Including patients with diabetes mellitus or coronary artery bypass grafting decreases the association between heart rate variability and mortality after myocardial infarction

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Background  Decreased heart rate variability (HRV) is often assumed to be associated with mortality in all patients after myocardial infarction (MI), independent of clinical factors or time after MI.

Method  HRV was determined from Holter tapes in the Cardiac Arrhythmia Suppression Trial (CAST). Patients were 71 ± 120 days after MI. A total of 735 pre-therapy tapes were analyzed in patients who had ventricular premature contractions (VPCs) suppressed on the first treatment. The period of follow-up was 362 ± 243 days (69 deaths). The association of clinical and demographic factors and 24-hour, daytime, and nighttime HRV to mortality in all patients, patients without coronary artery bypass graft (CABG) surgery between the qualifying MI and the Holter monitoring, and patients with neither CABG nor diabetes mellitus was determined with univariate Cox regression analysis.

Results  For the entire group and the subgroup without CABG, the strongest association was with increased daytime normalized high frequency power (NHF day). Further excluding patients with diabetes mellitus strengthened the association of HRV with mortality rate. Decreased natural logarithm (ln) 24-hour total and ultra low frequency (ULF) power were the strongest predictors of mortality. The best cutoff point for ln ULF for separating survivors and non-survivors was determined. After including a history of MI, congestive heart failure, or both as co-factors, ln ULF ≤7.85 identified patients at approximately 4-times the relative risk of mortality, but did not risk-stratify patients without prior MI or history of congestive heart failure.

Conclusions  HRV predicts mortality rate in a broad range of times after MI. Excluding patients with CABG after MI or with diabetes mellitus significantly strengthens the association of HRV with mortality. HRV measures beyond the peri-infarction period, with clinical factors, can identify subgroups at an elevated risk of mortality. (Am Heart J 2004;147: 309–16.)

The usefulness of 24-hour time and frequency domain heart rate variability (HRV) measured in the peri-infarction period for risk stratification of patients after myocardial infarction (MI) has been validated in numerous investigations, from the Multi-Center Post-Infarction Project (MPIP) in the late 1980s to the recent Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study.1–13 It is often assumed that decreased HRV is associated with an increased risk in virtually all patients after MI. Recent subgroup analyses have suggested that the same HRV risk factors may have different prognostic value in different groups. For example, in ATRAMI, the predictive value of low HRV in the subgroup with low left ventricular ejection fraction was far greater for patients aged ≥65 years. Studies combining HRV with other risk factors affirm that there are subgroups in which decreased HRV has especially high prognostic value.6,13–15

The association of decreased HRV and mortality rate has generally been validated for the peri-infarction period. The Cardiac Arrhythmia Pilot Study (CAPS), a pi-
lot study for the Cardiac Arrhythmia Suppression Trial (CAST), however, showed that decreased HRV measured at 1 year after MI continued to be predictive of mortality during an approximately 2-year follow-up period.\textsuperscript{12}

CAST was an historic post-MI study in which a large number of Holter recordings were collected during a broad range of times after MI, but the relationship of HRV to mortality rate was not explored. We have previously reported that patients with diabetes mellitus or coronary artery bypass graft (CABG) surgery after MI had markedly reduced HRV and that the ability of time domain HRV to add to risk stratification was diluted by their inclusion.\textsuperscript{16} This study is a more-detailed mortality analysis for a broad range of HRV indices. We determined which pre-treatment time and frequency domain HRV indices were significantly associated with mortality in CAST. We hypothesized that the exclusion of patients with CABG after MI or the further exclusion of patients with diabetes mellitus would increase the potential usefulness of both time and frequency domain HRV for risk stratification, even after adjusting for clinical covariates that were strongly associated with mortality.

