Correlation of Heart Rate Variability with Clinical and Angiographic Variables and Late Mortality After Coronary Angiography

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Decreased heart rate (HR) variability is associated with increased mortality after myocardial infarction, but the prognostic value of HR variability in patients without recent myocardial infarction and its correlation with other clinical and angiographic data have not previously been reported. In the present study, detailed clinical assessments and 24-hour ambulatory electrocardiograms were performed prospectively on 100 patients undergoing elective coronary angiography. HR variability was inversely correlated with HR ($r = -0.38$, $p = 0.0001$), diabetes mellitus ($r = -0.22$, $p = 0.025$) and digoxin use ($r = -0.29$, $p = 0.004$), but not with left ventricular ejection fraction, extent of coronary artery disease or other clinical, electrocardiographic or angiographic variables. All patients were followed for 1 year. Major clinical events after initial discharge occurred in 10 patients and included 6 deaths and 4 coronary bypass operations. Left ventricular ejection fraction was the only variable that correlated with the occurrence of a clinical event ($p = 0.002$). Decreased HR variability and ejection fraction were the best predictors of mortality (both $p < 0.01$), and the contribution of HR variability to mortality was independent of ejection fraction, extent of coronary artery disease and other variables. Furthermore, 11 patients with HR variability <50 ms had an 18-fold increase in mortality compared with patients with HR variability >50 ms (36 vs 2%, $p = 0.001$). Thus, decreased HR variability is a potent independent predictor of mortality in the 12 months following elective coronary angiography in patients without recent myocardial infarction.

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Decreased heart rate (HR) variability, as assessed by analysis of 24-hour ambulatory electrocardiographic recordings, has recently been shown to be associated with increased mortality following acute myocardial infarction.[1,2] Patients with sudden cardiac death also have depressed HR variability compared with normal control subjects.[3,4] Although the precise mechanism for these associations has not been established, it has been speculated that aberrant HR variability may reflect alterations in cardiac autonomic tone which could predispose to the development of lethal arrhythmias.[5] However, the association between HR variability and other clinical and angiographic parameters in patients with coronary heart disease has not been well defined. Furthermore, the value of decreased HR variability in predicting outcome in patients without recent myocardial infarction has not previously been reported. The present study prospectively examines the relation between HR variability and other clinical, electrocardiographic and angiographic variables in patients without recent myocardial infarction, and determines the utility of HR variability in predicting clinical cardiac events during a 12-month follow-up period.

METHODS

Patient selection: From November 1985 to May 1986, 112 patients <70 years of age undergoing nonemergent cardiac catheterization with coronary angiography for evaluation of known or suspected coronary artery disease were asked to participate in the study. Patients were excluded if they had a myocardial infarction within 4 weeks, known or suspected valvular heart disease other than mitral valve prolapse or nonischemic cardiomyopathy. Three patients refused to participate and 1 patient subsequently did not undergo coronary angiography. Five patients were later determined not to meet entry criteria (3 patients with cardiomyopathy, 1 with aortic stenosis and 1 patient older than 70 years of age) and were excluded from further analysis. Two patients had inadequate ambulatory electrocardiograms and 1 had atrial fibrillation which precluded analysis of HR variability. The remaining 100 patients form the study population for this report.

Data collection: After giving informed consent, each patient underwent a complete history and physical examination with particular emphasis placed on cardiac history, coronary risk factors, functional class and medications. All patients had a 24-hour ambulatory monitor

placed the night before cardiac catheterization (the monitor was removed during the procedure due to technical considerations). Tapes were scanned by a Delmar Avionics 9000A Trendsetter with previously validated supplemental software for analysis of HR variability. HR variability was calculated as the standard deviation of 5-minute means of sinus cycle lengths in milliseconds. All ectopic complexes and beats bounding ectopic complexes were excluded from the analysis, as were 5-minute intervals with fewer than 30 evaluable sinus cycles. Data on HR and atrial and ventricular arrhythmias were also recorded. Cardiac catheterization and coronary angiography were performed using standard techniques. Left ventricular angiography was performed in the 30° right anterior oblique projection and ejection fraction was calculated using the area-length method.[6] Coronary angiograms were read without knowledge of the clinical or electrocardiographic data, and ≥50% diameter narrowing of a major epicardial vessel or branch was considered significant.

