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Heart Rate Variability in Idiopathic Dilated Cardiomyopathy: Characteristics and Prognostic Value

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Objectives. **This study was designed to evaluate heart rate variability (HRV) in patients with idiopathic dilated cardiomyopathy (IDC), to determine its correlation with hemodynamic variables and ventricular arrhythmias and to evaluate its prognostic value in IDC.**

Background. **Previous studies have shown that HRV could predict arrhythmic events in patients after infarction, but the characteristics of HRV in IDC have not been fully established.**

Methods. **Time domain analysis of HRV on 24-h electrocardiographic (ECG) recording was performed in 93 patients with IDC, and results were compared with those in 63 control subjects.**

Results. **Patients with IDC, even those without congestive heart failure, had significantly lower values for HRV than those of control subjects. HRV was related to left ventricular shortening fraction ($R = 0.5$, $p = 0.0001$) and to peak oxygen uptake ($R = 0.53$, $p = 0.01$). HRV was not different in patients with runs of ventricular tachycardia or in patients with late potentials on the signal-averaged ECG. During a mean follow-up period (±SD) of 49.5 ± 35.6 months, patients with reduced HRV had an increased risk of cardiac death or heart transplantation ($p = 0.006$). On multivariate analysis, cardiac events were predicted by increased left ventricular end-diastolic diameter ($p = 0.0001$), reduced standard deviation of all normal to normal RR intervals ($p = 0.02$) and increased pulmonary capillary wedge pressure ($p = 0.04$).**

Conclusions. **Decreased HRV in patients with IDC is related to left ventricular dysfunction and not to ventricular arrhythmias. Analysis of HRV can identify patients with IDC who have an increased risk of cardiac death or heart transplantation.**

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Heart rate variability (HRV) gives information about the influences of the autonomic nervous system. Several studies (1–5) have shown correlations between decrease in HRV and severity of several cardiac diseases, particularly in patients recovering from acute myocardial infarction. Decreased HRV has been related to the risk of ventricular arrhythmias and of sudden death (4,5). We investigated HRV in patients with idiopathic dilated cardiomyopathy (IDC) to determine the correlation between HRV variables, hemodynamic data and ventricular arrhythmias in this disease and to evaluate the prognostic value of this method.

Methods

Patients. One hundred eleven patients with IDC according to the definitions of the World Health Organization (6) were continuously studied between February 1983 and May 1995. Diagnosis was established by echocardiography, normal coronary angiographic findings in all patients and radionuclide-gated blood pool ventriculography. Patients aged >70 years or with chronic renal failure, diabetes mellitus, atrial arrhythmias, sinus node dysfunction, atrioventricular block or a permanent pacemaker were excluded from analysis of HRV. Analysis of HRV was possible in 93 patients (75 men, 18 women). Twenty-seven patients (29%) had significant alcoholism (alcohol intake >80 g/day), seven (7.5%) had a history of paroxysmal atrial arrhythmia and six (6.6%) had moderate chronic respiratory insufficiency. Forty-three patients (46.2%) were receiving diuretic drugs, 42 (45.2%) digoxin, 29 (31.2%) angiotensin-converting enzyme inhibitors, 14 (15.1%) nitrates and 9 (9.7%) an antiarrhythmic agent (hydroxyquinidine in 5, amiodarone in 3, cibenzoline in 1). No patients were receiving beta adrenergic blocking agents either because they were treated before 1990 or because they were seen at the time of diagnosis of the disease. The control group included 63 healthy subjects (33 men, 30 women) aged 20 to 70 years with no cardiovascular symptoms, normal findings on a general examination, no medication that might affect autonomic nervous activity, normal results on electrocardiography and echocardiography and, in subjects aged >50 years, normal coronary angiographic findings.

24-h ambulatory electrocardiographic (ECG) recording. 24-h ambulatory ECG recording was performed by two-channel recorder. Antiarrhythmic agents were withdrawn ≥3

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Abbreviations and Acronyms

day HR/night HR = ratio of day mean heart rate to night mean heart rate
ECG = electrocardiogram, electrocardiographic
HRV = heart rate variability
IDC = idiopathic dilated cardiomyopathy
LV = left ventricular
mean RR = mean duration of all normal to normal RR intervals
NN interval = normal to normal RR interval
rmsSD = square root of the sum of the squares of differences between adjacent normal to normal RR intervals
SDNN = standard deviation of all normal to normal RR intervals
VT = ventricular tachycardia

days before the recording. All recordings were analyzed by using the Oxford Medilog Excel 5-1 HRV system with manual edition and correction of RR intervals and QRS complex. Tapes were eligible if they had ≥22 h of analyzable data. Ventricular arrhythmias were classified according to Lown grade (7).