**Methods**

**Patient population**

The goal of CAST was to determine the effect of suppression of ventricular premature contractions (VPCs) on mortality after MI.\textsuperscript{17} Patients were randomly assigned to receive encainide, moricizine, or flecainide, with flecainide omitted in the subgroup with the lowest ejection fraction. Patients who had a significant suppression of VPCs with a particular agent continued to be given that agent or placebo. More complete information about the study design may be found in the primary end point reports.\textsuperscript{18–20} 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 enrolled in CAST II were selected because they were at a higher risk for adverse outcomes than patients enrolled in CAST I.

Pre-treatment (qualifying) tapes from participants in CAST (N = 830) who had their VPCs successfully suppressed on their first randomly-assigned anti-arrhythmic treatment and continued to be given that agent or placebo. There was no equivalent placebo group, because patients randomized to receive placebo after their suppression tapes underwent anti-arrhythmic treatment until their second recording was made. Tapes with atrial fibrillation (N = 27) or paced rhythm (N = 9) were eliminated from this analysis, as were tapes with <12 hours of adequate data, without at least 50\% of both daytime and nighttime data, or with other technical problems. Some tapes were missing. The remaining tapes (N = 735, 69 deaths) served as the basis for this study. Of these patients, 263 were subsequently randomized to receive encainide, 206 were randomized to receive flecainide, and 266 were randomized to receive moricizine.

**Clinical and demographic data**

Clinical and demographic data were provided by the CAST coordinating center. Characteristics of the CAST patients and procedures for data validation have been reported.\textsuperscript{18,19}

**Analysis of HRV**

Tapes were analyzed on a Marquette SXP Laser Holter scanner (Marquette Electronics, Milwaukee, Wis, software version 5.8) by an experienced research Holter technician using standard Holter analysis procedures. Beat-stream files, representing the time and classification of each QRS complex, were transferred to a Sun Sparcstation computer (Sun Microsystems, Palo Alto, Calif), and careful secondary editing and HRV analysis were performed using previously reported and validated techniques.\textsuperscript{21,22}

**Time domain and frequency domain analysis of HRV**

Calculations were made on the basis of the set of normal (N-N) interbeat intervals. HRV indices calculated in this study are listed in Table I. Methods used for spectral analysis have been described in detail and will be covered briefly here.\textsuperscript{23} The sequence of N-N intervals was resampled to provide a uniformly spaced time series. Missing or noisy segments were replaced by linear interpolation from the neighboring time series of N-N intervals. The time series was demeaned by subtracting the average N-N interval, and fast Fourier transforms were performed to determine the frequency components underlying the cyclic activity in the time series. Measurement of total, ultra low frequency (ULF), and very low frequency power was made on the basis of en bloc analysis of the entire 24-hour recording, the entire daytime period, or the entire nighttime period. Other power spectral HRV indices reported here (low frequency [LF] and high frequency [HF] power, LF/HF ratio, normalized LF, and normalized HF) reflect the average of 5-minute segments in which >80\% of the beats were normal.

**Patient baseline variables**

Table II lists clinical and demographic predictors of outcomes considered in this analysis. Variables selected by the investigators were those that might influence end points.

**Statistical analyses**

HRV indices were tested for normality with the Kolmogorov-Smirnov and Shapiro-Wilk tests and graphical analysis. Natural log transformation was applied, when necessary, to provide a normal distribution appropriate for parametric statistical comparisons. Associations with mortality were evaluated with univariate and multivariate Cox proportional hazards regression. Univariate clinical, demographic, and HRV predictors of mortality were determined for 3 cohorts: 1) the entire CAST population, 2) the subgroup without CABG surgery after the qualifying MI, and 3) the subgroup without CABG surgery after the qualifying MI who also did not have diabetes mellitus. The cutoff point for natural logarithm (ln) ULF power that maximized the hazard ratio for mortality was also identified. The mortality rates higher and lower than this cutoff point for patients with and without a history of MI, chronic heart failure (CHF), or both were compared with $\chi^2$ analysis. The Statistical Package for the Social Sciences soft-
Table I. Definition for HRV indices used in this study

