Clin. Cardiol. 23, 187–194 (2000)

Clinical and Demographic Determinants of Heart Rate Variability in Patients Post Myocardial Infarction: Insights from the Cardiac Arrhythmia Suppression Trial (CAST)

PHYLLIS K. STEIN, PH.D., PETER P. DOMITROVICH, PH.D.,* ROBERT E. KLEIGER, M.D., KENNETH B. SCHECHTMAN, PH.D.†
JEFFREY N. ROTTMAN, M.D.,‡ FOR THE CAST INVESTIGATORS

Division of Cardiology, Department of Medicine, Washington University School of Medicine; *Barnes-Jewish Hospital; †Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri; ‡Departments of Medicine (Cardiology) and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

Summary

Background: Clinical and demographic determinants of heart rate variability (HRV), an almost universal predictor of increased mortality, have not been systematically investigated in patients post myocardial infarction (MI).

Hypothesis: The study was undertaken to evaluate the relationship between pretreatment clinical and demographic variables and HRV in the Cardiac Arrhythmia Suppression Trial (CAST).

Methods: CAST patients were post MI and had ≥6 ventricular premature complexes/h on pretreatment recording. Patients in this substudy (n = 769) had usable pretreatment and suppression tapes and were successfully randomized on the first antiarrhythmic treatment. Tapes were rescanned; only time domain HRV was reported because many tapes lacked the calibrated timing signal needed for accurate frequency domain analysis. Independent predictors of HRV were determined by stepwise selection.

Results: Coronary artery bypass graft surgery (CABG) after the qualifying MI was the strongest determinant of HRV. The markedly decreased HRV associated with CABG was not associated with increased mortality. Ejection fraction and diabetes were also independent predictors of HRV. Other predictors for some indices of HRV included beta-blocker use, gender, time from MI to Holter, history of CABG before the qualifying MI, and systolic blood pressure. Decreased HRV did not predict mortality for the entire group. For patients without CABG or diabetes, decreased standard deviation of all NN intervals (SDANN) predicted mortality. Clinical and demographic factors accounted for 31% of the variance in the average of normal-to-normal intervals (AVGNN) and 13–26% of the variance in other HRV indices.

Conclusions: Heart rate variability post MI is largely independent of clinical and demographic factors. Antecedent CABG dramatically reduces HRV. Recognition of this is necessary to prevent misclassification of risk in patients post infarct.

Key words: heart rate variability, postmyocardial infarction, coronary artery bypass graft surgery (CABG), diabetes

Introduction

Clinical and demographic predictors of heart rate variability (HRV) have not been systematically investigated in patient populations post myocardial infarction (MI). While decreased HRV is an almost universal and statistically independent predictor of poor outcome after MI,[1,2] clinical and demographic covariates may correlate with measures of HRV. Strong correlations between HRV and clinical variables could provide mechanistic insights into the robust predictive power of decreased HRV and define important covariates to include in future studies.

We evaluated the relationship among clinical and demographic variables and pretreatment (enrollment) HRV in the Cardiac Arrhythmia Suppression Trial (CAST), a large postinfarction trial for which Holter data and extensive covariates were available. We also evaluated the univariate predictive value of indices of HRV for mortality in CAST.[3]

This study was supported by NHLBI RO-3 Grant # HL53776.

Address for reprints:

Phyllis K. Stein, Ph.D.
Division of Cardiology
Barnes-Jewish Hospital
216 S. Kingshighway Blvd.
St. Louis, MO 63110, USA

Received: May 4, 1999
Accepted with revision: June 22, 1999

Methods

Patient Population

The purpose of CAST was to determine the effects of suppression of ventricular premature beats on mortality after MI.[3] Enrollment required an acute MI within the preceding 2 years and ≥6 ventricular premature beats/h on the pretreatment (qualifying) Holter recording. Those enrolled within 90 days of the index MI were required to have ejection fractions ≤55%, while those enrolled after this 90-day window were required to have ejection fractions ≤40%. After qualification, patients were randomly assigned to encainide, moricizine, or flecainide, with flecainide omitted in the subgroup with the lowest ejection fraction. Patients with significant suppression of ventricular premature beats with a particular agent were continued on that agent or placebo. More complete information concerning study design may be found in the primary endpoint reports.[4–6]

