Heart rate variability in idiopathic dilated cardiomyopathy: relation to disease severity and prognosis

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Abstract

Objective—To assess the clinical importance of heart rate variability (HRV) in patients with idiopathic dilated cardiomyopathy (DCM).

Patients and methods—Time domain analysis of 24 hour HRV was performed in 64 patients with DCM, 19 of their relatives with left ventricular enlargement (possible early DCM), and 33 healthy control subjects.

Results—Measures of HRV were reduced in patients with DCM compared with controls (P<0.05). HRV parameters were similar in relatives and controls. Measures of HRV were lower in DCM patients in whom progressive heart failure developed (n=28) than in those who remained clinically stable (n=36) during a follow up of 24 (20) months (P=0.0001). Reduced HRV was associated with NYHA functional class, left ventricular end diastolic dimension, reduced left ventricular ejection fraction, and peak exercise oxygen consumption (P<0.05) in all patients. DCM patients with standard deviation of normal to normal RR intervals calculated over the 24 hour period (SDNN)<50 ms had a significantly lower survival rate free of progressive heart failure than those with SDNN>50 ms (P=0.0002, at 12 months; P=0.0001, during overall follow up). Stepwise multiple regression analysis showed that SDNN<50 ms identified, independently of other clinical variables, patients who were at increased risk of developing progressive heart failure (P=0.0004).

Conclusions—HRV is reduced in patients with DCM and related to disease severity. HRV is clinically useful as an early non-invasive marker of DCM deterioration.

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Keywords: heart rate variability; idiopathic dilated cardiomyopathy; progressive heart failure; left ventricular enlargement

Idiopathic dilated cardiomyopathy (DCM) is a chronic heart muscle disease characterised by a dilated and poorly contractile left ventricle. Patients often present late in end stage heart failure and have a poor prognosis associated with sudden death or progressive heart failure. The identification of patients at increased risk of sudden death or progressive heart failure is problematic and remains a major management goal.

Heart rate variability (HRV) has been shown to be a powerful prognostic indicator after acute myocardial infarction and has recently been applied in other clinical settings. Reduced HRV has been consistently observed in patients with congestive heart failure and a relation between changes in HRV and extent of left ventricular dysfunction was controversially reported. Previous studies were mainly conducted in patients with chronic heart failure secondary to coronary artery disease. Little is known about the clinical value of HRV in patients with DCM and the value of reduced HRV in predicting clinical deterioration in these patients has never been reported. Consequently, this study assessed the relation between HRV and left ventricular performance in patients with DCM and examined the prognostic value of HRV in these patients.

Familial DCM is common (25%) and a high proportion of asymptomatic relatives of DCM patients have left ventricular enlargement, which may represent early DCM. Thus the secondary goal of the study was to assess whether depressed HRV is present in asymptomatic relatives of DCM patients with left ventricular enlargement and whether it can serve as a potential marker of early disease in these subjects.

Patients and methods

STUDY POPULATION

From January 1988 to October 1994, 186 consecutive cases of DCM were evaluated at our centre for management of heart failure or arrhythmia. Of these patients, 150 had their 24 hour ambulatory electrocardiograms (ECGs) recorded at presentation. Patients were excluded if they had diabetes (n=6) or systemic arterial hypertension (n=5). Forty two patients were in atrial fibrillation, eight were in non-sinus rhythm, four had an implanted cardiac pacemaker, five had atrioventricular block, six had frequent atrial or ventricular arrhythmia, and seven recordings had technical faults, all of which precluded analysis of HRV. Three further patients younger than 18 years were excluded on the grounds of age. The remaining 64 patients formed the study population of this report (mean age 42±9 (12-1) years, range 18-0–71-8 years; 46 men).

Patients were diagnosed according to strict criteria as recommended by the WHO and the National Heart, Lung and Blood Institute.
Fifty six patients (88%) had selective coronary angiography and ventriculography, and 42 (66%) had myocardial biopsy which was assessed by light microscopy according to the Dallas Criteria. All patients who did not undergo angiography were diagnosed on the basis of echocardiographic criteria together with an absence of ischaemia confirmed by history, examination, and/or exercise electrocardiography. The patients were followed up for 24 (20) months (range 1–60). In each patient, clinical examination, two dimensional echocardiography, 12 lead ECGs, and 24 hour Holter ECG recordings were performed during the follow up period.