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>Normal-to-normal (N-N) intervals only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term time domain</td>
<td>Standard deviation of N-N intervals</td>
</tr>
<tr>
<td>SDNN</td>
<td>Standard deviation of the 5-minute average of N-N intervals</td>
</tr>
<tr>
<td>Intermediate-term time domain</td>
<td>Average of the standard deviations of N-N intervals over 5 minutes</td>
</tr>
<tr>
<td>CV (%)</td>
<td>Coefficient of variance. Average of averaged N-N intervals standard deviation of N-N intervals for each 5 minutes</td>
</tr>
<tr>
<td>Long-term frequency domain</td>
<td>Total spectral power (1.15 × 10⁻⁰.⁵ Hz)</td>
</tr>
<tr>
<td>Total power (TP)</td>
<td>Ultra-low frequency (ULF) Ultra low frequency power (1.15 × 10⁻⁰.⁰⁰³ Hz)</td>
</tr>
<tr>
<td>Intermediate-term frequency domain</td>
<td>Very-low frequency (VLF) Very low frequency spectral power (0.0033-0.04 Hz)</td>
</tr>
<tr>
<td>Low-frequency (LF)</td>
<td>Low frequency spectral power (0.04-0.15 Hz)</td>
</tr>
<tr>
<td>Normalized LF</td>
<td>Low frequency power divided by (TP-VLF)</td>
</tr>
<tr>
<td>Short-term time domain</td>
<td>Root mean square of differences between successive N-N intervals</td>
</tr>
<tr>
<td>rMSSD</td>
<td>Percent of N-N intervals &gt;50 ms different from the prior interval</td>
</tr>
<tr>
<td>pNN50</td>
<td>Percent of N-N intervals &gt;6.25% of 5-min local average different from the prior interval</td>
</tr>
<tr>
<td>pNN625</td>
<td>High frequency spectral power (0.15-0.4 Hz)</td>
</tr>
<tr>
<td>Normalized HF</td>
<td>High frequency power divided by (TP-VLF)</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>Low to high frequency power ratio averaged for every 5 minutes</td>
</tr>
</tbody>
</table>

Table II. Clinical and demographic variables considered in the univariate analyses (dichotomous variables coded as present or absent)

Clinical and demographic: *age, sex (1 = M, 2 = F), race (1 = white, 2 = non-white), *LVEF; MI, CABG; time since the qualifying MI*
Clinical history preceding qualifying MI: congestive heart failure, angina, MI, sustained hypertension, diabetes, cardiac arrest, ventricular tachycardia
Cardiac procedures preceding qualifying MI: CABG
Cardiac procedures since onset of qualifying MI: thrombolysis, PTCA, CABG
Baseline physical examination: *systolic BP, *diastolic BP, *body mass index, S3 heart sound, tobacco use (current smoking or quit within the last year vs quit >1 year ago or never smoked), NYHA category (1 = ≤1, 2 = 1-3, 3 = 3-4, 4 = ≥4)

From the 12-lead ECG documenting qualifying MI: Q-waves, ST elevation, ST-depression, T-wave inversion, posterior MI, pathological R-waves, *PR interval, *QRS interval, QT interval CAST drug (enceinade/flecainide or moricizine)

*Entered as continuous variables, all others coded as dichotomous variables (1 = present, 2 = absent). LVEF, Left ventricular ejection fraction; MI, myocardial infarction; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; BP, blood pressure.

Results
Clinical and demographic associations with mortality

Table II defines the clinical and demographic variables considered in this analysis. Table III lists the clinical and demographic factors significantly associated with mortality (P <.01) for the entire group, the subgroup of patients without CABG after the qualifying MI, and the subgroup of patients without CABG or diabetes mellitus. The median period of follow-up after MI was 323.5 days (range, 13-1411 days). Among subjects in this study, neither time from MI to Holter monitoring nor the drug to which patients were randomized to receive was predictive of outcome (P <.20). As can be seen from the table, a history of congestive heart failure and a history of MI each remained strong predictors of mortality (P <.001), even after excluding patients with CABG or patients with both CABG and diabetes mellitus.