Follow-up: Complete 12-month follow-up data were collected on all patients by mailed questionnaires, telephone contact or both. Major events during the follow-up period were defined as documented acute myocardial infarction, revascularization by percutaneous transluminal coronary angioplasty or aortocoronary bypass surgery, and death from any cause. One patient successfully resuscitated from cardiac arrest was also classified as a death. Information was obtained from patients' families or private physicians or both regarding circumstances of death for the 6 patients who died during follow-up.

Statistical analysis: All clinical, electrocardiographic, angiographic and follow-up data were analyzed on the Washington University IBM mainframe computer using the Statistical Analysis System (SAS) software package.[7] Correlation coefficients between specific variables and HR variability, all endpoints and mortality were calculated. Groups were compared using *t* tests for continuous variables and chi-square analysis or Fisher exact test for discrete variables. Multiple regression analysis was performed to test for variable independence in association with specific outcomes. The value of α was 0.05 for all analyses.

RESULTS

Patient characteristics: The mean age of our patients was 55 years (range 24 to 69) and 66 were men. Systemic hypertension (43%), diabetes mellitus (22%) and cigarette smoking (47%) were common, and the plasma total cholesterol averaged 226 mg/dl. All patients had New York Heart Association functional class I through III angina (mean 2.3); only 5 patients had a past history of congestive heart failure. Most patients were taking 1 or more antianginal medications and 10 patients were also taking digoxin.

The catheterization findings are shown in Table I. Twenty-eight patients had no significant coronary stenosis, while 5 patients had significant obstruction of the left main coronary artery. The remaining patients were evenly distributed between those with 1, 2 and 3-vessel coronary disease. Most patients had normal ventricular function, with a mean ejection fraction of 65%. Fifteen patients had an ejection fraction <50%.

TABLE I Results of Cardiac Catheterization and 24-Hour Ambulatory Monitoring

	No. of Pts or Mean ± SD	Percentage or Range
Catheterization results		
Extent of CAD (vessels with ≥50% diameter stenosis)		
0	28	28%
1	23	23%
2	23	23%
3	21	21%
Left main	5	5%
LVEF (%)	65 ± 14	14–96
LVEDP (mmHg)	17 ± 7	6–38
Ambulatory ECG results		
Heart rate (beats/min)	68 ± 10	44–100
HRV (ms)	86 ± 30	30–162
APC/hr	7 ± 34	0–285
VPC/hr	36 ± 155	0–1375
Couplets	16	16%
Triplets	6	6%
Ventricular tachycardia	5	5%

APC = atrial premature complex; CAD = coronary artery disease; ECG = electrocardiogram; HRV = heart rate variability; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; VPC = ventricular premature complex.

The results of 24-hour ambulatory electrocardiographic monitoring are also listed in Table I. Mean HR was 68 beats/min with an average HR variability of 86 ± 30 ms. Atrial premature complexes were relatively infrequent (mean 7/hour), while ventricular premature beats were more common (mean 36/hour). Sixteen patients had ventricular couplets and 11 patients had more advanced grades of ventricular ectopy.

Correlation of heart rate variability with other variables: HR variability was inversely correlated with HR ($r = -0.38$, $p = 0.0001$), use of digoxin ($r = -0.29$, $p = 0.004$) and presence of diabetes mellitus ($r = -0.22$, $p = 0.025$). These was also a trend toward lower HR variability in women (79 ± 27 vs 90 ± 31 ms, $p = 0.07$). No significant correlation was found with age, other risk factors, functional class, other medications, angiographic variables or other data from 24-hour ambulatory monitoring.

Follow-up: Major clinical events occurring during the 12-month follow-up period are listed in Table II. There were no documented myocardial infarctions, but 4 patients had coronary bypass surgery. There were 6 deaths, including 1 patient resuscitated from cardiac arrest.