One hundred and twenty six relatives of the patients participated in a prospective family screening, which consisted of clinical examination, two dimensional echocardiography, and 12 lead ECGs. All echocardiographies were performed by an independent experienced operator and reviewed blindly. Left ventricular diastolic dimension was measured at the level of the papillary muscle using M mode echocardiography. Percentage predicted left ventricular diastolic dimension was calculated according to age and body surface area by Henry’s method. Thirty relatives were classified as having left ventricular enlargement (left ventricular diastolic dimension > 112% of predicted). Because our screening protocol included Holter recordings only in those relatives with symptomatic palpitations, 21 relatives with left ventricular enlargement had a 24 hour Holter ECG recorded. Two of them were aged 15 and were excluded from the HRV analysis. The mean age of the 19 relatives studied was 39.1 (12.2) years (range 18.7–63.5 years) and 12 were male. Left ventricular diastolic dimension was 56 (4) mm and percentage predicted left ventricular diastolic dimension was 119 (63)% (range 112–133%). None of these relatives had symptomatic ischaemic heart disease, systemic arterial hypertension, or evidence of autonomic neuropathy. All relatives studied had a normal 12 lead ECG and a 24 hour Holter recording performed in sinus rhythm.

Normal controls in the study consisted of 33 healthy volunteers (mean age 43.1 (11.6) years, 20–66 years, 22 men). They were not related to the patients or relatives. None had any cardiovascular symptoms and all had normal clinical examination and a normal 12 lead ECG.

### DATA PROCESSING

A 24 hour Holter monitoring ECG was obtained at presentation from each subject. Two channel recordings (modified lead II and CMS) were made using tracker recorders (Reynolds Medical or Marquette Electronics). All data were processed using a Holter analysis system (Marquette, Series 8000) and all of the Holter ECG recordings were carefully manually edited. Three non-spectral measurements of HRV and the mean sinus rhythm RR interval were derived from each recording. The measurements were as follows:

- **mNN**—mean of all coupling intervals between successive normal sinus rhythm beats
- **SDNN**—standard deviation of normal to normal RR intervals calculated over the 24 hour period; **SDANN**—standard deviation of normal to normal intervals in all 5-minute segments of the entire recording; and
- **RMSSD**—root-mean square of differences between successive normal to normal intervals. The SDNN measure represents the overall HRV, the SDANN is an estimate of long term components of HRV, and the RMSSD measure characterises short term variation of heart rate.

### STATISTICAL ANALYSIS

All data are expressed as mean (SD). Analysis of variance, Student’s *t* test, U test, and chi-square test (or Fisher’s exact test) were used where appropriate. P values < 0.05 were considered as statistically significant.

We used the Kaplan–Meier method for survival analysis. Survival status and censored observations were retrieved from medical records independently of this study. Patients were censored at the time of cardiac transplant or the date of last follow up.

### Results

#### CLINICAL CHARACTERISTICS

Of 64 DCM patients for whom HRV analysis was available, 28 had progressive heart failure defined as a deterioration in New York Heart Association (NYHA) functional class that was refractory to maximal medical therapy (21 of these received orthotopic heart transplantation, two had clinical deterioration followed by sudden cardiac death) and the other 36 patients remained clinically stable during follow up. The clinical characteristics of the 64 patients are listed in table 1. There was no sig-

