Heart rate variability and its relation to ventricular arrhythmias in congestive heart failure

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Abstract

Background—It has been shown that heart rate variability is decreased in patients with congestive heart failure and that depressed heart rate variability is associated with a propensity to ventricular arrhythmias. Little is known, however, about heart rate variability in patients with both congestive heart failure and ventricular arrhythmias.

Methods—Spectral heart rate variability was analysed from 24 hour ambulatory electrocardiograms in 15 controls, 15 patients with non-sustained ventricular tachycardia associated with clinically normal hearts (NHVT group), and 40 patients with congestive heart failure (CHF group) secondary to either ischaemic heart disease (n = 15) or idiopathic dilated cardiomyopathy (n = 25). Of the 40 patients with congestive heart failure 15 had no appreciable ventricular arrhythmias (ventricular extrasystoles < 10 beats/h and no salvos) and formed the CHF-VA⁻ group. Another 15 patients with congestive heart failure and non-sustained ventricular tachycardia formed the CHF-NSVT group.

Results—Heart rate variability was significantly lower in the CHF group than in controls (mean (SD) total frequency 23 (12) v 43 (13) ms; low frequency 12 (8) v 28 (9) ms; high frequency 8 (5) v 14 (7) ms; $p < 0.001$). The differences in heart rate variability between controls and the NHVT group, between ischaemic heart disease and dilated cardiomyopathy, and between the CHF-VA⁻ and CHF-NSVT groups were not significant. In the CHF group heart rate variability was significantly related to left ventricular ejection fraction but not associated with ventricular arrhythmias. The frequency of ventricular extrasystoles was significantly related to the high frequency component of heart rate variability ($r = 0.54$, $p < 0.05$) in the NHVT group. Stepwise multiple regression analysis showed that in the CHF group, heart rate variability was predominantly related to left ventricular ejection fraction ($p < 0.05$). There was no significant difference in heart rate variability between survivors (n = 34) and those who died suddenly (n = 6) at one year of follow up in the CHF group.

Conclusion—In patients with congestive heart failure, heart rate variability is significantly decreased. The depressed heart

rate variability is principally related to the degree of left ventricular impairment and is independent of aetiology and the presence of ventricular arrhythmias. The data suggest that analysis of heart rate variability does not help the identification of patients with congestive heart failure at increased risk of sudden death.

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Ventricular arrhythmias often occur in patients with compromised cardiac function^{1,2} and seem to be significantly related to impairment of left ventricular function.³⁻⁵ The underlying mechanisms of the ventricular arrhythmogenesis in these patients remain to be fully elucidated. Although some studies have noted an association between the presence of frequent ventricular extrasystoles or non-sustained ventricular tachycardia and risk of sudden cardiac death in patients with congestive heart failure, there are substantial controversies about the prognostic value of ventricular arrhythmias in these patients.^{2,6-8} It has been reported that many invasive and non-invasive techniques, such as the signal averaged electrocardiogram and electrophysiological study, are not helpful for identification of those patients with congestive heart failure who are at risk of sudden cardiac death.⁶ Recently, analysis of heart rate variability has provided a non-invasive measure of autonomic influence on the heart and can be used for risk stratification in patients after a myocardial infarction.⁹⁻¹³ Its prognostic significance in patients with congestive heart failure, however, remains unknown.

The finding that heart rate variability is decreased in patients with congestive heart failure suggests that there is a significant alteration of autonomic activity in these patients.¹⁴⁻¹⁶ Whether the most often found ventricular arrhythmias are related to the altered autonomic tone in patients with congestive heart failure remains unknown. It has been reported that heart rate variability is also decreased in electrically unstable patients susceptible to ventricular arrhythmias.¹⁷⁻²⁰ Therefore, heart rate variability may be associated with both the electrical and the mechanical function of the heart. The determinants of heart rate variability have not yet been well described in patients with both congestive heart failure and ventricular arrhythmias.