Qualifying tapes from among the 3,549 participants in CAST were obtained from the data coordinating center. Patients in the current study (n = 830) were selected on the basis of having usable qualifying and suppression tapes to permit later evaluation of the predictive value for outcome of the change in HRV with treatment. For the same reason, only patients who had their ventricular premature beats successfully suppressed on their first, randomly assigned, antiarrhythmic treatment and who were continued on that agent were studied. Tapes with atrial fibrillation (n = 27) or paced rhythm (n = 9) were eliminated from this analysis, as were tapes with < 18 h of usable data (n = 24). The remaining qualifying tapes (n = 769) served as the basis for this study. Of these 769 patients, 273 were subsequently randomized to encainide, 219 to flecainide, and 277 to moricizine. It is important to emphasize that HRV data reported here are from the pretreatment tapes recorded prior to antiarrhythmic therapy.

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 procedures for data validation have been reported previously.[4–6]

Analysis of Heart Rate Variability

Tapes were scanned on a Marquette SXP Laser Holter scanner (software version 5.8) (Marquette Electronics, Milwaukee, Wisc., USA). Beat-stream files, representing the time and classification of each QRS complex, were transferred to a Sun Sparcstation computer (Sun Microsystems, Palo Alto, Calif., USA), where careful secondary editing and HRV analysis were performed using previously reported and validated techniques.[7,8]

Calculations were based on the set of normal–normal (N-N) interbeat intervals. The following commonly reported time domain measures of HRV were calculated for 24-h periods: average N-N in ms (AVGNN), the standard deviation of N-Ns in ms (SDNN), the standard deviation of 5-min mean N-Ns in ms (SDANN), the average of standard deviations of N-Ns for each 5-min interval in ms (SDNNIDX), and the root mean square successive difference of N-Ns in ms (rMSSD). The rMSSD primarily reflects parasympathetically mediated changes in heart rate.[9] The other time domain variables reflect a mixture of parasympathetic, sympathetic, and other physiologic influences.[7]

Accurate frequency domain analysis of HRV requires recording with a timing track to compensate for the effects of tape speed variation. Approximately half of the tapes from CAST were recorded on reel-to-reel or other recorders that lacked a timing track. To avoid possible selection bias by center or recording equipment choice, frequency domain indices of HRV were not included in this analysis. In general, time domain measures provide close correlates for the standard frequency domain measures, and time domain HRV may be less subject to computational artifacts.

Statistical Analyses

Indices of HRV were tested for normality, and log transformation was applied when necessary to provide a normal distribution appropriate for parametric statistical comparisons. To identify candidate variables for the multivariate model, Student's *t*-tests evaluated univariate associations between categorical pretreatment clinical and demographic variables and indices of HRV from the pretreatment tapes. Correlation analysis tested continuous variables as candidate predictors of HRV. Statistical significance was based on single comparisons, but the exact p values are presented to allow direct evaluation of the likelihood that a significant result arose as a result of the multiple a priori comparisons. Stepwise linear regression assessed independent clinical and demographic predictors of HRV. Only variables that were univariate predictors of each index of HRV ($p < 0.10$) were candidates variable for the stepwise model for that index. A univariate Cox proportional hazards regression separately tested the predictive value of each index of HRV for mortality.

Results

Distributions for SDANN, SDNNIDX, and rMSSD were skewed and corrected by log transformation. Other time–domain HRV variables showed approximately normal distributions in this population. The expected correlations between time- and frequency-domain measures of HRV were observed in those tapes in which both could be accurately evaluated.[10] Further results are presented in terms of time domain HRV only because these measures could be computed on all tapes in the study.