Table III lists the correlation of specific variables with the occurrence of clinical events during follow-up. Left ventricular ejection fraction was the only variable predictive of subsequent clinical events. However, HR variability was significantly lower in patients who died (55 vs 88 ms, $p = 0.008$). Reduced left ventricular ejection fraction, low cholesterol, HR and digoxin use also correlated with death during follow-up. Using multiple

TABLE II Clinical Events During Follow-Up

Pt	Age (yrs), Sex	HRV (ms)	LVEF (%)	Time to Event (mo)	Event
10	35, M	43	42	2	Sudden cardiac death
30	62, M	93	63	7	Bypass surgery
37	59, M	102	40	6	Sudden cardiac death
46	57, F	97	79	1	Bypass surgery
48	47, M	148	29	6	Bypass surgery
53	68, M	34	75	7	Sudden cardiac death*
61	65, F	30	71	8	Died, lung cancer
78	55, M	92	54	1	Bypass surgery
89	57, M	34	45	12	Died, GI bleeding
92	69, M	89	14	11	Died, pulmonary edema

* Successfully resuscitated.
GI = gastrointestinal; HRV = heart rate variability; LVEF = left ventricular ejection fraction.

regression analysis, HR variability remained an independent predictor of mortality after adjusting for ventricular function, extent of coronary disease, digoxin use, diabetes mellitus and smoking ($p < 0.05$).

To assess the effect of markedly reduced HR variability on prognosis, the data were dichotomized at 50 ms. Thus, 11 patients with low HR variability were compared with 89 patients with HR variability >50 ms. Extent of coronary artery disease and left ventricular function was not different between groups. During follow-up the incidence of major clinical events was significantly higher in patients with depressed HR variability (36 vs 7%, relative risk 5.1, $p = 0.01$). This difference was due entirely to a markedly increased mortality in the low HR variability group (36 vs 2%, relative risk 18, $p = 0.001$).

DISCUSSION

Heart rate during sinus rhythm is modulated by a complex array of parasympathetic and sympathetic influences. In healthy young adults, resting HR is mediated predominantly by vagal tone. Beat-to-beat fluctuations in resting HR—particularly in association with respiration—produce sinus arrhythmia, which may be quite marked in conditioned athletes and has been generally regarded as indicative of cardiovascular fitness.[8] With vigorous activity or stress, vagal tone is withdrawn and HR is regulated principally by adrenergic activity to the extent that a maximum HR >200/minute can be readily achieved in young subjects. Thus, wide variations in HR both at rest and with activity are commonly seen in healthy individuals.[9,10]

By contrast, a number of physiologic and disease states produce alterations in autonomic function which attenuate the incremental changes in HR occurring both at rest and with stress.[11–16] Although resting HR does not change significantly with increasing age, there is a decrease of resting sinus arrhythmia and a linear decline in maximal attainable HR.[9] These changes can be attributed to a decline in efferent vagal cardiac tone and decreased β-adrenergic responsiveness associated with increased age. Diabetic autonomic neuropathy has also been associated with attenuation of the normal fluctuations in HR.[17,18]

TABLE III Correlation of Clinical, Electrocardiographic and Angiographic Variables with Clinical Events During Follow-Up