In this case-control study, we aimed to

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assess (a) heart rate variability in patients with congestive heart failure and ventricular arrhythmias, (b) the effects of different aetiologies of congestive heart failure (either ischaemic heart disease or idiopathic dilated cardiomyopathy) on heart rate variability, (c) the relation between heart rate variability and the frequency and severity of ventricular arrhythmias in the presence of congestive heart failure, and (d) the prognostic significance of the analysis of heart rate variability in patients with congestive heart failure.

Patients and methods

PATIENTS

In this investigation, heart rate variability was studied in normal subjects, patients with idiopathic ventricular tachycardia, and patients with congestive heart failure with and without ventricular tachycardia (table 1). Fifteen healthy subjects ((eight men), mean (SD) age 47 (10) years) served as controls. None of them had significant cardiac or other medical problems, and their 12 lead and 24 hour ambulatory electrocardiograms were normal. Fifteen patients (nine male), age 41 (13), with non-sustained ventricular tachycardia associated with clinically normal hearts formed the NHVT group. Non-sustained ventricular tachycardia was defined as uniform broad QRS complexes lasting from ≥ 3 beats to < 30 s and ending spontaneously without haemodynamic compromise, with an effort to match the number of beats in the longest salvos to patients with congestive heart failure and salvos. All of the NHVT group were normal on physical examination, chest radiography, resting electrocardiograms, echocardiography (including right ventricular views), left ventricular angiography, and coronary artery angiography. Left ventricular ejection fraction (LVEF) was $> 55\%$. Right ventricular endomyocardial biopsy was normal in all except two patients who had mild non-specific fibrosis of uncertain clinical significance.

Sixty patients with congestive heart failure in the New York Heart Association functional classes II to IV secondary to either ischaemic heart disease or idiopathic dilated cardiomyopathy were enrolled in this study. Congestive heart failure was defined as exertional dyspnoea or fatigue for more than six months, a dilated left ventricle, and a LVEF $\leq 40\%$ at rest determined by angiography or radionuclide ventriculography. Twenty patients were excluded because of sinus node dysfunction

(three), atrial fibrillation (two), abnormal atrioventricular conduction (one), artificial ventricular pacing (permanent pacemaker one and implantable cardioverter defibrillator one), noisy recording of Holter tapes (three), and antiarrhythmic drug treatment (nine). In the remaining 40 patients with congestive heart failure (the CHF group) there were 15 patients with ischaemic heart disease (14 men) and 25 patients with idiopathic dilated cardiomyopathy (eight men). All 40 of the CHF group were taking diuretics (40–120 mg frusemide / day) and two were taking digoxin. None of the 40 patients was being treated with antiarrhythmic drugs or had other severe medical disorders. Of the 40 patients in the CHF group 15 (11 men) had no significant ventricular arrhythmias (ventricular extrasystoles < 10 beats/h and no non-sustained ventricular tachycardia) and formed the CHF-VA⁻ group. They consisted of seven patients with ischaemic heart disease and eight patients with idiopathic dilated cardiomyopathy. Another 15 patients (14 men) in the CHF group who showed non-sustained ventricular tachycardia on Holter monitoring were taken to be the CHF-NSVT group. They consisted of four patients with ischaemic heart disease and 11 with idiopathic dilated cardiomyopathy. This subgrouping of patients within the CHF group according to the presence or absence of non-sustained ventricular tachycardia was designed to specifically assess the influence of the presence of non-sustained ventricular tachycardia on heart rate variability in patients with congestive heart failure compared with those without cardiac dysfunction, (the NHVT group). Therefore 10 of the CHF group with frequent ventricular extrasystoles but without ventricular tachycardia were not categorised in either group CHF-VA⁻ or CHF-NSVT. The definition of ventricular arrhythmias was based on data from the same Holter electrocardiograms from which heart rate variability was calculated in this study.

