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Prognostic Value of Heart Rate Variability for Sudden Death and Major Arrhythmic Events in Patients With Idiopathic Dilated Cardiomyopathy

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OBJECTIVE This study was designed to evaluate the prognostic value of heart rate variability for sudden death, resuscitated ventricular fibrillation or sustained ventricular tachycardia in patients with idiopathic dilated cardiomyopathy.

BACKGROUND Previous studies have shown that heart rate variability could predict arrhythmic events and sudden death in postinfarction patients, but the prognostic value of heart rate variability for arrhythmic events or sudden death in patients with idiopathic dilated cardiomyopathy has not been established.

METHODS Time and frequency domain analysis of heart rate variability on 24-h electrocardiographic (ECG) recording was assessed in 116 patients with idiopathic dilated cardiomyopathy (91 men, aged 51 ± 12 years, left ventricular ejection fraction 34 ± 12%).

RESULTS Mean follow-up (± SD) was 53 ± 39 months. Sixteen patients reached one of the defined study end-points (sudden death, resuscitated ventricular fibrillation or sustained ventricular tachycardia) during follow-up. Using multivariate analysis, only reduced standard deviation of all normal-to-normal intervals (SDNN) ($p = 0.02$) and ventricular tachycardia during 24-h ECG recording ($p = 0.02$) predicted sudden death and/or arrhythmic events. For SDNN, a cutoff level of 100 ms seemed the best for the risk stratification.

CONCLUSIONS Decrease in heart rate variability is an independent predictor of arrhythmic events and sudden death in idiopathic dilated cardiomyopathy, whether the mechanism of sudden death is ventricular tachyarrhythmia or not. (J Am Coll Cardiol 1999;33:1203–7) © 1999 by the American College of Cardiology

Imbalanced regulation of the cardiac autonomic nervous system is one of the important pathophysiological changes in congestive heart failure, and analysis of heart rate variability (HRV) provides information about these disturbances. Several studies have shown that a decrease in HRV is associated with poor prognosis after acute myocardial infarction (1–4). Decreased HRV has been related to the risk of ventricular arrhythmias and of sudden death (1,3,4). We investigated the prognostic value of HRV for sudden death and arrhythmic events (resuscitated ventricular fibrillation or sustained ventricular tachycardia) in patients with idiopathic dilated cardiomyopathy (IDC), a population in whom this element has not previously been demonstrated.

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METHODS

Patients. One hundred and forty patients with IDC according to the definitions of the World Health Organization (5) were continuously studied between February 1983 and June 1998. Diagnosis was established by normal coronary angiography in all patients, echocardiography and radionuclide-gated blood pool ventriculography. Patients with chronic renal failure, diabetes mellitus, atrial arrhythmias, sinus node dysfunction, atrioventricular block or with a permanent pacemaker were excluded for analysis of HRV. Analysis of HRV was possible in 116 patients. At the time of the 24-h ambulatory electrocardiographic (ECG) recording, patients were treated with diuretics (47%), digoxin (45%), angiotensin-converting enzyme (ACE) inhibitors (45%), and/or nitrates (14%). Because they were seen at the time of the diagnosis of disease, 36% of the patients were not receiving medical treatment. None of the patients were receiving beta-blockers or antiarrhythmic agents. All the

Abbreviations and Acronyms

CHF	=	congestive heart failure
ECG	=	electrocardiogram
HF	=	high frequency power
HRV	=	heart rate variability
IDC	=	idiopathic dilated cardiomyopathy
LF	=	low frequency power
LV	=	left ventricle
Mean RR	=	mean duration of all normal-to-normal
NN	=	normal-to-normal intervals
NYHA class	=	New York Heart Association function class
pNN50	=	number of NN intervals differing by more than 50 ms from adjacent interval divided by the total number of all NN intervals
rmsSD	=	square root of the sum of the squares of differences between adjacent NN intervals
SDANN	=	standard deviation of the averages of NN intervals in all 5-min segments
SDNN	=	standard deviation of all NN intervals
Tot P	=	total frequency power
VLF	=	very low frequency power
VF	=	ventricular fibrillation
VT	=	ventricular tachycardia

patients were treated during follow-up with long-term ACE inhibition, and/or diuretics or digoxin if necessary.

