Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure

M. Galinier[1,2], A. Pathak[1,2], J. Fourcade[1], C. Androdias[1], D. Curnier[2], S. Varnous[1], S. Boveda[1], P. Massabuau[1], M. Fauvel[1], J. M. Senard[2] and J. P. Bounhoure[1]

[1]*Department of Cardiology, Rangueil University Hospital, Toulouse, France;* [2]*Pharmacology Laboratory, Toulouse, France*

Aims Identification of patients with chronic heart failure at risk for sudden death remains difficult. We sought to assess the prognostic value for all-cause and sudden death of time and frequency domain measures of heart rate variability in chronic heart failure.

Methods and Results We prospectively enrolled 190 patients with chronic heart failure in sinus rhythm, mean age 61 ± 12 years, 109 (57·4%) in NYHA class II and 81 (42·6%) in classes III or IV, mean cardiothoracic ratio $57·6 \pm 6·4\%$ and mean left ventricular ejection fraction $28·2 \pm 8·8\%$, 85 (45%) with ischaemic and 105 (55%) with idiopathic dilated cardiomyopathy. Time and frequency domain measures of heart rate variability were obtained from 24 h Holter ECG recordings, spectral measures were averaged for calculation of daytime (1000h–1900h) and night-time (2300h–0600h) values. During follow-up (22 ± 18 months), 55 patients died, 21 of them suddenly and two presented with a syncopal spontaneous sustained ventricular tachycardia. In multivariate analysis, independent predictors for all-cause mortality were: ischaemic heart disease, cardiothoracic ratio $\geq 60\%$ and standard deviation of all normal RR intervals <67 ms (RR=2·5, 95% CI 1·5–4·2). Independent predictors of sudden death were: ischaemic heart disease and daytime low frequency power <3·3 ln (ms^2) (RR=2·8, 95% CI 1·2–8·6).

Conclusion Depressed heart rate variability has independent prognostic value in patients with chronic heart failure; spectral analysis identifies an increased risk for sudden death in these patients.
(Eur Heart J 2000; 21: 475–482)
© 2000 The European Society of Cardiology

Key Words: Heart rate variability, sudden death, heart failure.

See page 435 for the Editorial comment on this article

Introduction

Despite recent advances in the management of chronic heart failure, mortality remains high and death often occurs suddenly[1]. Identification of patients at risk for sudden death remains difficult[2]. Among several prognostic factors, the extent of neurohormonal activation[3], particularly plasma norepinephrine levels[4], has been found to be independently related to survival in patients with heart failure. Profound abnormalities in autonomic control, characterized by generalized sympathetic overactivity and parasympathetic withdrawal, are a typical feature of neuroendocrine activation in heart failure[5].

Analysis of heart rate variability is a non-invasive tool enabling autonomic control of the heart to be studied[6]. Several studies have shown disturbed heart rate variability in patients with heart failure, and the degree of impairment of heart rate variability appears to be related to the severity of the disease[7–11]. Whereas the first studies investigating the prognostic value of heart rate variability in chronic heart failure have produced conflicting results[12–15], three recent studies have proved that the prognostic value of a depressed standard deviation of all normal RR intervals is an independent predictor of all-cause mortality[16–18]. However, in these studies, time domain measures of heart rate variability failed to predict the risk of sudden death. Spectral analysis of heart rate variability, which allows a more detailed study of the autonomic environment of the heart, may be a powerful predictor of sudden death. Its use as a method of identifying patients with chronic

heart failure at high risk of sudden death has not been investigated in an adequately sized prospective study. The purpose of the present study was to examine the prognostic value for all-cause and sudden death of time and frequency domain measures of heart rate variability in a large population of ambulatory patients with moderate to severe chronic heart failure.

Methods

Patients

From May 1992 until December 1997, 190 consecutive patients (166 men and 24 women, mean age 61 ± 12 years) who gave informed consent, in sinus rhythm, who were in New York Heart Association (NYHA) classes II to IV and were clinically stable for at least 2 weeks, were prospectively enrolled in this study which was approved by the ethics committee of our institution. This study population consisted mainly of in-patients hospitalized for heart failure evaluation without history of syncope or cardiac arrest. Chronic heart failure was characterized by clinical signs and symptoms and a left ventricular ejection fraction <45%. Exclusion criteria included: age >77 years, atrial fibrillation or flutter, implanted pacemaker or defibrillator, myocardial infarction or unstable angina within the last 6 months, significant valvular or congenital heart disease, active myocarditis, severe hepatic or renal disease, insulin-dependent diabetes mellitus and autonomic neuropathy. Clinical investigations included 12-lead electrocardiography, chest radiography, two-dimensional Doppler echocardiography, 24-h ambulatory Holter ECG, cardiac catheterization with coronary angiography and left ventricular angiography. None of the patients was on beta-blocker therapy before or during Holter ECG recording. Left ventricular ejection fraction was determined by technetium-99 m radionuclide ventriculography. The aetiologies of chronic heart failure were ischaemic, hypertensive or idiopathic dilated cardiomyopathy. The diagnosis of idiopathic dilated cardiomyopathy was made according to usual criteria, in the presence of a depressed left ventricular ejection fraction and in the absence of significant coronary artery disease and other specific heart muscle diseases.