Univariate associations between HRV and historical and demographic variables are presented in Table I. Lower values for AVGNN (i.e., higher heart rates) were associated ($p < 0.1$) with female gender, nonwhite race, history of congestive heart

failure, history of sustained hypertension [defined as a documented history of systolic blood pressure (SBP) ≥ 160 or diastolic blood pressure (DBP) ≥ 90 mmHg] and diabetes, and these were retained as candidate variables for the multivariate model. All of the historical and demographic variables tested were associated with reduced SDNN, natural logarithm (ln) SDANN and ln SDNNIDX, and were retained to be tested in the multivariate model. Female gender, diabetes, and history of CABG sur-gery before the qualifying MI were associated with reduced ln rMSSD and retained. Also, as can be seen in Table I, differences in HRV between groups are not surrogates for differences in age or ejection fraction.

The relationship between procedures subsequent to the qualifying MI and HRV is shown in Table II. Coronary artery bypass graft surgery was retained as a predictor variable for all indices of HRV. Although patients with PTCA or thrombolysis were younger, this difference was not associated with any differences in HRV. The dramatic reduction in HRV associated with CABG surgery was not associated with any reduction in ejection fraction.

A variety of medications are known to alter HRV.[7] We therefore compared HRV by specific pretreatment medications in CAST. Many patients were taking multiple medications, but interactions were not considered in this univariate

TABLE I Univariate comparisons of age, left ventricular ejection fraction, and indices of heart rate variability by demographics and history preceding qualifying myocardial infarction (total n= 769). P values for SDANN, SDIDX, and rMSSD reflect comparisons of log-transformed values

	Group	Age	LVEF	AVGNN	SDNN	SDANN	SDIDX	rMSSD
Sex								
(n=632)	M	60 ± 10	37 ± 10	815 ± 140	97 ± 40	86 ± 37	42 ± 20	27 ± 19
(n=137)	F	63 ± 8	39 ± 10	768 ± 126	83 ± 31	75 ± 29	34 ± 16	25 ± 16
		p = 0.003	p = 0.056	p = 0.0004	p = 0.0001	p = 0.002	p < 0.0001	p = 0.055
Race								
(n=628)	White	61 ± 10	38 ± 10	816 ± 141	97 ± 39	87 ± 37	41 ± 20	27 ± 19
(n=141)	Non-	59 ± 9	35 ± 10	767 ± 117	85 ± 36	74 ± 33	38 ± 18	26 ± 17
	white	p = 0.061	p = 0.002	p = 0.0001	p = 0.0005	p = 0.0001	p = 0.070	p = 0.597
Hx CHF								
(n=92)	Yes	64 ± 7	32 ± 10	781 ± 124	83 ± 37	74 ± 34	36 ± 20	28 ± 21
(n=677)	No	60 ± 10	38 ± 10	810 ± 140	96 ± 39	87 ± 36	41 ± 10	27 ± 18
		p = 0.0003	p < 0.0001	p = 0.055	p = 0.003	p = 0.001	p = 0.0007	p = 0.809
Hx Angina								
(n=342)	Yes	61 ± 9	36 ± 10	809 ± 146	90 ± 37	80 ± 34	38 ± 18	26 ± 18
(n=427)	No	60 ± 10	38 ± 10	804 ± 133	99 ± 40	88 ± 37	42 ± 20	27 ± 20
		p = 0.178	p = 0.002	p = 0.625	p = 0.002	p = 0.004	p = 0.004	p = 0.591
Hx Htn								
(n=239)	Yes	61 ± 9	36 ± 10	789 ± 138	90 ± 38	81 ± 36	38 ± 19	27 ± 19
(n=530)	No	61 ± 10	38 ± 10	814 ± 138	97 ± 39	86 ± 36	42 ± 19	27 ± 19
		p = 0.181	p = 0.049	p = 0.022	p = 0.018	p = 0.040	p = 0.003	p = 0.596
Diabetes								
(n=161)	Yes	63 ± 9	34 ± 11	769 ± 120	78 ± 31	70 ± 28	32 ± 16	23 ± 13
(n=608)	No	60 ± 10	38 ± 10	816 ± 142	99 ± 39	88 ± 37	43 ± 20	28 ± 20
		p = 0.004	p = 0.0001	p = 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001
Hx MI								
(n=311)	Yes	62 ± 9	34 ± 10	807 ± 140	91 ± 36	80 ± 34	39 ± 21	28 ± 23
(n=458)	No	60 ± 10	39 ± 10	806 ± 138	98 ± 40	87 ± 38	41 ± 18	26 ± 15
		p = 0.059	p < 0.0001	p = 0.884	p = 0.012	p = 0.035	p = 0.046	p = 0.664
Hx CABG								
(n=112)	Yes	62 ± 8	36 ± 11	800 ± 135	86 ± 31	77 ± 29	35 ± 17	25 ± 19
(n=657)	No	61 ± 10	37 ± 10	808 ± 139	96 ± 40	86 ± 37	41 ± 20	27 ± 19
		p = 0.057	p = 0.148	p = 0.566	p = 0.007	p = 0.057	p = 0.002	p = 0.026