24-h ambulatory ECG recording. Twenty-four hour ambulatory ECG recording was performed by a two-channel recorder. All recordings were analyzed using an HRV system (Medilog Excel 5-1; Oxford) with manual edition and correction of RR intervals and QRS. Tapes were eligible if they had at least 20 h of analyzable data. Ventricular arrhythmias were classified according to Lown's grades, and nonsustained ventricular tachycardia was defined as three or more consecutive premature ventricular beats, each lasting less than 30 s (6).

The time domain analysis of HRV included Mean RR (mean duration of all normal-to-normal [NN] intervals, ms), SDNN (standard deviation of all NN intervals, ms), SDANN (standard deviation of the averages of NN intervals in all 5-min segments, ms), rmsSD (square root of the sum of the squares of differences between adjacent NN intervals, ms) and pNN50 (number of NN intervals differing by more than 50 ms from adjacent interval divided by the total number of all NN intervals, %).

The spectral analysis algorithm used a fast Fourier transform. Data were analyzed in 10-min epochs throughout the recording. The results from each 10-min epoch were averaged to form a composite spectrum. The range 0 to 0.5 Hz was represented by 1,000 harmonics. The data were presented in a nonlinear scale (ms^2). Frequency domain measurements included: total power (Tot P: 0–0.4 Hz), very low frequency (VLF: 0.0033–0.04 Hz), low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz).

Table 1. Clinical Characteristics and Results of Investigations in Patients With IDC

Age (years)	51 ± 12
Gender (M/F)	92/24
NYHA class:	
I–II n (%)	66 (57%)
III–IV n (%)	50 (43%)
Duration of heart failure symptoms (months)	23 ± 35
Left bundle branch block n (%)	35 (30%)
LV end diastolic diameter (mm)	67 ± 9
LV end systolic diameter (mm)	54 ± 11
LV shortening fraction (%)	20 ± 9
Mean pulmonary artery pressure (mm Hg)	19 ± 9
Pulmonary capillary wedge pressure (mm Hg)	13 ± 8
Cardiac index (liters/min/m^2)	2.95 ± 0.8
LV ejection fraction (%)	34 ± 12
Lown 4B on ambulatory 24-h ECG n (%)	36 (31%)

LV = left ventricle; NYHA class = New York Heart Association function class.

Statistical analysis. The power spectral measures were transformed in natural logarithms (ln) to achieve normal distributions. Event-free curves were estimated by the Kaplan-Meier method, and curves were compared with the log rank test. Sudden death was defined as instantaneous death or death occurring within 1 h of the onset of symptoms in a patient without evidence of the presence of progressive heart failure or death during sleep (7). The effects of hemodynamic parameters, HRV and runs of ventricular tachycardia were studied with univariate analysis and multivariate regression analysis (proportional hazards model). A forward stepwise model with a p value for entry of 0.05 was used. All values are given as mean ± standard deviation. Statview 4.5 software (Abacus Concepts) was used for statistical analysis.

RESULTS

Characteristics of patients. The mean age of the patients on hospital admission was 51 ± 12 years (range 21 to 70). Ninety-one (78%) were men. Clinical data and results of ECG, radionuclide ventriculography, hemodynamic investigations and 24-h ambulatory ECG are summarized in Table 1. Measurements of HRV are in Table 2.