	With Event (n = 10)	Without Event (n = 90)	p Value
Age (yrs)	58 ± 10	55 ± 9	NS
Male sex (%)	9 (90)	56 (62)	NS
Systemic hypertension (%)	4 (40)	39 (43)	NS
Diabetes mellitus (%)	2 (20)	20 (22)	NS
Cigarette smoking (%)	6 (60)	41 (46)	NS
Total cholesterol (mg/dl)	220 ± 56	227 ± 46	NS
NYHA class	2.5 ± 0.8	2.3 ± 0.7	NS
History of CHF (%)	1 (10)	4 (4)	NS
Medications			
Nitrates (%)	5 (50)	53 (59)	NS
β blockers (%)	4 (40)	49 (54)	NS
Calcium antagonists (%)	4 (40)	39 (43)	NS
Digoxin (%)	3 (30)	7 (8)	NS
Angiographic data			
Narrowed arteries	2.0 ± 1.2	1.5 ± 1.2	0.20
LVEF (%)	51 ± 21	67 ± 12	0.002
LVEDP (mm Hg)	17 ± 7	17 ± 7	NS
Electrocardiographic data			
Heart rate (beats/min)	73 ± 13	68 ± 10	0.18
HR variability	76 ± 37	88 ± 29	NS
APC/hr	1 ± 1	8 ± 36	0.07
VPC/hr	40 ± 109	36 ± 160	NS

APC = atrial premature complex; CHF = congestive heart failure; HR = heart rate; LVEDP = left ventricular end diastolic pressure; LVEF = left ventricular ejection fraction; NS = not significant; NYHA = New York Heart Association; VPC = ventricular premature complex.

A number of lines of evidence suggest an association between alterations in resting HR, attenuation of HR variability and cardiovascular prognosis.[1–4,19–23] In the Framingham study,[21] resting HR at study entry in patients free of cardiac disease was found to correlate with subsequent cardiovascular mortality and in particular with sudden cardiac death. This association was independent of other known cardiovascular risk factors. Persistent sinus tachycardia has been associated with a poor prognosis in patients with acute myocardial infarction[22,23] or chronic congestive heart failure. Patients with documented sudden cardiac death have recently been shown to have decreased HR variability relative to normal control subjects.[3] Patients with diabetic autonomic neuropathy may also be at increased risk for sudden cardiac death despite the absence of documented preexisting heart disease.[19] Finally, in a recent report by Kleiger et al,[1] decreased HR variability was found to be a potent predictor of cardiac mortality after acute myocardial infarction, an effect that was independent of ventricular function, ventricular ectopic activity, HR and other previously identified prognostic indicators.

In the present study, HR variability was found to correlate inversely with HR, diabetes and digoxin use, but not with other clinical, angiographic or Holter variables. Kleiger et al[1] also found a moderate inverse correlation with HR ($r = -0.52$). However, HR variability was a much more potent predictor of subsequent mortality than HR alone.[1] The present study supports these findings.

Table III illustrates the value of selected clinical, Holter and angiographic variables in predicting cardiac events during follow-up. Left ventricular ejection fraction was the only predictor, consistent with numerous

prior studies demonstrating the prognostic importance of this variable.[24-26] Although left ventricular dysfunction was the best predictor of late mortality, reduced HR variability also correlated strongly and independently with this endpoint. The combination of reduced ejection fraction (<50%) and low HR variability (<50 ms) was particularly ominous: both patients with these findings died during follow-up.

In the study by Kleiger et al,[1] HR variability <50 ms was associated with a particularly poor prognosis. Although the method for HR variability calculation in the present study differed from that used by Kleiger, there was again a strikingly higher mortality in patients with HR variability <50 ms. Thus, reduced HR variability is associated with a poor prognosis, not only in patients with recent myocardial infarction[1] but in those without infarction undergoing elective coronary angiography.

The mechanism underlying the increased mortality in patients with low HR variability is not known. The fact that decreased HR variability is due predominantly to a reduction in underlying vagal tone has been documented by several studies.[10,15,16] Furthermore, in experimental studies attenuation of vagal activity predisposed to malignant ventricular arrhythmias,[27] while vagal stimulation was found to be protective.[28,29] However, the relative role of parasympathetic and sympathetic effects on HR variability remains to be fully elucidated.

Data limitations: This study is limited by the relatively small sample size and thus requires verification with larger series. Although the present data expand the role of HR variability as a prognostic indicator in patients with coronary heart disease, its value in other cardiovascular disorders is unknown. An analysis of the components of HR variability[2,30] might also provide information not obtainable with present methodology. Finally, the data do not provide insight into the mechanisms of HR variability. Further studies addressing these issues are needed.

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