Abbreviations: M= males, F= females, LVEF = left ventricular ejection fraction, AVGNN = average normal-to-normal interbeat interval for the entire tape, SDNN = standard deviation of normal-to-normal interbeat intervals for the entire tape, SDANN=standard deviation of the 5-min averages of normal-to-normal interbeat intervals for the entire tape, SDIDX = SDNNIDX= average 5-min standard deviation of normal-to-normal interbeat intervals for the entire tape, rMSSD= root mean square successive differences of normal-to-normal interbeat intervals for the entire tape, Hx CHF = history of congestive heart failure prior to the qualifying MI, Hx Angina = history of angina prior to the qualifying MI, Hx Htn= history of sustained hypertension prior to the qualifying MI, Hx MI= history of MI prior to the qualifying MI.

TABLE II Univariate comparisons of age, left ventricular ejection fraction, and heart rate variability by procedures following qualifying myocardial infarction (total n = 769). Those with percutaneous transluminal coronary angioplasty did not have subsequent coronary artery bypass grafting. P values for SDANN, SDIDX, and rMSSD reflect comparisons of log-transformed values.

	Group	Age	EF	AVGNN	SDNN	SDANN	SDIDX	rMSSD
Thrombolysis								
(n=245)	Yes	59±9	37±10	797±127	95±37	84±35	41±18	25±15
(n=524)	No	62±9	37±10	811±144	95±39	84±37	40±20	28±20
		p<0.0001	p=0.938	p=0.180	p=0.859	p=0.724	p=0.275	p=0.105
PTCA[a]								
(n=112)	Yes	58±10	39±9	819±132	97±34	86±31	42±18	26±12
(n=642)	No	62±10	37±10	830±134	100±38	89±36	43±19	29±21
		p=0.0007	p=0.040	p=0.450	p=0.585	p=0.526	p=0.755	p=0.225
CABG								
(n=123)	Yes	60±9	37±10	694±103	69±33	61±39	28±15	20±12
(n=646)	No	61±10	37±10	828±134	100±38	89±36	43±19	28±20
		p=0.020	p=0.997	p=<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001

[a] Patients with both PTCA and CABG before Holter excluded.

Abbreviations: PTCA = percutaneous transluminal angioplasty after the qualifying myocardial infarction (MI), CABG = coronary artery bypass graft surgery after the qualifying MI. Other abbreviations as in Table I.

TABLE III Univariate comparisons of age, ejection fraction, and heart rate variability by medications at the time of the qualifying Holter (total n= 769). P values for SDANN, SDIDX, and rMSSD reflect comparisons of log-transformed values