Analysis of mortality and cardiac events. Mean follow-up was 53 ± 39 months. Eighteen patients died during follow-up: nine progressive congestive heart failure (CHF), seven sudden deaths and two noncardiac deaths (cancer). Four patients could be resuscitated from documented ventricular fibrillation (VF) and 6 more patients had sustained ventricular tachycardia (VT). Of these 10 patients, seven were treated with an implantable cardioverter-defibrillator, one was treated with sotalol and had no recurrence, one underwent heart transplantation and the last one was treated

Table 2. Time-Domain and Frequency-Domain Measurements of HRV on 24-h Ambulatory ECG in Patients With IDC

Mean RR (ms)	740 ± 128
SDNN (ms)	97 ± 39
SDANN (ms)	84 ± 18
rmsSD (ms)	25 ± 14
pNN50 (%)	5.8 ± 7.6
ln Tot P (ln ms^2)	7.5 ± 1.0
ln VLF (ln ms^2)	3.4 ± 0.5
ln LF (ln ms^2)	5.5 ± 1.2
ln HF (ln ms^2)	4.4 ± 1.0

HF = high frequency power; LF = low frequency power; ln = natural logarithm; Mean RR = mean duration of all normal-to-normal (NN) intervals; pNN50 = number of NN intervals differing by more than 50 ms from adjacent interval divided by the total number of all NN intervals; rmsSD = square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDANN = standard deviation of the averages of NN intervals in all 5-min segments; SDNN = standard deviation of all NN intervals; Tot P = total frequency power; VLF = very low frequency power.

Table 3. Characteristics, Time-Domain and Frequency-Domain Measurements of HRV on 24-h Ambulatory ECG in Patients With Sudden Death, Arrhythmic Events or Free of Event

	Free of Event (n = 100)	Sudden Death (n = 7)	Arrhythmic Event (n = 10)
Age (yrs)	51 ± 12	50 ± 12	53 ± 15
Duration of FU (months)	53 ± 41	31 ± 24	37 ± 9
LVEF (%)	35 ± 13	34 ± 9	37 ± 9
Mean RR (ms)	727 ± 119	717 ± 87	778 ± 167
SDNN (ms)	101 ± 39	69 ± 24	80 ± 27
SDANN (ms)	84 ± 17	80 ± 11	85 ± 12
rmsSD (ms)	25 ± 15	29 ± 12	25 ± 8
pNN50 (%)	5.7 ± 7.8	9.4 ± 6.3	5.3 ± 4.7
ln Tot P (ln ms^2)	7.6 ± 1.0	6.9 ± 1.2	7.1 ± 1.0
ln VLF (ln ms^2)	3.5 ± 0.5	3.0 ± 0.6	3.2 ± 0.5
ln LF (ln ms^2)	5.6 ± 1.2	4.9 ± 1.3	5.0 ± 1.2
ln HF (ln ms^2)	4.4 ± 1.0	4.4 ± 1.1	4.3 ± 0.9

FU = follow-up; other abbreviations as in Table 2. Data of one patient with arrhythmic event who suffered sudden death are included both in column 2 and in column 3.

with amiodarone but had poor therapy compliance and suffered sudden death. Eleven patients underwent heart transplantation and were censored at the time of the transplantation for statistical analysis of survival. After follow-up, 16 patients reached one of the prospectively defined study end-points (sudden death, resuscitated VF or sustained VT). The event-free curves of cardiac deaths (CHF or sudden death), of sudden death alone and of arrhythmic events (resuscitated VF or spontaneous sustained VT) are shown in Figure 1.

Main characteristics and measurements of HRV in patients with sudden death, arrhythmic events or free of events are in Table 3. Statistical analysis was not performed on these data because a *t* test would not take into account the duration of the follow-up. Univariate regression analysis demonstrated that nonsustained ventricular tachycardia on 24-h ambulatory ECG recording (p = 0.01), decreased SDNN (p = 0.02), decreased Tot P (p = 0.04) and decreased VLF (p = 0.04) were predictors of sudden death and/or arrhythmic events. Age, New York Heart Association function (NYHA) class, left ventricular ejection fraction and other hemodynamic parameters were not predictors of end-point. When univariate predictors were included in the multivariate analysis, only reduced SDNN (p = 0.02) and ventricular tachycardia during 24-h ECG recording (p = 0.02) were independent predictors of sudden death and/or arrhythmic events.