HRV and mortality in the entire population

Table IV lists HRV indices significantly associated with mortality for the entire group. The overall mortality rate was 9.4%. There were no significant time domain predictors of mortality. As shown in the table, decreased normalized LF power, increased normalized HF power, and decreased LF/HF ratio were predictive of mortality for both 24-hours and daytime. Increased daytime normalized HF power had the strongest association with mortality. Daytime normalized HF power >27.5% had a sensitivity of 74% and a specificity of 8.9% for mortality, with a mortality rate of 16.9% in the 83 patients in the higher-risk group and 8.1% in the 458 patients in the lower-risk group (log rank, 6.0; P = .014)

HRV and mortality after excluding CABG

HRV was not associated with mortality among patients with CABG surgery. Table V lists univariate HRV predictors of mortality when patients with CABG surgery after MI were excluded. The overall mortality rate was 8.9%. The association with mortality of each index...
in Table IV (the entire group) increased, and the number of HRV indices associated with mortality also increased. As can be seen in Table V, In total power and ln ULF power were the strongest 24-hour HRV predictors of mortality in the group without CABG. The strongest association with mortality, however, remained increased daytime ln HF power. Daytime normalized HF power >27.5% had a sensitivity of 75% and a specificity of 9.1% for mortality, with a 19.7% mortality rate in the 67 patients with higher values and a 8.5% mortality rate in the 438 patients with lower values (log rank, 6.97; \( P = .008 \)).

HRV indices and mortality after excluding CABG and diabetes mellitus

Despite the high mortality rate (17%), HRV was not associated with outcome in patients with diabetes mellitus. Table VI shows the association between HRV and mortality when patients with diabetes mellitus were removed from the analysis. The overall mortality rate in the cohort was 8.1%. Despite the reduced number of patients and events, the association of HRV with mortality increased. Decreased ln total power or ln ULF power measured over 24 hours had the strongest association with mortality. Ln 24-hour total power equaling 9.26 had a sensitivity of 75% and a specificity of 49% for mortality, and ln ULF equaling 9.13 had a sensitivity of 75% and a specificity of 45% for mortality.

To explore the ability of ln ULF to separate survivors and non-survivors in CAST, we also determined the value that maximized the hazard ratio for the Cox regression for mortality. For ln ULF equaling 7.85, the high risk subgroup (\( N = 31 \)) had a 29% mortality rate, compared with 6.4% in the lower-risk group. Figure 1 shows survival curves for patients with rates higher and lower than this cutoff point.