	Group	Age	EF	AVGNN	SDNN	SDANN	SDIDX	rMSSD
Beta blocker								
(n=254)	Yes	61±9	39±9	868±148	100±35	88±31	43±19	27±20
(n=515)	No	61±10	36±10	776±123	92±40	83±39	39±19	27±18
		p=0.730	p<0.0001	p<0.0001	p=0.013	p=0.004	p=0.0005	p=0.165
Calcium blocker								
(n=370)	Yes	61±10	38±10	821±127	97±36	86±34	42±20	29±22
(n=399)	No	61±10	36±10	793±147	93±41	82±38	39±19	25±14
		p=0.663	p=0.004	p=0.005	p=0.080	p=0.012	p=0.009	p=0.0003
Digitalis								
(n=178)	Yes	63±9	33±10	771±128	85±40	76±39	35±20	24±19
(n=591)	No	60±10	39±10	817±140	98±38	87±35	42±19	27±19
		p=0.002	p<0.0001	p=0.0001	p<0.0001	p<0.0001	p<0.0001	p=0.0007
Diuretic								
(n=250)	Yes	64±9	33±10	773±126	85±38	77±38	35±18	26±19
(n=519)	No	59±10	39±9	823±141	99±38	88±35	43±19	27±19
		p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p=0.062
Vasodilator								
(n=197)	Yes	62±9	32±10	778±130	89±40	79±38	37±19	25±19
(n=572)	No	60±10	39±9	816±140	97±38	86±35	42±19	27±19
		p=0.139	p<0.0001	p=0.0007	p=0.010	p=0.007	p=0.0008	p=0.022
Nitrates								
(n=363)	Yes	62±9	37±10	819±138	96±38	85±36	41±20	28±22
(n=406)	No	60±10	38±10	796±138	94±39	84±36	40±19	25±16
		p=0.007	p=0.077	p=0.022	p=0.667	p=0.508	p=0.185	p=0.026

Abbreviations as in Table I.

analysis. Results are shown in Table III. All medications tested were retained as candidate predictors of AVGNN. The direction of the effect was different across drugs: beta blockers, calcium-channel blockers, and nitrates were associated with increased AVGNN (slower heart rates), while the other classes of medications were associated with decreased AVGNN. All

medications except nitrates were retained as candidate variables for prediction of SDNN, ln SDANN, and ln SDNNIDX. Again, the direction of the effect was different across medications, with beta blockers and calcium-channel blockers being associated with increased HRV. Calcium-channel blockers and nitrates were associated with increased ln rMSSD, while vasodilators and digitalis were associated with decreases in ln rMSSD.

The relationship between continuous demographic and clinical variables and HRV is displayed in Table IV ($p \leq 0.1$). The AVGNN was positively associated with age, left ventricular ejection fraction, and systolic blood pressure, and negatively associated with New York Heart Association class. The SDNN and ln SDNNIDX were each negatively associated with age and New York Heart Association class and positively associated with left ventricular ejection fraction, time from MI to Holter, and systolic and diastolic blood pressure. Associations with ln SDANN were similar except that age was not a predictor. Ln rMSSD was the only variable associated with ventricular premature beats/h and was also positively related to left ventricular ejection fraction and systolic and diastolic blood pressure.

Stepwise multiple linear regression analysis was performed to identify the extent of independence among univariate predictors of HRV in the pretreatment CAST recording. Variables that entered the model for each index of HRV, their coefficients, and their level of statistical significance are listed in Table V(A). Only predictors that contributed at least $R^2 = 0.009$ to the model were included. Independent predictors for ln SDANN were similar to those for SDNN and are not shown. Total explained variance for ln SDANN was $R^2 = 0.24$. Coronary artery bypass graft surgery after the qualifying MI entered the model first for each of the HRV measures, followed by ejection fraction or the presence of diabetes mellitus. Gender was an independent predictor of all indices except rMSSD. Age and use of beta blockers were predictive for AVGNN only. Time from MI to index Holter was an independent predictor of SDNN, ln SDANN, and ln SDNNIDX.

Finally, a univariate proportional hazards (Cox) model regression evaluated the predictive value of each index of HRV (n = 769, 70 deaths). There were no significant univariate HRV predictors of mortality [Table V(B)]. When patients with CABG were removed from the analysis, the predictive value of decreased SDNN and of decreased ln SDANN achieved borderline statistical significance [$p < 0.06$, Table V(B)]. When patients with diabetes were also removed, the predictive power for mortality of decreased ln SDANN increased further ($p = 0.02$).

Discussion

The CAST trial encompassed patients with a broad range of clinical and demographic data together with high-quality Holter data and long-term follow-up. It is a superb population in which to investigate the association between risk stratifying variables and HRV and to determine the effects of subsequent alteration with therapy.