ANALYSIS OF HEART RATE VARIABILITY

All subjects underwent two channel (modified V5 and V1 leads) 24 hour ambulatory electrocardiographic monitoring (Marquette Series 8500). Heart rate variability was analysed from the 24 hour ambulatory electrocardiogram with a Holter analysis system (Marquette Series 8000, digitisation frequency 128 Hz). After classification of the QRS morphology the longest and the shortest RR intervals on the RR interval histogram were manually confirmed until no QRS complex was mislabelled as either an artifact or an extrasystole. The largest and the smallest RR ratios on the RR ratio histogram were also visually checked to ensure that all normal and abnormal QRS complexes on the ambulatory electrocardiogram were correctly labelled. When calculating the heart rate variability values, only normal to normal intervals were used. Each interval that was to be excluded due to extrasystoles or artifacts was replaced by holding the previous coupling interval level

Table 1 Clinical characteristics of controls and patients with congestive heart failure

	Controls	NHVT	CHF	CHF-VA ⁻	CHF-NSVT
No	15	15	40	15	15
Mean (SD) age (yr)	47(10)	41(13)	50(12)	48(9)	51(14)
Sex (men/women)	8/7	9/6	22/28	11/4	14/1
Ventricular arrhythmias	None	NSVT	—	OVEs	NSVT
Mean (SD) LVEF (%)	—	> 55	26(8)	26(5)	24(8)

CHF, congestive heart failure; CHF-VA⁻ congestive heart failure without significant ventricular arrhythmias; CHF-NSVT, congestive heart failure with non-sustained ventricular tachycardia; NHVT, clinically normal heart associated with salvos; NSVT, non-sustained ventricular tachycardia; OVEs, occasional ventricular extra systoles.

throughout the time interval to the next valid coupling interval. The beat to beat fluctuations were transformed to frequency domain by fast Fourier transformation and the spectral measures were computed as the square root of areas under the power spectrum. In this study, heart rate variability was expressed as total (TF, 0.01–1.00 Hz), low (LF, 0.04–0.15 Hz), and high (HF, 0.15–0.40 Hz) frequency components.

STATISTICAL ANALYSIS

Unpaired Student's *t* test, analysis of variance, and multivariate correlation and regression analysis were used where appropriate. Because of the relation of heart rate variability to age,^{21–23} analysis of covariance (with age as a covariate) was used to compare the between group differences in values of heart rate variability adjusted for the influence of age. Stepwise multiple regression analysis was used to assess the relations of heart rate variability with other clinical variables. All data are expressed as means (SD). The frequency of ventricular arrhythmias was normalised as necessary by logarithmic transformation. A two tailed *p* value < 0.05 was considered significant.

Results

There was no significant difference between groups in age for any comparisons (table I) except between the NHVT and the CHF-NSVT groups (41 (13) *v* 51 (14), *p* < 0.05), and between patients with ischaemic heart disease and idiopathic dilated cardiomyopathy (59 (6) *v* 44 (12), *p* < 0.001). No significant differences were found in LVEF between patients with ischaemic heart disease and idiopathic dilated cardiomyopathy (25% (5%) *v* 25% (10%) NS), or between the CHF-VA and the CHF-NSVT groups (26% (5%) *v* 24% (8%) NS).

MEAN HEART RATE

There was no significant difference in mean heart rate between controls and the NHVT group (69 (9) *v* 67 (12) beats/min NS), or between the CHF-VA and the CHF-NSVT groups (86 (8) *v* 88 (14) beats/min NS). The difference in mean heart rate was statistically significant between patients with ischaemic

Figure 1 Association of (A) TF, (B) LF, and (C) HF components of heart rate variability (HRV) with LVEF in patients with congestive heart failure.

heart disease and idiopathic dilated cardiomyopathy (83 (8) *v* 91 (14) beats/min, *p* = 0.023). Mean heart rate was significantly higher in the CHF group than in the controls (88 (12) *v* 69 (9) beats/min, *p* < 0.001). Mean heart rate was also significantly (*p* < 0.001) higher in the CHF-VA and the CHF-NSVT groups compared with controls and the NHVT group.