Time domain analysis of HRV included mean RR (mean duration [ms] of all normal to normal RR [NN] intervals), SDNN (standard deviation [ms] of all NN intervals), rmsSD (square root of the sum of the squares of differences between adjacent NN intervals [ms]) and day HR/night HR (ratio of day mean heart rate [from 9 AM to 9 PM] to night mean heart rate [from 0 AM to 6 AM]). SD estimates overall HRV, rmsSD estimates short-term components of HRV, and day HR/night HR estimates long-term components of HRV (1).

Signal-averaged ECG. Signal-averaged ECGs were analyzed with an Arrhythmia Research Technology model 101. Cardiac beats were averaged until the noise level was <0.5 μV. The high pass filter was set at 25 Hz and the low pass filter at 250 Hz; the sampling frequency was 2,000 Hz. Analysis was based on published standards of measurement (8). Results were considered positive if the filtered QRS complex was >120 ms, root-mean-square voltage was <25 μV during the last 40 ms of the filtered QRS complex and duration of the filtered QRS complex was >35 ms after the voltage decreased to <40 μV. In cases of bundle branch block, results were considered positive if the filtered QRS complex was >145 ms, root-mean-square voltage was <17 μV during the last 40 ms of the filtered QRS complex and duration of the filtered QRS complex was >45 ms after the voltage decreased to <40 μV (9).

Statistical analysis. Comparisons between groups were made by using the Student *t* test and analysis of variance for continuous variables. Linear regression analysis was carried out to correlate quantitative variables. Survival curves were estimated by the Kaplan-Meier method, and curves were compared with the log rank test. Sudden death was defined as death during sleep or instantaneous death within 1 h of the onset of symptoms in a patient without evidence of the presence of progressive heart failure (10). The effect of hemodynamic variables, HRV, signal-averaged ECG and runs of ventricular tachycardia (VT) was 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 value ± SD. A p value <0.05 was considered statistically significant. Statview 4.5 software (Abacus Concepts) was used for statistical analysis.

Table 1. Clinical Characteristics and Results of Echocardiography, Hemodynamic Investigations, 24-h Ambulatory ECG Recording and Signal-Averaged ECG in 93 Patients With IDC

Age (yr)	51.3 ± 11
Gender (male/female)	75/18
NYHA class	
I	33 (35.5%)
II	28 (30.1%)
III	23 (24.7%)
IV	9 (9.7%)
Duration of heart failure symptoms (mo) (n = 60)	24.6 ± 36
Systolic blood pressure (mm Hg)	121 ± 15
Diastolic blood pressure (mm Hg)	75 ± 9
Right bundle branch block	7 (7.5%)
Left bundle branch block	26 (28%)
LV end-diastolic diameter (mm)	66.3 ± 8.9
LV end-systolic diameter (mm)	53.1 ± 11.2
LV shortening fraction (%)	20.9 ± 9
Pulmonary capillary wedge pressure (mm Hg)	12.5 ± 8.6
Cardiac index (liters/min per m^2)	3.01 ± 0.77
LV ejection fraction	34.5 ± 12%
Peak oxygen uptake (ml/kg per min) (n = 31)	20.5 ± 4.2
Holter ECG, Lown grade 4b	29 (31.2%)
LVP on signal-averaged ECG (n = 85)	20 (23.5%)

Data presented are mean value ± SD or number (%) of patients. ECG = electrocardiogram, electrocardiographic; IDC = idiopathic dilated cardiomyopathy; LV = left ventricular; LVP = late ventricular potentials; NYHA class = New York Heart Association function class.

Results

Characteristics of patients. The mean age of the patients with IDC on hospital admission was 51.3 ± 11 years (range 21 to 70). Seventy-five (80%) were men. The mean age of the control group was 48.2 ± 11.8 years and was not statistically different from that of the patients with IDC. Clinical data and results of 24-h ambulatory, signal-averaged and standard ECG, radionuclide ventriculography and hemodynamic investigations are summarized in Table 1.