Analysis of heart rate variability

Patients underwent 24-h electrocardiographic monitoring using a three-channel Marquette 8500 recorder (Marquette Electronics Inc.). Tapes were analysed by an experienced analyst, supervised by one physician, using the Marquette 8000 Laser Holter System to identify and label each QRS complex. Recordings with more than 15% noise or ectopic beats during 24 h were excluded from the heart rate variability analysis. A preliminary analysis allowed exclusion of noise, artefacts, premature beats, or post extrasystolic pauses from further analysis. All tapes were subsequently analysed to measure heart rate variability using a validated Marquette heart rate variability program (version 002A, Marquette Electronic Inc.).

Time domain analysis

The mean RR (mean of all normal RR intervals) duration from the whole recording and the following time domain measures of heart rate variability were calculated: standard deviation of all normal RR intervals (SDNN), standard deviation of the averages of RR intervals in all 5 min segments (SDANN), mean of the standard deviations of all RR intervals for all 5 min segments (SD), root-mean square of difference of successive RR intervals (RMSSD), percentage of adjacent normal RR intervals >50 ms different (pNN50).

Spectral analysis

Spectral measures were computed using the fast-Fourier transform method. A spectral plot for 1 h was the average of the spectra computed over a 2-min period (256 points). A Hanning window was applied to minimize spectral leakage, and the time series function consisted of sampling RR intervals every 469 ms. Spectral measures were plotted hour-by-hour and then averaged for calculation of daytime (1000h–1900h) and night-time (2300h–0600h) values. Spectral plots allowed identification of the total oscillatory power of 0·01 to 1·0 Hz as well as two subsets of the frequency domain: low frequency (0·04–0·15 Hz) and high frequency (0·15 to 0·40 Hz). The spectral power was evaluated quantitatively and expressed in ln (ms^2), where ln is the natural logarithm of the absolute values, corresponding to the areas under the curve of each band of interest[6].

Follow-up

Survival data were obtained by direct patient examination or from patients' general practitioners. The cause of patient death was determined from hospital records or by direct communication with patients' general practitioners or families. Every effort was made to discriminate between pump failure death and sudden death, defined as death occurring within 1 h of onset of symptoms in a previously medically stable patient, death during sleep, or unwitnessed death (occurring within 1 h of the patient last being seen alive). Spontaneous syncopal sustained ventricular tachycardia or ventricular fibrillation was considered as sudden death. Patients who underwent cardiac transplantation during follow-up were considered alive at the date of intervention and excluded from further analysis.

Statistical analysis

Data are expressed as mean $\pm$ SD. Mean values of time domain parameters of heart rate variability were

calculated for the complete 24-h period. Mean values of spectral indexes of heart rate variability were calculated for daytime and night-time periods. In the Cox proportional-hazards model, the association of the following baseline patient characteristics with survival was assessed: age, heart failure aetiology, NYHA class, cardiothoracic ratio, ejection fraction, presence of non-sustained ventricular tachycardia on Holter monitoring, and time and frequency domain measures of heart rate variability. The following continuous variables were transformed into dichotomized variables: age <60 or ≥60 years, cardiothoracic ratio ≤60 or >60%, left ventricular ejection fraction ≥30 or <30%. When estimating the association of heart rate variability parameters with mortality, the patients were dichotomized by the 25th or 33rd percentile of the examined variable. Survival time estimate was calculated by the method of Kaplan–Meier and statistical comparisons between survival curves were done using the log-rank test. The significance of each categorical variable was determined by a $P<0.05$. Multivariate survival analysis was performed with the Cox proportional hazards model to determine which factors were significantly associated with all-cause or sudden death after adjustment for the other variables. Variables selected to be tested in multivariate analysis were those with a $P<0.10$ in the univariate model. A stepwise selection was done using a P to remove from and a P to enter into the model ≤0·05 with both prior backward selection after inclusion of all selected variables (satured model) and then forward selection. The P value refers to the likelihood ratio test of the hypothesis that the regression coefficient was zero. Results are expressed as relative risk with confidence intervals (CI 95%). A significant increase of risk is obtained if CI 95% excludes l and P of Wald test ≤0·05 (Computed with STATVIEW package).