HEART RATE VARIABILITY

There was no significant difference in heart rate variability between controls and the NHVT group (TF, 43 (13) *v* 48 (14) ms; LF, 28 (9) *v* 33 (11) ms; and HF, 14 (7) *v* 15 (6) ms; NS), between the CHF-VA and CHF-NSVT groups (TF, 26 (9) *v* 23 (12) ms; LF, 15 (6) *v* 13 (8) ms; and HF, 8 (4) *v* 7 (4); NS), or between patients with ischaemic heart

Table 2 *p* Values for the between group differences in heart rate variability

Component of heart rate variability	Controls	NHVT	CHF-VA	CHF-NSVT
Mean (SD) TF (ms)	43(13)	48(14)	26(9)	23(12)
Controls	—	—	—	—
NHVT	= 0.63	—	—	—
CHF-VA	< 0.001	< 0.001	—	—
CHF-NSVT	< 0.001	< 0.001	= 0.71	—
Mean (SD) LF (ms)	28(9)	33(11)	15(6)	13(8)
Controls	—	—	—	—
NHVT	= 0.44	—	—	—
CHF-VA	< 0.001	< 0.001	—	—
CHF-NSVT	< 0.001	< 0.001	= 0.74	—
Mean (SD) HF (ms)	14(7)	15(6)	8(4)	7(4)
Controls	—	—	—	—
NHVT	= 0.94	—	—	—
CHF-VA	< 0.001	= 0.005	—	—
CHF-NSVT	= 0.001	= 0.001	= 0.40	—

Abbreviations as in table 1.

Figure 2 Total number of ventricular extrasystoles (VEs) during the 24 hour recordings v frequency components of heart rate variability (HRV), (A) TF (B) LF, and (C) HF in patients with congestive heart failure and VEs ≥ 10 beats/h (NS).

disease and idiopathic dilated cardiomyopathy (TF, 23 (10) v 23 (13) ms; LF, 12 (6) v 13 (9) ms; and HF, 7 (4) v 8 (6) ms; NS). The difference in heart rate variability, however, was highly significant between the CHF group and the controls (TF, 23 (12) v 43 (13) ms; LF, 12 (8) v 28 (9) ms; HF, 8 (5) v 14 (7) ms; $p < 0.001$). Heart rate variability was significantly lower in the CHF-VA⁻ and the CHF-NSVT groups than in controls and the NHVT group (table 2).

CORRELATIONS BETWEEN HEART RATE VARIABILITY AND OTHER CLINICAL MEASURES

Heart rate variability was inversely related to age in controls (TF, $r = -0.54$; LF, $r = -0.63$; and HF, $r = -0.55$; $p < 0.05$), but not in the CHF group (TF, $r = -0.03$; LF, $r = -0.09$; and HF, $r = -0.01$; NS). There was a significant relation between heart rate variability and LVEF in the CHF group (figure 1).

It has been shown that the total number of ventricular extrasystoles and the number of beats in the longest salvos of ventricular extrasystoles over a 24 hour period may be associated with a poor prognosis in patients with congestive heart failure.^{6 7 24 25} We there-

Figure 3 Number of beats in the longest salvo of ventricular extrasystoles (VTmax) during 24 hour recordings v frequency components of heart rate variability (HRV)—namely, (A) TF, (B) LF, and (C) HF—in patients with congestive heart failure and salvos (NS).

fore examined their association with heart rate variability in patients with congestive heart failure and ventricular arrhythmias. No significant associations could be found in these patients before or after logarithmic transformation (figs 2 and 3). Neither the total number of ventricular extrasystoles ($r = 0.11$, NS) nor the number of beats for the longest episode of salvos ($r = 0.15$; NS) over the 24 hour recordings was significantly related to LVEF in patients with congestive heart failure. As peak oxygen consumption during exercise may also be related to a poor prognosis in patients with congestive heart failure,^{26 27} we correlated peak oxygen consumption during exercise with heart rate variability. No significant correlation was found between them (TF, $r = 0.23$; LF, $r = 0.18$; HF, $r = 0.23$; NS). Based on stepwise multivariate regression analysis, of

Figure 4 Relation between the total number of ventricular extrasystoles (VEs) during the 24 hour recordings and the frequency components of heart rate variability (HRV), (A) TF, (B) LF, and (C) HF in patients with idiopathic ventricular tachycardia.

the predictive variables including age, LVEF, peak oxygen consumption during exercise, the number of beats for the longest episode of salvos, and the logarithmic value of the total number of ventricular extrasystoles on 24 hour recordings, heart rate variability was shown to be predominantly related to LVEF in patients with congestive heart failure.