### Table 1: Clinical characteristics of patients with idiopathic dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Progressive heart failure</th>
<th>Clinically stable</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>All study patients</td>
<td>43 (12)</td>
<td>44 (11)</td>
<td>42 (13)</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>72%</td>
<td>81%</td>
<td>67%</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1-3 (0-6)</td>
<td>1-4 (0-6)</td>
<td>1-3 (0-5)</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>31%</td>
<td>50%</td>
<td>17%</td>
</tr>
<tr>
<td>Left ventricular diastolic dimension (mm)</td>
<td>70 (11)</td>
<td>75 (11)</td>
<td>66 (10)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>22 (11)</td>
<td>25 (11)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Peak oxygen consumption (mL/kg/min)</td>
<td>21-6 (9.5)</td>
<td>15 (6.1)</td>
<td>15 (6.3)</td>
</tr>
<tr>
<td>Mean heart rate (beats/min)</td>
<td>90 (21)</td>
<td>100 (22)</td>
<td>82 (14)</td>
</tr>
<tr>
<td>Ventricular ejection fraction (%)</td>
<td>37 (12)</td>
<td>34 (10)</td>
<td>32 (8)</td>
</tr>
<tr>
<td>Ventricular ejection fraction (%)</td>
<td>219 (694)</td>
<td>3470 (6369)</td>
<td>3168 (5983)</td>
</tr>
<tr>
<td>Ventricular ejection fraction (%)</td>
<td>149 (260)</td>
<td>155 (261)</td>
<td>145 (263)</td>
</tr>
<tr>
<td>Ventricular ejection fraction (%)</td>
<td>63%</td>
<td>65%</td>
<td>55%</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>44%</td>
<td>73%</td>
<td>39%</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association. P values are for comparisons between patients with progressive heart failure and those who remained clinically stable.
Table 2 Heart rate variability and mean NN intervals in study populations

<table>
<thead>
<tr>
<th>Condition</th>
<th>mNN (ms)</th>
<th>SDNN (ms)</th>
<th>SDANN (ms)</th>
<th>RMSSD (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive heart failure</td>
<td>629 (141)</td>
<td>57 (30)</td>
<td>51 (29)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>Clinically stable</td>
<td>757 (138)</td>
<td>121 (41)</td>
<td>109 (39)</td>
<td>29 (13)</td>
</tr>
<tr>
<td>Relatives</td>
<td>806 (113)</td>
<td>138 (39)</td>
<td>121 (37)</td>
<td>33 (14)</td>
</tr>
<tr>
<td>Normal controls</td>
<td>859 (92)</td>
<td>144 (35)</td>
<td>123 (43)</td>
<td>37 (19)</td>
</tr>
<tr>
<td>P values (ANOVA)</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*P = 0.05 for patients who remained clinically stable v normal controls.
**P = 0.001 for patients who remained clinically stable.
***P = 0.0001 for patients with progressive heart failure v patients who remained clinically stable; patients with progressive heart failure v relatives; patients with progressive heart failure v normal controls.

ANOVA, analysis of variance; mNN, mean of all coupling intervals between normal beats; SDNANN, standard deviation of normal to normal intervals in all 5-minute segments of the entire recording; SDNN, the standard deviation of normal to normal RR intervals calculated over the 24 hour period; RMSSD, root-mean square of difference of successive normal to normal intervals.

![Figure 1](https://example.com/figure1.png)

**Figure 1** Scatter plot of the relation between SDNN values and left ventricular ejection fraction (A) and peak exercise oxygen consumption (B) in patients with idiopathic dilated cardiomyopathy. Solid dots indicate patients in whom progressive heart failure (PHF) developed and open circles indicate those who remained clinically stable (stable). The lines indicate the trend in groups of PHF (bold line) and clinically stable (fine line) patients.

Table 3 Correlation between heart rate variability (SDNN) and clinical variables in all study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.21</td>
<td>0.09</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>-0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Left ventricular end diastolic dimension</td>
<td>-0.26</td>
<td>0.045</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.52</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak exercise oxygen consumption</td>
<td>0.54</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

HEART RATE VARIABILITY

All measurements of HRV and mNN were found to be significantly reduced in patients with DCM compared with relatives with left ventricular enlargement and normal controls (table 2). HRV measurements were further reduced in patients who developed progressive heart failure during follow up compared with those who remained clinically stable (P = 0.0001). On the contrary, all HRV measurements and mNN in the relatives with left ventricular enlargement were similar to normal controls (P = NS).

