[11] Second, although the current study was based on pretreatment HRV, the CAST population was selected for its high prevalence of ventricular ectopy and subsequently randomized to three different antiarrhythmic therapies that are no longer generally used in post-MI patients. However, in this subset of patients, the significant difference in mortality between patients later treated with encainide and flecainide compared to moricizine was not seen, so treatment assignment did not influence mortality. Also, the mean time from MI to Holter was 70 days, and patients had to undergone both a qualifying and suppression recording to be enrolled in CAST, so many higher-risk patients died before they entered the study. Thus, our sample, although based on the first recording, included only patients who survived to the second CAST recording and whose arrhythmias could be suppressed on the first antiarrhythmic treatment. Also, the endpoint was all-cause mortality, so no estimate can be made of the degree to which HRV is associated with arrhythmic mortality. However, because of the increasing importance of

implantable cardioverter defibrillators, risk stratification of post-MI patients has gained greater urgency. Thus, the potential clinical applicability of our approach to patients in a clinical setting, in whom HRV can be measured beyond the peri-infarction period, should be tested in patients receiving current therapy. In addition, the ability of the combination of traditional and nonlinear HRV to risk stratify, with and without patients with diabetes or CABG post-MI excluded, can be validated in other already collected post-MI datasets.

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