Figure 4 shows the relation between heart rate variability and the total number of ventricular extrasystoles over 24 hours in patients with NHVT. Stepwise multivariate regression analysis showed that the total number of ventricular extrasystoles over 24 hours was predominantly related to the HF component of heart rate variability ($r = 0.54$, $p < 0.05$). There was no significant relation between the number of beats in the longest episode of salvos and heart rate variability in these patients (TF, $r = 0.43$; LF, $r = 0.39$; and HF, $r = 0.17$; NS).

FOLLOW UP

All patients with congestive heart failure were followed up in a heart failure clinic at least every three months. Patient deaths were identified by direct communication with the patients' families and their general practitioners. Every effort was made to discriminate sudden death from pump failure. As in the cardiac arrhythmia pilot study sudden death

in this study was defined as death within one hour of the onset of new symptoms.²⁸ The definition also included instantaneous death, death during sleep, and unwitnessed death that occurred within one hour of the patient last being seen alive. In all cases death certificates and necropsy reports were examined to establish cause of death. During one year of follow up of the 40 patients with congestive heart failure, nine patients died and six patients underwent heart transplantation.

Of the nine patients who died, six died suddenly (one of them had been resuscitated from sudden death). One of the six who died suddenly had ischaemic heart disease, and the other five had idiopathic dilated cardiomyopathy. These patients who died suddenly were significantly younger than the survivors (41(14) v 52(11) years, $p < 0.05$). After excluding patients with ischaemic heart disease, the difference in age between patients who died suddenly and those who survived among patients with idiopathic dilated cardiomyopathy was still significant (32(5) v 47(11) years, $p < 0.01$). There was no significant difference in LVEF between survivors and patients who died suddenly (25%(8%) v 27%(9%) NS). The difference in heart rate variability between patients who died suddenly and survivors was not significant (TF, 29(18) v 23(11) ms; LF, 17(12) v 12(7) ms; HF, 10(8) v 8(5) ms; NS).

Discussion

The finding in this study that heart rate variability was significantly decreased in patients with congestive heart failure is consistent with previous reports.¹⁴⁻¹⁶ Although heart rate variability has been shown to decrease with age in normal subjects,²¹⁻²³ it seems unlikely that the difference in heart rate variability between patients with normal and abnormal left ventricular function was due to the difference in age, as there was no significant difference in age between these two groups and the difference in heart rate variability remained significant after statistical adjustment was made for age. None of our patients was receiving antiarrhythmic drug treatment and only two patients were taking digoxin. There is no evidence to suggest that frusemide decreases heart rate variability in patients with congestive heart failure. Therefore, the effects of drugs would also not seem to explain the significant decrease in heart rate variability in these patients.

The low frequency component of heart rate variability gives a measure of sympathetic activity with some influence from vagal activity,^{29,30} whereas the high frequency component is almost exclusively modulated by vagal activity.^{30,31} Overall heart rate variability is thought to be mainly influenced by cardiac vagal activity.³²⁻³⁴ The finding that heart rate variability was decreased in patients with congestive heart failure suggests that there is an abnormal autonomic influence on the heart in these patients. It has been reported that β blockers rather than class I antiarrhythmic

agents can reduce the risk of sudden cardiac death in patients with a low LVEF.³⁵ This beneficial action of β blockers may result from an improvement in the abnormal autonomic activity. Eriksson and colleagues have reported that heart rate variability (measured as the mean difference in duration of consecutive RR intervals in relation to the mean duration of RR intervals from 10 minutes of electrocardiographic recording in the supine position and expressed as a percentage) may be an independent risk factor for heart failure.³⁶ These findings suggest that abnormal autonomic activity may contribute importantly to the pathophysiology of congestive heart failure.