**HRV measurements and left ventricular performance**

HRV measurements, especially the SDNN measure, correlated with the reduction in left ventricular performance in patients with DCM. The correlation between SDNN and age, NYHA functional class, the measurements of left ventricular end diastolic dimension, left ventricular ejection fraction, and peak oxygen consumption is shown in table 3. There was a strong correlation between SDNN values and left ventricular ejection fraction and peak oxygen consumption (fig 1).

**SDNN and progressive heart failure**

Figure 2 shows SDNN values in different subject groups. SDNN < 50 ms was found more frequently in patients with DCM who developed progressive heart failure compared with those who remained clinically stable (46% v 3%; P = 0.0001). On the contrary, SDNN was never < 50 ms in the relatives with left ventricular enlargement or in the normal controls. Conversely, more of the controls and relatives with left ventricular enlargement had SDNN measurement > 100 ms than patients with DCM who remained stable or had progressive heart failure (91% and 79% v 67% and 11%; P = 0.0001). Among patients with SDNN > 100 ms, 12% (3 of 26) developed progressive heart failure compared with 66% (25 of 38) of those with SDNN < 100 ms (P = 0.0001).
The sensitivity, specificity, positive predictive accuracy, and negative predictive accuracy for prediction of progressive heart failure were 46%, 97%, 93%, and 70% (P = 0.0001) respectively, when using SDNN < 50 ms as the dichotomy point. Figure 3 shows the predictive accuracies corresponding to systematically varied dichotomy points of SDNN for prediction of progressive heart failure.

**SDNN and progressive heart failure free survival**

Using the cut-off point of SDNN < 50 ms, progressive heart failure free survival curves were constructed (fig 4). The survival analysis showed that DCM patients with SDNN < 50 ms had a much lower progressive heart failure free survival rate compared with those with SDNN ≥ 50 ms (23% ± 82%, P = 0.0002 at 12 months; 8% ± 73%, P = 0.0001 at 24 months).

**Relation between mean NN interval and HRV measurements**

When all study subjects were considered as a single group, mNN intervals showed a significant linear relation with all HRV parameters (r = 0.6–0.7, P = 0.0001; fig 5). However, this correlation varied in different subject groups (table 4). A significant correlation was found between mean NN intervals and SDNN and SDANN measurements in patients with or without progressive heart failure and in relatives with left ventricular enlargement, but not in normal controls. On the contrary, the strongest correlation between mean NN intervals and RMSSD measurements was observed in normal controls and similar correlation was also seen in the relatives. A weak but significant correlation between mNN and RMSSD existed in patients who remained clinically stable but it was nearly lost in those who developed progressive heart failure.

**HRV as an independent predictor of progressive heart failure**

Univariate analysis showed that the presence of left bundle branch block, markedly dilated left ventricle, decreased exercise capacity, non-sustained ventricular tachycardia on Holter monitoring, mean NN interval and SDNN values were all significantly related to the development of progressive heart failure in patients with DCM (table 5). To evaluate the independent effect of SDNN and other clinical variables on the development of progressive heart failure, stepwise multiple regression analysis was performed in 51 of 64 patients who had peak oxygen consumption evaluated on exercise testing. The result showed that SDNN was independently related to clinical deterioration (P = 0.0004) in the study population (table 5).

**Discussion**

The present study confirms that HRV is reduced in patients with DCM and that HRV reduction is related to disease severity. A significant relation between reduced SDNN and the development of progressive heart failure.
have reduced HRV and identified a significant correlation between the severity of left ventricular dysfunction and the extent of parasympathetic impairment. Casolo et al reported that HRV evaluated during the acute phase of myocardial infarction is related to clinical and haemodynamic indices of severity and recently confirmed this findings in patients with congestive heart failure secondary to coronary artery disease. However, although based on a smaller group of patients (n = 23) another study provided conflicting data. All these previous studies were conducted on patients with chronic heart failure mainly secondary to coronary artery disease. Few data exist on HRV in patients with DCM. Nonetheless, the results of our study are consistent with previous reports. The association between HRV reduction and the severity of left ventricular impairment and disease progression suggests that patients with severe impairment of left ventricular function have maximal saturation of the sympathetic system and impaired parasympathetic function.