Comparison of HRV in patients with IDC and control subjects. The mean HRV data for the 93 patients with IDC and the control subjects are presented in Table 2. The two groups differed significantly in heart rate and all HRV variables. Table 3 compares HRV variables in patients with IDC with and without congestive heart failure with HRV variables in the control group. HRV was lower in patients with IDC without congestive heart failure than in the control group

Table 2. HRV Variables in Control Group and Patients With IDC

	Control Group (n = 63)	IDC (n = 93)	p Value
Age (yr)	48.2 ± 11.8	51.3 ± 11	NS
Mean RR (ms)	783 ± 101	732 ± 116	*
SDNN	131 ± 41	99 ± 39	†
rmsSD (ms)	41.7 ± 18.8	25.6 ± 14.1	†
Day HR/night HR	1.31 ± 0.13	1.21 ± 0.1	†

*p < 0.001. †p < 0.0001. Data presented are mean value ± SD. Day HR/night HR = ratio of mean heart rate during the day (9 AM to 9 PM) to mean heart rate during the night (0 AM to 6 AM); HRV = heart rate variability; IDC = idiopathic dilated cardiomyopathy; Mean RR = mean duration of all normal to normal (NN) RR intervals; rmsSD = square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN = standard deviation of all NN intervals.

(whereas mean RR was not significantly different). Among patients with IDC, those with congestive heart failure showed a significantly lower mean RR, SDNN and day HR/night HR ratio. HRV was significantly correlated with mean RR in the control group for all variables, and in patients with IDC with and without congestive heart failure for SDNN and day HR/night HR (Table 4).

Correlation between HRV and hemodynamic variables, ventricular arrhythmias and signal-averaged ECG in patients with IDC. Correlations between measurements of HRV and echocardiographic and hemodynamic variables and peak oxygen uptake in patients with IDC are presented in Table 5. HRV variables (especially SDNN and day HR/night HR ratio) were related to left ventricular (LV) shortening fraction, LV ejection fraction and peak oxygen uptake, but they were poorly related to LV end-diastolic diameter, cardiac index and pressure measurements on right heart catheterization. All HRV variables correlated with LV shortening fraction. The highest correlation coefficients were obtained with peak oxygen uptake.

Patients with sustained or nonsustained VT on the 24-h ambulatory ECG had no significant difference in HRV variables from those of patients without VT. Similarly HRV variables did not differ between the patients with positive and negative signal-averaged ECG findings (Table 6).

Table 3. HRV Variables in Control Group and Patients With IDC Without and With CHF

	Control Group (n = 63)	IDC Without CHF (NYHA class I) (n = 33)	IDC With CHF (NYHA class II to IV) (n = 60)
Age (yr)	48.2 ± 11.8	52.6 ± 9.8	50.6 ± 11.7
Mean RR	783 ± 101	790 ± 120	701 ± 102*†
SDNN	131 ± 41	116 ± 28*	90 ± 42*†
rmsSD	41.7 ± 18.8	28.4 ± 13.5*	24 ± 14.4*
Day HR/night HR	1.31 ± 0.13	1.26 ± 0.09*	1.18 ± 0.1*†

*p < 0.05 versus control group. †p < 0.05 versus IDC without CHF. Data presented are mean value ± SD. CHF = congestive heart failure; other abbreviations as in Tables 1 and 2.

Table 4. Correlation Between Mean RR and HRV Variables in Control Group and Patients With IDC Without and With CHF

	Control Group (n = 63)	IDC Without CHF (NYHA class I) (n = 33)	IDC With CHF (NYHA class II to IV) (n = 60)
SDNN	0.43†	0.64†	0.6†
rmsSD	0.46†	0.59*	0.47*
Day HR/night HR	0.4*	—	—

*p < 0.01 versus control group. †p < 0.001. — = nonsignificant correlation; other abbreviations as in Tables 1 to 3.

Analysis of mortality and cardiac events. The mean follow-up period was 49.5 ± 35.6 months. Fourteen patients died during follow-up: eight with progressive congestive heart failure, four with sudden death and two with noncardiac death (cancer). Eight patients underwent heart transplantation and one had cardiomyoplasty. Three patients had sustained VT: The first had an implantable cardioverter-defibrillator, the second underwent heart transplantation and the third had poor therapy compliance and died suddenly. The survival curves of patients with cardiac death (congestive heart failure or sudden death), sudden death and cardiac events (cardiac death, heart transplantation, cardiomyoplasty) are shown in Figure 1.