The most striking finding in our analysis is the association between CABG after MI and a marked reduction (~ 70%) in all indices of pretreatment HRV ($p < 0.0001$). This reduction was not associated with a concomitant difference in left ventricular ejection fraction and with a decrease in survival—a nearly universal co-occurrence with decreased HRV in most patient populations [mortality after 1.1 ± 1.0 years of follow-up was 4.86% for CABG, 4.84% for percutaneous transluminal coronary angioplasty (PTCA), and 11.4% for neither PTCA nor CABG].

It is impossible to assign definite causation in a cross-sectional, post hoc analysis. However, we suspect that the re-

TABLE IV Correlations with $p < 0.1$ between continuous demographic and clinical variables and indices of heart rate variability (total n = 769)

	AVGNN	SDNN	Ln SDANN	Ln SDNNIDX	Ln rMSSD
Age (years)	r = 0.14 (p = 0.0001)	r = −0.08 (p = 0.024)	NS	r = −0.11 (p = 0.002)	NS
LVEF (%)	r = 0.24 (p = 0.0001)	r = 0.19 (p = 0.0001)	r = 0.18 (p = 0.0001)	r = 0.19 (p = 0.0001)	r = 0.17 (p = 0.0001)
MI-to-Holter (days)	NS	r = 0.10 (p = 0.007)	r = 0.12 (p = 0.001)	r = 0.07 (p = 0.043)	NS
VPB/h	NS	NS	NS	NS	r = 0.08 (p = 0.022)
Systolic BP (mmHg)	r = 0.10 (p = 0.0006)	r = 0.08 (p = 0.035)	r = 0.10 (p = 0.004)	r = 0.07 (p = 0.056)	r = 0.11 (p = 0.0015)
Diastolic BP (mmHg)	NS	r = 0.078 (p = 0.030)	r = 0.10 (p = 0.005)	r = 0.08 (p = 0.025)	r = 0.09 (p = 0.012)
NYHA class	r = −0.06 (p = 0.097)	r = −0.10 (p = 0.006)	r = −0.09 (p = 0.012)	r = −0.13 (p = 0.0002)	NS

Abbreviations: Ln = natural logarithm, r = Pearson correlation coefficient, VPB/h = ventricular premature beats/h, BP = blood pressure, NS = not significant, NYHA class = New York Heart Association class. Other abbreviations as in Table I.

TABLE V(A) Independent predictors of heart rate variability in CAST (n = 769) for which contribution to total $R^2 \geq 0.009$. Dichotomous variables are coded 1 = yes, 2 = no

Variable	Coefficient	Contribution to total R^2	p Value
AVGNN (model $R^2 = 0.31$)			
CABG after qualifying MI	119.60	0.126	0.0001
Beta-blocker use	−66.28	0.073	0.0001
Ejection fraction	2.62	0.040	0.0001
Age	2.12	0.012	0.0001
Sex (M = 1, F = 2)	−47.66	0.023	0.0001
Diabetes	29.64	0.009	0.0017
SDNN (model $R^2 = 0.217$)			
CABG after qualifying MI	33.03	0.088	0.0001
Diabetes	13.74	0.047	0.0001
Ejection fraction	0.58	0.026	0.0001
Sex (M = 1, F = 2)	−13.74	0.020	0.0001
Time from MI to Holter	0.04	0.019	0.0001
Ln SDNNIDX (model $R^2 = 0.259$)			
CABG after qualifying MI	0.46	0.111	0.0001
Diabetes	0.21	0.057	0.0001
Diuretic use	0.14	0.029	0.0001
Sex (M = 1, F = 2)	−0.20	0.015	0.0001
Ejection fraction	<0.01	0.017	0.0001
Time from MI to Holter	<0.01	0.014	0.0002
History of CABG before qualifying MI	0.15	0.010	0.0011
Ln RMSSD (model $R^2 = 0.129$)			
CABG after qualifying MI	0.32	0.054	0.0001
Ejection fraction	0.01	0.030	0.0001
Diabetes	0.15	0.015	0.0004
Systolic blood pressure	<0.01	0.010	0.0038

Abbreviation: CAST = Cardiac Arrhythmia Suppression Trial.
Other abbreviations as in Table II.