Event-free curves for total patients according to SDNN are displayed in Figure 2 for cardiac death and in Figure 3 for sudden death and/or arrhythmic events. One patient with arrhythmic event suffered sudden death and was plotted with the follow-up at the time he had sustained VT on the event-free curves of sudden death and/or arrhythmic events. For SDNN, we used a cutoff level of 100 ms as used in previous studies concerning HRV in congestive heart

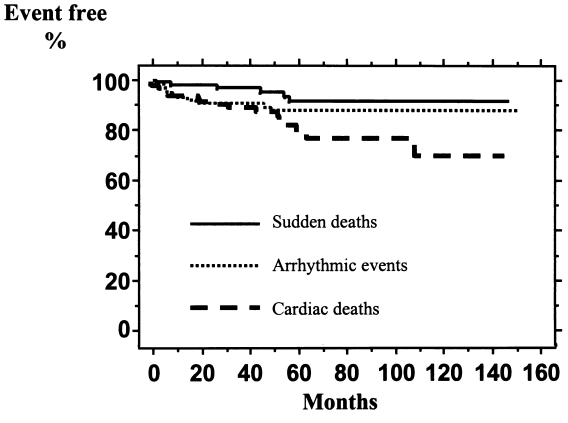

Figure 1. Event-free curves of cardiac deaths, sudden deaths and arrhythmic events (resuscitated ventricular fibrillation or spontaneous sustained ventricular tachycardia) in patients with idiopathic dilated cardiomyopathy.

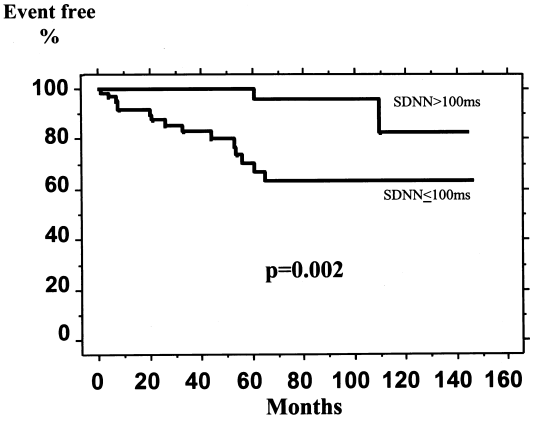

Figure 2. Event-free curves of cardiac death (progressive congestive heart failure or sudden death) according to standard deviation of all normal-to-normal intervals in patients with idiopathic dilated cardiomyopathy.

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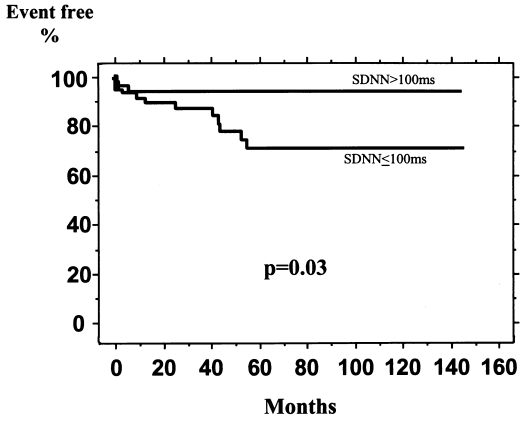

Figure 3. Event-free curves of sudden death and arrhythmic events according to standard deviation of all normal-to-normal intervals in patients with idiopathic dilated cardiomyopathy.

failure (8,9), and it was possible to determine two groups of patients with significantly different event-free curves of cardiac death ($p = 0.002$) and event-free curves of sudden death and/or arrhythmic event ($p = 0.03$).

DISCUSSION

To the best of our knowledge, this study is the first to show that decreased SDNN is an independent predictor of sudden death, resuscitated VF or sustained VT in idiopathic dilated cardiomyopathy (IDC) and to suggest that HRV is a method for stratification of major arrhythmic events in CHF without coronary artery disease. Moreover, it was confirmed that a low SDNN was also a predictor of cardiac mortality of all causes in patients with IDC.