Survival curves of patients with cardiac events were compared according to SDNN (Fig. 2). For this variable, it was possible to determine a cutoff level that distinguished two groups of patients with significantly different survival curves. Such a cutoff level was not found for rmsSD and day HR/night HR ratio. Univariate regression analysis showed that cardiovascular events were more frequent in patients with increased LV end-diastolic diameter ($p = 0.0001$), increased pulmonary capillary wedge pressure ($p = 0.0001$), decreased LV shortening fraction ($p = 0.0001$), decreased LV ejection fraction ($p = 0.0001$), decreased mean RR ($p = 0.014$) and decreased SDNN ($p = 0.018$). Multivariate regression analysis demonstrated that increased LV end-diastolic diameter ($p = 0.001$), depressed SDNN ($p = 0.02$) and increased pulmonary capillary wedge pressure ($p = 0.04$) were the only predictors of cardiac events.

Discussion

To our knowledge, a decrease in HRV in patients with IDC without congestive heart failure has not previously been described. In addition, our study is the first to correlate HRV with both hemodynamic variables and ventricular arrhythmias in a homogeneous group of patients with IDC. The longer follow-up interval than that of previous studies allowed evaluation of the prognostic value of HRV in IDC. The few studies (11–16) that have focused on HRV in IDC all studied <25 patients and examined the relation between HRV and LV systolic function or hemodynamic status but rarely the relation with ventricular arrhythmias or the signal-averaged ECG.

We emphasize that HRV was reduced in patients with IDC

Table 5. Correlation Between HRV Variables and Hemodynamic Indexes in Patients With IDC

	LVEDD	LVSF	PCWP	CI	LVEF	Peak O_2
Age	—	—	—	0.25 *	—	—
Mean RR	−0.24 *	0.53 §	−0.24 *	—	0.45 §	—
SDNN	—	0.5 §	−0.27 †	—	−0.36 ‡	0.53 †
rmsSD	—	0.26 *	—	—	—	0.39 *
Day HR/Night HR	—	0.35 †	0.26 *	0.27 *	0.33 †	0.46 †

*$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$. §$p < 0.0001$. CI = cardiac index; LVEDD= left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVSF = left ventricular shortening fraction; PCWP = pulmonary capillary wedge pressure; Peak O_2 = peak oxygen uptake; — = nonsignificant correlation; other abbreviations as in Table 2.

without congestive heart failure although mean RR was similar to that of the control group. Some investigators have recommended close attention to the relation between heart rate and HRV: An increase in heart rate involves more limited variations in RR intervals and makes interpretation of HRV difficult (17), as illustrated by the correlations of mean RR and HRV variables shown in Table 4.

Using spectral analysis of HRV, Binkley et al. (11) demonstrated a reduction in high frequencies and in the high frequency/low frequency ratio in 10 patients with IDC and congestive heart failure and suggested that parasympathetic withdrawal and augmentation of sympathetic drive were both components of autonomic imbalance in congestive heart failure. In fact, HRV analysis cannot really estimate sympathetic or parasympathetic tone, only tone variations and modulation of neural autonomic activity, and the changes of HRV variables induced by tone variations probably vary at different stages of congestive heart failure (18,19). Congestive heart failure is associated with an increase in sympathetic tone (with increased plasma norepinephrine), whereas HRV variables are reduced. Similarly, maximal physical exercise induces maximal sympathetic stimulation that cannot be modulated by other control mechanisms (20–22).

Correlations between a decrease in HRV and alteration of systolic LV function in IDC are frequent but not constant (12,14). The highest correlations in our study were obtained with the recognized prognostic markers in congestive heart failure: LV ejection fraction and peak oxygen uptake. IDC could be one of the cardiac diseases with the most severe decrease in HRV (13,15). For Mbaissouroum et al. (16), a decrease in HRV could be the mechanism by which optimal heart rate is set to optimize cardiac output.

There was no correlation in our study between HRV and ventricular arrhythmias or signal-averaged ECG in patients with IDC. In contrast, Vester et al. (15) found a weak (but not significant) correlation between the presence of late ventricular potentials on signal-averaged ECG and a decrease in HRV. Lown grade may have limits in patients with IDC, as perhaps polymorphic premature ventricular contractions are more severe than monomorphic nonsustained VT (23). Moreover, the value of the signal-averaged ECG is probably limited by frequent bundle branch block in patients with IDC, particularly in those with severe LV dysfunction (8,9).