TABLE V(B) Univariate heart rate variability predictors of mortality in CAST (n = 769, 70 deaths)

Variable	RR (95% CI)	Significance (p value)
AVGNN	1.001 (0.999–1.002)	0.36
SDNN	0.997 (0.991–1.003)	0.36
Ln SDANN	0.800 (0.485–1.319)	0.38
Ln SDNNIDX	0.919 (0.581–1.452)	0.72
Ln rMSSD	1.271 (0.803–2.010)	0.31
Univariate heart rate variability predictors of mortality in patients without coronary artery bypass grafting in CAST (n = 627, 63 deaths)		
AVGNN	1.000 (0.998–1.002)	0.77
SDNN	0.994 (0.987–1.001)	0.09
Ln SDANN	0.576 (0.322–1.028)	0.06
Ln SDNNIDX	0.740 (0.435–1.257)	0.26
Ln rMSSD	1.127 (0.683–1.860)	0.64
Univariate heart rate variability predictors of mortality in patients without coronary artery bypass grafting and without diabetes in CAST (n = 497, 39 deaths)		
AVGNN	1.000 (0.998–1.003)	0.77
SDNN	0.992 (0.982–1.001)	0.07
Ln SDANN	0.400 (0.184–0.871)	0.02
Ln SDNNIDX	0.748 (0.360–1.553)	0.44
Ln rMSSD	1.371 (0.735–2.557)	0.32

Abbreviations: CAST = Cardiac Arrhythmia Suppression Trial, RR = risk ratio, CI = confidence interval. Other abbreviations as in Table I.

duction in HRV with CABG was primarily a consequence of the surgical procedure. Our multiple regression analysis confirms that the presence of CABG was not a direct proxy for other clinically predictive variables. In fact, the most likely clinical predictors of decreased HRV, such as elapsed time since index MI, were very similar between patients with and without CABG (time from the index MI to the qualifying Holter recording was 77 ± 113 days in those with and 70 ± 122 days in those without CABG).

Although little is known about the effect of CABG on HRV, Hogue *et al.* have reported that HRV is substantially reduced in the days immediately following surgery.[11] Results of CAST are consistent with those of Niemela *et al.*[12] who reported that HRV was markedly decreased 1 week after CABG and remained decreased at 6 weeks. Piha and Hämäläinen[13] administered standard cardiovascular reflex tests before and 3 months after CABG. A significant diminution of heart rate responses was noted, suggesting a blunting of autonomic responses. Such changes are likely to be reflected in decreases in some measures of HRV, although we observed decreases in HRV measures which strongly reflect circadian rhythms as well. Piha and Hämäläinen suggested that the changes in heart rate response were due to local mechanical damage to the heart or to its autonomic pathways, rather than to baroreceptor or central nervous system alterations, since blood pressure and pupillometric variables were unchanged. Because most of the CABGs were relatively close to the time of the Holter recording, our data do not address the extent or rate at which HRV normalizes over time in these patients.

Other independent predictors of HRV in this study are consistent with those seen in post-MI populations. Bigger *et al.*[14] examined the relationship of gender and HRV in patients with coronary heart disease. As we also observed, most indices of HRV were higher in men than in women. The correlation between SDNN and left ventricular ejection fraction reported in the Multicenter Post Infarction Project ($r = 0.24$) was similar to that in the CAST population ($r = 0.20$). We observed a smaller relationship between SDNN and age ($r = -0.08$) than was noted in the Multicenter Post Infarction Project ($r = -0.19$).[1] While the association between diabetes and decreased HRV has been observed in numerous studies, diabetes as an independent predictor of HRV post MI has not previously been reported. Taken together, these comparisons suggest that although CAST patients were selected because of having a large number of ventricular premature beats at entry, the relationship between HRV and clinical and demographic predictors is similar to that in the general post-MI population.

Consistently in our study, markers of more severe cardiovascular disease were associated with decreased HRV. However, the extensive set of clinical and demographic factors evaluated here could account for only 13–31% of the variance in the various HRV indices. Approximately 5–13% of this was accounted for by CABG after the qualifying MI, and diabetes accounted for another 1–6%. Thus, variations in HRV are not substantially predicted by clinical measurements, and may provide additional information in studies even when extensive clinical covariates are known.