Spectral analysis of HRV was performed in all patients but it provided only redundant information at the time of multivariate statistical analysis. It is well known that the results of frequency-domain analysis are equivalent to those of time-domain analysis, which is easier to perform (1), particularly for SDNN. It should be noticed that total power had less power than SDNN after multiregression, whereas these two parameters give similar information about overall HRV from a theoretical point of view. The technical explanation might be that total power in this study was the average of the total power of each 10-min period. It thus excludes the ultra-low-frequency power of HRV, a possible predictor of mortality. However, we give the results of the spectral analysis, because Bigger et al. found that the very-low-frequency power after myocardial infarction was more strongly associated with arrhythmic death than with all-cause mortality or cardiac death (3), although the physiological mechanisms for this component has not been fully identified. Moreover, a recent study by Mortara et al. suggested that breathing disorders are not uncommon in congestive heart failure, and they are associated with an increase in the VLF power that can affect measurement of HRV (10). It was found that VLF accounted for 55% of total HRV in subjects with normal breathing, whereas VLF was 77% and 87% of Tot P in patients with periodic breathing or Cheyne-Stokes respiration, respectively. In our study, the ratio of VLF to Tot P was 53% for the whole group; it was also 53% in patients who suffered sudden death and 54% in patients with arrhythmic events, thus similar to subjects with normal breathing in the study by Mortara. It appears, therefore, that our study was not affected by this confounding effect.

Hoffmann et al. had already evaluated HRV in 71 patients with IDC and major arrhythmic events (sustained VT, VF and sudden death) (11). With a relatively short follow-up of 15 ± 5 months, they found a nonsignificant trend toward lower parasympathetic activity in the time-domain in patients with major arrhythmic events. In this study, as in most others, sudden death was considered to be an arrhythmic event, due to ventricular tachyarrhythmias. However, the incidence of cerebral or pulmonary embolism, severe bradycardia or electromechanical dissociation is probably underestimated in patients with advanced heart failure (12).

There is a high incidence of spontaneous ventricular arrhythmias during 24-h ambulatory ECG in patients with IDC, but the prognostic value of these abnormalities for sudden death remains controversial (13–15). The value of signal-averaged ECG is limited by frequent bundle branch block in patients with IDC. Moreover, this method only explores the possible re-entrant substrate for ventricular arrhythmias, and has a controversial prognostic value for sudden death in IDC (14,15). Electrophysiological testing has a poor negative predictive value for sudden death in IDC (15). QT dispersion, a measurement of the inhomogeneity of myocardial repolarization that could in some cases be a marker of arrhythmic events when abnormally increased, has not been shown to be a predictor of death or arrhythmic events in IDC (16). Negative results with these three methods of investigation are further arguments, suggesting that ventricular tachyarrhythmias could be only one of the several mechanisms of sudden death in IDC. Decrease in HRV might be a predictor of both "arrhythmic" and "nonarrhythmic" sudden death in IDC.

In a previous study concerning the general characteristics of HRV in IDC, we found that analysis of HRV in association with hemodynamic parameters allows better identification of patients at high risk of cardiac death or heart transplantation but that there was no correlation between HRV and ventricular arrhythmias or signal-averaged ECG in patients with IDC (9). Sudden death was the cause of only 35% of deaths in both studies. Hence, our results provide new information about the prognostic value of HRV in IDC in comparison with the previous study. Our results do not contradict the hypothesis that a decrease in HRV is mainly a reflection of the deterioration in hemodynamic status, as previously described in CHF (17).

Not all patients in this study had the same treatment at the time of the ambulatory ECG recording. It is known that

ACE inhibition and digoxin affect heart rate variability (18–21). However, the groups of patients with sudden death, arrhythmic events or free of events did not differ in their medical treatment at this time, and they were thereafter treated with a similar standard treatment for chronic heart failure. Whether an increase in SDNN with medical treatment may reverse the poor prognosis of patients with decreased SDNN should be investigated in the future.

Conclusions. This study is one of the first to show that HRV provides a stratification of sudden death and/or major arrhythmic events in CHF without coronary artery disease. Our results, which were obtained in a relatively large group of patients with long follow-up, indicate that reduction in SDNN is an independent prognostic marker of these events in IDC, whether the mechanism of sudden death is ventricular tachyarrhythmia or not.

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