Table III. Significant univariate clinical and demographic predictors of mortality (\( P < .01 \)) for all patients with usable 24-hour time domain HRV data (\( n = 735, 69 \) deaths), the subgroup without CABG surgery since the qualifying MI (\( n = 596, 63 \) deaths) and for the subgroup of nondiabetic patients without CABG surgery (\( n = 468, 38 \) deaths)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (( n = 735, 69 ) deaths)</th>
<th>No CABG (( n = 596, 63 ) deaths)</th>
<th>No diabetes and no CABG (( n = 468, 38 ) deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio ( P )</td>
<td>Hazard ratio ( P )</td>
<td>Hazard ratio ( P )</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.95 (&lt; .001)</td>
<td>0.96 (&lt; .001)</td>
<td>0.96 (&lt; .010)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>2.98 (&lt; .001)</td>
<td>2.92 (&lt; .001)</td>
<td>3.79 (&lt; .001)</td>
</tr>
<tr>
<td>History of angina</td>
<td>3.18 (&lt; .001)</td>
<td>3.23 (&lt; .001)</td>
<td>3.49 (&lt; .019)</td>
</tr>
<tr>
<td>History of MI</td>
<td>2.62 (&lt; .001)</td>
<td>3.16 (&lt; .001)</td>
<td>4.52 (&lt; .001)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.21 (\text{N.A.})</td>
<td>2.35 (\text{N.A.})</td>
<td>2.77 (&lt; .004)</td>
</tr>
<tr>
<td>History of CABG</td>
<td>2.32 (&lt; .001)</td>
<td>2.56 (\text{N.A.})</td>
<td>2.77 (&lt; .004)</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0.26 (&lt; .001)</td>
<td>0.25 (\text{N.A.})</td>
<td>0.23 (&lt; .007)</td>
</tr>
<tr>
<td>Race</td>
<td>1.71 (&lt; .001)</td>
<td>1.60 (&lt; .014)</td>
<td>N.S. (\text{N.S.})</td>
</tr>
<tr>
<td>S3 heart sound</td>
<td>2.30 (&lt; .002)</td>
<td>2.51 (&lt; .020)</td>
<td>3.44 (&lt; .007)</td>
</tr>
<tr>
<td>NYHA category</td>
<td>2.04 (&lt; .013)</td>
<td>2.19 (&lt; .007)</td>
<td>3.30 (&lt; .001)</td>
</tr>
<tr>
<td>ST-depression</td>
<td>1.86 (&lt; .012)</td>
<td>2.06 (&lt; .005)</td>
<td>2.51 (&lt; .005)</td>
</tr>
<tr>
<td>QRS width</td>
<td>(3.87 \times 10^9) (&lt; .001)</td>
<td>(4.34 \times 10^9) (&lt; .001)</td>
<td>(1.71 \times 10^9) (&lt; .011)</td>
</tr>
</tbody>
</table>

Table IV. Significant univariate 24-hour and daytime HRV predictors of mortality for all patients with usable HRV data

<table>
<thead>
<tr>
<th>Variable</th>
<th>24 Hours (( n = 625, 59 ) deaths, 9.4%)</th>
<th>Daytime (( n = 541, 51 ) deaths, 9.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio ( P )</td>
<td>Hazard ratio ( P )</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized LF</td>
<td>0.98 ( 5.5) (0.96-0.996) ( P = .019 )</td>
<td>0.97 ( 5.4) (0.95-0.996) ( P = .02 )</td>
</tr>
<tr>
<td>Short-term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized HF</td>
<td>1.03 ( 6) (1.01-1.06) ( P = .015 )</td>
<td>1.04 ( 11.9) (1.02-1.07) ( P = .001 )</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>0.84 ( 5.7) (0.72-0.97) ( P = .017 )</td>
<td>0.82 ( 5.7) (0.70-0.97) ( P = .017 )</td>
</tr>
</tbody>
</table>
Table VI. Significant univariate 24-hour and daytime HRV predictors of mortality for all patients with usable HRV data and without diabetes or CABG surgery post-MI