**STUDY IMPLICATIONS**

Probably the most important of our findings is the potential to identify by global measures of 24 hour HRV those patients with DCM who are at increased risk of developing progressive heart failure. We found that reduced HRV is a strong independent indicator of adverse events during follow up, as it was shown to be in previous studies of risk stratification after myocardial infarction. On the basis of the predictive accuracy curves (fig 3), the cut-off point of SDNN values may be selected according to clinical need to obtain optimal sensitivity, specificity, or predictive accuracy. Analysis of HRV is also perhaps more practical than more conventional risk stratifiers. Although peak exercise oxygen consumption usually indicates the severity of disease and predicts the clinical outcome it is not applicable to every patient and is not always accurate. On the contrary, HRV can be measured cheaply. Thus in patients in sinus rhythm, HRV is an important parameter to be collected for the assessment of DCM severity and for identification of patients at increased risk of developing progressive heart failure.

In accord with previous reports, we found that HRV values correlated significantly with mean NN intervals, but the correlation varied in different subject groups. Because vagal activity is a major contributor to RMSSD, the differences in correlations between RMSSD and mean NN interval may reflect the fact that resting heart rate is predominantly mediated vagally in healthy subjects while this correlation is weaker in patients. Presumably, vagal tone is withdrawn and because of sympathetic overdrive, heart rate is regulated principally by adrenergic activity in patients with left ventricular dysfunction. Although mean heart rate was demonstrated to correlate with clinical outcome, SDNN was a much more potent predictor of clinical deterioration than the mean NN interval.

**Figure 5** Scatterplot of the correlation between mean NN intervals and SDNN (A), SDANN (B), and RMSSD (C) in all study subjects. Diamonds indicate patients in whom progressive heart failure developed, dots indicate those who remained clinically stable, triangles indicate relatives with left ventricular enlargements, and open circles indicate normal subjects.
A previous study has shown that cardiac parasympathetic control is defective in patients with heart disease.24 Left ventricular enlargement in relatives of patients with DCM may represent early DCM,14 and underlying pathological changes may already cause parasympathetic impairment at this stage. It is therefore plausible to speculate that changes in HRV will be detectable in these subjects. Increased sympathetic and endocrine activation in patients with chronic heart failure25 26 may explain the presence of parasympathetic impairment in patients with overt DCM and it is possible that parasympathetic function is impaired even at an early (pre-failure) stage of DCM.27 However, our results showed that all HRV measurements in the relatives with left ventricular enlargement were similar to those in normal controls. Thus if parasympathetic function is impaired at an early stage of DCM, the simple measures of HRV used in this study are unable to detect it. Consequently, simple time domain measurement of HRV seems to be unhelpful in family screening.

STUDY LIMITATIONS
Medication may affect HRV measurements2 and clinical outcome. However, at presentation no patient of this study was on any specific therapy which is known to alter HRV measures. During a long follow up, it would not be practical to restrict the medication in all study patients. Nevertheless, medication could not explain the reduction of HRV and its relation to clinical outcome because all patients were under similar supervision and on conventional therapy.

Although the present data expand the role of HRV as a prognostic indicator in patients with DCM, its value in prediction of sudden death or sustained ventricular tachycardia has not been specifically assessed because there were too few such cases among our patients.

An analysis of HRV components by spectral analysis might provide more information not obtainable with the methods we used. It is known that in post infarction patients, the risk of adverse outcome is best predicted from global 24 hour HRV measures and we can only speculate that the same applies to patients with DCM. On the contrary, however, impaired parasympathetic function associated with pre-failure stage of DCM might be more appropriately investigated by spectral analysis of HRV in short-term recordings made under standardised conditions (for example, response to tilt).

CONCLUSIONS
HRV is reduced in DCM patients, especially in those who are liable to clinical deterioration of the disease and the association of reduced HRV with adverse clinical outcome is independent of other recognised risk markers. Thus HRV measurement is a valuable risk assessment test in patients with overt DCM who are in sinus rhythm. On the contrary, relatives of DCM patients with left ventricular enlargement and who may have an early preclinical form of DCM have 24 hour HRV measures similar to those in the normal population. Thus simple global HRV assessment is unlikely to be useful in family screening.

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