In this study, heart rate variability was significantly related to LVEF in patients with congestive heart failure. This is consistent with previous reports.^{16,37} In the study of Saul *et al* there was a weak correlation ($r \approx 0.5$) between the low frequency component (0.04–0.07 Hz) of heart rate variability and haemodynamic variables including cardiac index and pulmonary artery wedge pressure.¹⁶ A similar correlation between heart rate variability and LVEF has recently been reported by Nolan *et al* ($r = 0.49$, $p < 0.05$).³⁷ Among the clinical variables that indicate a poor prognosis in patients with congestive heart failure, multivariate analysis showed that LVEF was the single best independent determinant of heart rate variability in these patients. On the other hand, in our study heart rate variability was significantly depressed in patients with impaired left ventricular function irrespective of the different aetiologies of disease and the frequency and severity of ventricular arrhythmias (discussed later). Thus severity of myocardial dysfunction would seem to be an important determinant of heart rate variability in patients with both congestive heart failure and ventricular arrhythmias. In multivariate analysis of patients after a myocardial infarction,³⁸ variables reflecting the mechanical state of the left ventricle are better at predicting cardiac mortality than those reflecting the electrical state of the heart. The overwhelming modulation of heart rate variability by left ventricular function in a failing heart may be responsible for the non-significant relation between age and heart rate variability in patients with congestive heart failure. Also the decrease in heart rate variability with age in normal subjects may be, at least in part, due to depressed nervous reflexes in elderly people.³⁹ It is worth noting that the determinants of heart rate variability in patients with congestive heart failure may be quite different from those in normal subjects although this remains to be fully elucidated.

It is well known that the autonomic nervous system plays an important part in the pathogenesis of ventricular arrhythmias and sudden cardiac death.⁴⁰ The role of autonomic activity in the genesis of ventricular tachycardias in congestive heart failure, however, remains uncertain. In this study, we compared heart rate variability between patients with and without non-sustained ven-

tricular tachycardia and attempted to correlate directly the frequency and severity of ventricular arrhythmias with heart rate variability. In patients with salvos associated with clinically normal hearts, the frequency of ventricular extrasystoles over 24 hours of recording was significantly related to the high frequency component of heart rate variability. This accords with the hypothesis that vagal activity may have protective effects in preventing the development of ventricular tachycardias and sudden cardiac death.⁴⁰ There was, however, no significant difference in heart rate variability in patients with and without non-sustained ventricular tachycardia in the presence of congestive heart failure in this study. We also did not find any significant association between heart rate variability and the frequency and severity of ventricular arrhythmias, which have otherwise been shown to be related to a poor prognosis in these patients. It has been shown that there is considerable spontaneous variability of ventricular arrhythmias on Holter electrocardiographic monitoring from recording to recording.^{41,42} It seems unlikely that the non-significant relations were due to the variability of arrhythmias as ventricular arrhythmias were identified from the same Holter recordings from which heart rate variability was calculated. This suggests that the overall depression of heart rate variability in patients with congestive heart failure may not be the main substrate for ventricular arrhythmogenesis. Cardillo *et al* have reported that there was no relation between the severity of ventricular extrasystoles and autonomic outflow to the heart as detected by analysis of heart rate variability in hypertensive patients without heart failure.⁴³ Diverse pathophysiological mechanisms underlying arrhythmogenesis may be one explanation for the different findings in the different clinical settings. Although our results cannot preclude the possibility of a role for the autonomic nervous system in the pathogenesis of ventricular arrhythmias in patients with congestive heart failure, they do not support this hypothesis.

It has been shown that decreased heart rate variability is an independent risk factor in patients after acute myocardial infarction. Like the signal averaged electrocardiogram and electrophysiological study,⁶ our findings do not suggest that analysis of heart rate variability will be helpful in identifying patients at risk of sudden cardiac death in the presence of congestive heart failure. This may be due to the diverse mechanisms of sudden cardiac death as well as ventricular tachycardias in congestive heart failure, such as bradycardia or electromechanical dissociation.⁴⁴ Another possible explanation may be the predominant influence of LVEF on heart rate variability. A larger prospective study is warranted to fully define the predictive value of heart rate variability in patients with congestive heart failure in different functional classes.

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