Some limitations of this study must be noted. First, patients were all suppressible on their first antiarrhythmic treatment. It is possible that such patients are different in some way from those CAST patients who were not. In addition, patients later randomized to encainide, flecainide, or moricizine were suppressible on that particular therapy, and it is possible that they could be different from each other. When the clinical and demographic predictors of HRV were compared between subsequent drug treatments, our results were essentially unchanged. Coronary artery bypass graft surgery, diabetes, and ejection fraction remained the strongest predictors of HRV, and the amount of variance in HRV explained by clinical and demographic variables did not increase.

Finally, HRV did not predict mortality in the entire CAST population. This somewhat surprising result may partly reflect the broad range of times from MI to the qualifying Holter recording (mean 71 ± 119 days, range 4–730 days) and the relatively good prognosis of this population. The removal from the analysis of patients post CABG, a group whose HRV was approximately 70% of values in those without CABG without a concomitant increase in mortality, increased the predictive value of HRV. Similarly, removal from the analysis of the diabetics whose decreased HRV may reflect the severity of their diabetes rather than just the severity of their cardiovascular disease, identified a post-MI population in which decreased HRV was a predictor of mortality.

Our findings reinforce the utility of studies in which HRV is used in addition to standard clinical and demographic variables. They also suggest that antecedent CABG can result in misclassification of risk in both individuals and in population studies and consequently underscore the importance of controlling for antecedent CABG when HRV is used in risk prediction. Our results also suggest that the magnitude of the reduction in HRV may be less useful in risk stratification among diabetics after MI. Reanalyses of data from prior studies of the relationship of HRV and mortality post MI, in which patients who had CABG or diabetes were included, may provide additional insights into the predictive value of HRV post MI.

References

1. Kleiger RE, Miller JP, Bigger JT: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;59:256
2. Stein PK, Kleiger RE: Insights from the study of heart rate variability. *Ann Rev Med* 1999:50:249–261
3. Epstein AE, Bigger JT Jr, Wyse DG: Events in the Cardiac Arrhythmia Suppression Trial (CAST): Mortality in the entire population enrolled. *J Am Coll Cardiol* 1991;18:14–19
4. Hallstrom AI, Pratt CM, Greene HL: Relations between heart failure, ejection fraction, arrhythmia suppression and mortality: Analysis of the Cardiac Arrhythmia Suppression Trial. *J Am Coll Cardiol* 1005;25:1250–1257
5. Echt DS, Liebson PR, Mitchell LF: Mortality and morbidity in patients receiving encainide, flecainide or placebo. *N Engl J Med* 1991;324:781–788
6. The Cardiac Arrhythmia Suppression Trial II Investigators: Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992;327:227–233

7. Berger, RD, Akselrod S, Gordon D: An efficient algorithm for spectral analysis of heart rate variability. *IEEE Trans Biomed Eng* 1986;9:900–904
8. Rottman JN, Steinman RC, Albrecht P: Efficient estimation of the heart period power spectrum suitable for physiologic or pharmacologic studies. *Am J Cardiol* 1990;66:1522–1524
9. Kleiger RE, Stein PK, Bosner MS: Time domain measurements of heart rate variability. *Cardiol Clin N Am* 1992;10:478–487
10. Bigger JT, Fleiss JL, Steinman RC: Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. *Am J Cardiol* 1992;69:891–898
11. Hogue CW, Stein PK, Apostolidou I: Alterations in temporal patterns of heart rate variability after coronary bypass surgery. *Anaesthesiology* 1994;81:1356–1364
12. Niemela MJ, Airaksinen KE, Tahvanainen KU: Effect of coronary artery bypass grafting on cardiac parasympathetic nervous function. *Eur Heart J* 1992;13:932–935
13. Piha S, Hämäläinen H: Effect of coronary bypass grafting on autonomic cardiovascular reflexes. *Ann Med* 1994;26:53–56
14. Bigger JT, Fleiss LF, Steinman RC: RR variability in healthy, middle-age persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation* 1995;91:1936–1943