Overall and cardiac mortality rates at 5 years in our study (19.1% and 15.3%) were similar to those of recent studies of mortality in IDC (24). Mortality in IDC is closely related to left ventricular function (24,25). There is a high incidence of asymptomatic ventricular arrhythmias during 24-h ambulatory ECG monitoring in patients with IDC, but the prognostic value of these abnormalities remains controversial, even for sudden death (26,27). The negative predictive value of the signal-averaged ECG for prediction of sudden death is probably good, but its positive predictive value remains low (27). Our study shows that HRV is an independent prognostic marker in IDC with more frequent cardiac events (cardiac death, heart transplantation) in patients who have depressed SDNN (esti-

Table 6. HRV Variables According to Presence or Absence of Severe Ventricular Arrhythmia (Lown grade 4b) or Late Ventricular Potentials in Patients With IDC

	Lown Grade on 24-h ECG			LVP on Signal-Averaged ECG		
	Lown <4b (n = 64)	Lown 4b (n = 29)	p Value	Absent (n = 65)	Present (n = 20)	p Value
Mean RR	733 ± 111	730 ± 129	NS	730 ± 114	743 ± 125	NS
SDNN	99.7 ± 40.7	97.8 ± 37.9	NS	100 ± 38	91 ± 36	NS
rmsSD	23.2 ± 12.4	30.8 ± 16.3	< 0.05	26.3 ± 15	23.6 ± 8.8	NS
Day HR/night HR	1.22 ± 0.09	1.19 ± 0.1	NS	1.21 ± 0.12	1.21 ± 0.09	NS

LVP = late ventricular potentials; other abbreviations as in Tables 1 and 2.

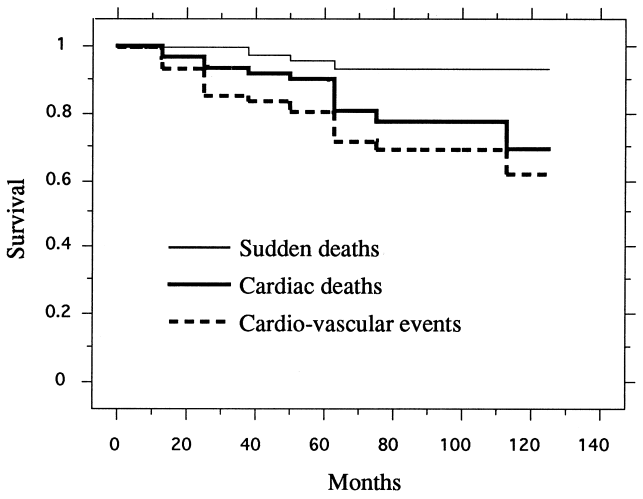
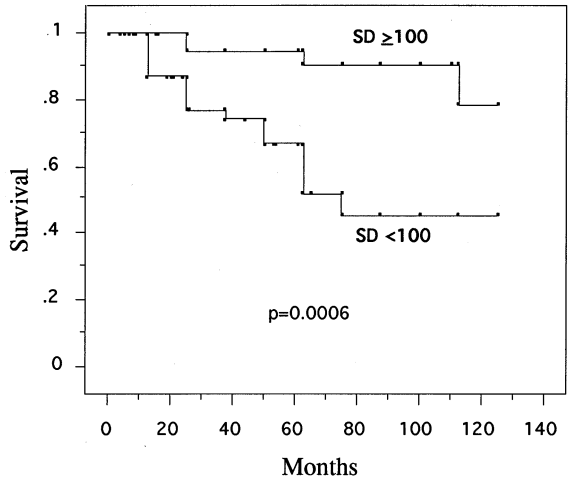


Figure 1. Survival curves showing cardiac deaths, sudden deaths and cardiac events (cardiac deaths and heart transplantations) in patients with IDC.

mating overall HRV). Thus, analysis of HRV, in association with hemodynamic variables, allows better identification of patients at high risk of cardiac death. In our study, a decrease in HRV did not identify patients who experienced sudden death (which is only 29% of overall mortality), a finding in agreement with other studies of HRV in congestive heart failure (1,28). This finding differs from that of studies of HRV after myocardial infarction in larger patient groups (4,5). It has often been assumed (29) that sudden death in IDC is 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, and these different mechanisms of sudden death may explain differences between sudden death in IDC and after acute myocardial infarction (30,31).

Figure 2. Survival curves showing cardiac events according to SDNN in patients with IDC (comparison by log rank test).



Conclusions. This study in 93 patients shows a reduction of HRV in IDC, even in patients without congestive heart failure. However, HRV becomes more depressed when hemodynamic status deteriorates. HRV in IDC does not seem to be influenced by the severity of ventricular arrhythmias. Our results indicate that a reduction in SDNN is a prognostic marker of cardiac events. The mechanisms of these abnormalities and the effect on HRV of medical treatment to improve prognosis remain to be demonstrated.

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