| HRV index | 24 Hours | | | 24 Hours | | | Daytime | | | Daytime |
|-----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|            | Hazard ratio | Wald $\chi^2$ | (95% CI) | P | Hazard ratio | Wald $\chi^2$ | (95% CI) | P |
| Time domain HRV* | | | | | | | | | | | | |
| Long-term | | | | | | | | | | | | |
| SDNN | 0.99 | 6.2 | (0.98-0.998) | .013 | 0.99 | 5.6 | (0.98-0.998) | .018 |
| SDANN | 0.99 | 6.2 | (0.98-0.998) | .013 | 0.99 | 5.5 | (0.98-0.998) | .019 |
| Ln SDNN | 0.48 | 6.1 | (0.27-0.86) | .014 | 0.44 | 6.3 | (0.23-0.83) | .012 |
| Ln SDANN | 0.49 | 6 | (0.28-0.87) | .014 | 0.46 | 5.9 | (0.25-0.86) | .015 |
| Intermediate | | | | | | | | | | | | |
| Ln SDNNIDX | 0.55 | 4.9 | (0.33-0.93) | .026 | 0.52 | 5.3 | (0.29-0.91) | .022 |
| CV | 0.83 | 5.2 | (0.71-0.98) | .023 | 0.80 | 6.7 | (0.68-0.95) | .010 |
| Frequency domain HRV† | | | | | | | | | | | | |
| Long-term | | | | | | | | | | | | |
| Ln TP | 0.58 | 12 | (0.42-0.79) | <.001 | 0.58 | 8.7 | (0.40-0.83) | .003 |
| Ln ULF | 0.57 | 12.2 | (0.42-0.78) | <.001 | 0.64 | 8.5 | (0.41-0.84) | .004 |
| Intermediate | | | | | | | | | | | | |
| Ln VLF | 0.69 | 8.8 | (0.53-0.88) | .003 | 0.64 | 10 | (0.49-0.84) | .002 |
| Ln LF | 0.69 | 10.4 | (0.55-0.87) | .001 | 0.71 | 7 | (0.55-0.92) | .008 |
| Normalized LF | 0.96 | 9.1 | (0.94-0.99) | .003 | 0.96 | 8.7 | (0.94-0.99) | .003 |
| Short-term | | | | | | | | | | | | |
| Normalized HF | 1.04 | 7.9 | (1.01-1.07) | .005 | 1.06 | 15 | (1.03-1.09) | <.001 |
| LF/HF ratio | 0.81 | 6.2 | (0.69-0.96) | .013 | 0.8 | 6.6 | (0.67-0.95) | .01 |

*24 Hours: n = 596, 63 deaths, 10.6%; daytime: n = 553, 58 deaths, 10.5%.
†24 Hours: n = 504, 53 deaths, 10.5%; daytime: n = 438, 46 deaths, 10.5%.
Multivariate predictors of mortality

As can be seen from a comparison of Tables III and VI, in the cohort of patients without CABG or diabetes mellitus, the strength of association for either ln total power or ln ULF and mortality was similar ($P < .001$) to that for patients with history of MI or history of CHF. The effect of prior MI or CHF on the association between ln ULF and survival was further explored by comparing survival rates higher and lower than ln ULF equaling 7.85 for patients with and patients without a history of MI or CHF. Results are shown on Table VII. As can be seen from the table, the group of patients without a history of MI or CHF had an excellent survival rate, and dichotomizing ln ULF did not add to risk stratification. However, in each of the higher-risk groups (ie, patients with a history of either CHF or MI or with a history of both), decreased HRV identified a subgroup at significantly elevated risk of mortality.

24-hour, daytime, and nighttime HRV as predictors of mortality

As can be seen from Tables IV, V, and VI, HRV measured in 24 hours did not always have the strongest association with mortality. When all the patients or only the patients without CABG were considered, increased normalized HF power during the daytime had the strongest association. When patients with diabetes mellitus were also excluded, 24-hour indices became more powerful. Nighttime HRV had a far weaker association with mortality. In the group of patients without CABG, nighttime values for ln very LF power ($P = .049$), ln LF power ($P = .006$), and normalized LF power ($P = .034$) were associated with mortality. When patients with diabetes mellitus were also excluded, nighttime values for ln TP ($P = .013$), ln very LF ($P = .014$), ln LF ($P = .003$), and normalized LF power ($P = .047$) were significantly associated with mortality.

### Discussion

Our results support the potential usefulness of HRV for risk stratification in patients who are beyond the peri-infarction period and have a broad range of times after MI. HRV recorded pre-therapy was strongly associated with mortality, despite subsequent anti-arrhythmic therapy, but the association of HRV and mortality was affected by the inclusion of patients with diabetes mellitus or CABG after MI. Our results suggest that HRV may not be useful for risk stratification in patients who have diabetes mellitus or have had CABG surgery after MI. In CAST, after CABG, patients had decreased HRV and a decreased mortality rate, whereas patients with diabetes mellitus had decreased HRV, which reflected their disease and resultant higher-risk status and was not predictive of outcome during the relatively short follow-up period.24 We suggest, therefore, that the sensitivity and specificity of HRV for clinical risk stratification after MI would be improved by excluding both groups. However, this hypothesis needs to be tested in patients after MI who are receiving modern therapy.

Lack of prior MI or CHF identified a post-MI population that, despite its frequent VPCs, were at a low risk for mortality. HRV measured beyond the peri-infarction period did not add to risk stratification in this group. Results suggest, however, that HRV would continue to be useful for risk stratification in higher risk groups (ie, patients with a history of MI, CHF, or both). The
results of our study, that decreased ln total power and
decreased ln ULF measured in 24 hours are strongly
associated with mortality in patients beyond the peri-
infarction period, are consistent with the findings of
Bigger et al in the CAPS study. Also consistent with
reports from Bigger et al from the MPIP study, in our
study frequency domain HRV had a stronger associa-
tion with mortality than did time domain HRV. For
example, in our study, decreased SDNN (standard
deviation of all normal-to-normal interbeat intervals),
the best-known time domain predictor of mortality
after MI, while significant, was far weaker than its
frequency domain correlate total power. Thus, when
careful scanning is available, frequency domain HRV
should prove more useful for risk stratification.

The association of increased HRV (ie, higher day-
time normalized HF power) with mortality might, at
first, seem surprising. On the surface, it would ap-
pear to imply that a relative vagal predominance
during the daytime might be associated with higher
risk in a subset of individuals. Alternatively, we
speculate that this markedly increased normalized
HF power might represent a high degree of non-
respiratory sinus arrhythmia (ie, a highly irregular
sinus rhythm presumably caused by sinoatrial node
dysfunction) rather than an increase in vagal modu-
lation of heart rate. This effect may be more promi-
nent during the daytime when vagal modulation of
heart rate is normally low. It is therefore possible
that patients with this rhythm might be at higher
risk. Limited support for this hypothesis comes from
the Rotterdam Study, in which HRV was determined
from resting 12-lead electrocardiograms in older
adults. Both decreased and increased HRV predicted
mortality. In addition, it was observed that the higher
HRV that was associated with increased mor-
tality did not appear to reflect respiratory modula-
tion of heart rate. Results are also consistent with
the finding that decreased short-term fractal scaling
exponent, which reflects greater randomness in
heart rate patterns, is a predictor of mortality in pa-
tients with depressed left ventricular ejection frac-
tion after acute MI.

Limitations to the generalizability of this study
must be noted. First, post-MI therapy has changed
since the time of the CAST trial, and although 31% of
CAST patients underwent thrombolytic therapy
and 18% underwent percutaneous transluminal coro-
nary angioplasty, specific results need to be vali-
dated in a population receiving current therapy. Sec-
ond, although this study was conducted on the basis
of pre-treatment HRV, the CAST population was se-
lected for its high prevalence of ventricular ectopy
and subsequently randomized to 3 different anti-ar-
rhythmic therapies that are no longer generally used
in patients after MI. Also, the mean time from MI to
Holter monitoring was 70 days, and patients had to
have both a qualifying and suppression recording to
be enrolled in CAST, so many higher-risk patients
had died before they could enter the study. Thus,
our sample included only patients who survived to
the second CAST recording and whose arrhythmias
could be suppressed on the first anti-arrhythmic
treatment, and yet HRV continued to be associated
with outcome. Also, the end point was all-cause
mortality, so no estimate can be made of the degree
to which HRV is associated with arrhythmic mortal-
ity. However, because of the increased uses of im-
plantable cardiac defibrillators, risk stratification of
patients after MI has gained increasing importance.
Thus, the potential clinical applicability of our ap-
proach to patients in whom HRV is measured be-
ond the peri-infarction period should be tested. In
addition, the ability of HRV to risk stratify when pa-
tients with diabetes mellitus or patient who undergo
CABG after MI are excluded should be validated in
other already collected post-MI datasets.

References
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