Results

Patient characteristics

At the time of the study, 109 patients were in NYHA class II, 74 in class III and 7 in class IV. Heart failure was due to coronary artery disease in 85 patients, hypertensive dilated cardiomyopathy in nine and idiopathic dilated cardiomyopathy in 96. The mean cardiothoracic ratio was $57·6 ± 6·4\%$, the average left ventricular end diastolic diameter was $68 ± 8·5$ mm, and the mean left ventricular ejection fraction was $28·2 ± 8·8\%$. Fifty-four patients had episodes of non-sustained ventricular tachycardia on Holter ECG recording. Treatment included angiotensin-converting enzyme inhibitors in 169 patients (89%), diuretics in 164 (86%), digoxin in 119 (63%) and nitrates in 77 (40%); 72 patients (38%) were receiving amiodarone which was the only antiarrhythmic drugs used.

Follow-up data

During a mean follow-up of $22 ± 18$ months, 55 patients died, including 21 from sudden death. Two patients presented spontaneous syncopal sustained ventricular tachycardia. Thirteen patients underwent heart transplantation. For two patients no follow-up data could be obtained and they were excluded from the survival analysis and considered as lost from study. The 3-year mortality rate was 38·9%.

Predictors of survival

The baseline characteristics for survivors and non-survivors are listed in Table 1. There was no difference in age, sex, serum potassium level, mean heart rate and the incidence of non-sustained ventricular tachycardia on Holter ECG between survivors and non-survivors. Patients who died had a higher incidence of ischaemic heart disease, NYHA class and cardiothoracic ratio, and a lower ejection fraction and serum sodium level. The following heart rate variability parameters were significantly depressed in patients who died: SDNN, SDANN, SD, daytime and night-time total power and low frequency power. Except for night-time high frequency power, heart rate variability measures predominantly reflecting vagal activity (pNN50, RMSSD, daytime high frequency power) did not differ between survivors and non-survivors. Treatments (diuretics, digoxin and amiodarone) showed no significant difference between survivors and non-survivors.

The univariate relative risk of mortality in relation to clinical variables is listed in Table 2. The presence of coronary artery disease, a cardiothoracic ratio ≥60% and a left ventricular ejection fraction <30% were related to all-cause and sudden death. An NYHA class III to IV and the presence of non-sustained ventricular tachycardia on Holter ECG were related to all-cause mortality but not to sudden death. The following heart rate variability parameters were significantly related to all-cause mortality: SDNN, SDANN, SD, RMSSD, total power and low frequency power during daytime and night-time and high frequency power during night-time. When Kaplan–Meier curves for 3-year mortality were constructed, patients with SDNN <67 ms (inferior tercile of distribution) had a 3-year mortality rate of 55·9% compared with 30·6% in those with SDNN ≥67 ms ($P<0.0001$) (Fig. 1). In contrast, only SDANN, RMSSD and total power and low frequency power during daytime were significantly related to sudden death. In Kaplan–Meier analysis, patients with a low frequency power during daytime <3·3 ln (ms^2) (inferior quartile of distribution) had a 3-year sudden death rate of 33% compared with 14·6% in those with this value ≥3·3 ln (ms^2) ($P=0·007$) (Fig. 2). The following heart rate variability parameters were significantly associated with progressive heart failure death: SDNN (RR : 3·2, 95% CI 1·5–6·9), SD (RR :2·5, 95% CI 1·1–5·0), SDANN (RR : 2·5, 95% CI 1·25–5·0),

Table 1   Clinical characteristics, heart rate variability measures and treatments in patients who died or survived during follow-up

	Survivors (n=135)	Non-survivors (n=55)	P value
Clinical variables			
Age (years)	56·5 ± 12·3	58·7 ± 11·2	0·2456
Gender (male/female)	120/15	46/9	0·3200
Aetiology (CAD/NIDC)	51/84	34/21	0·0025
NYHA class II/III–IV (n)	84/51	35/20	0·0340
Cardiothoracic ratio (%)	56·7 ± 6·1	59·7 ± 6·6	0·0024
Left ventricular ejection fraction (%)	29·3 ± 8·5	25·6 ± 9·2	0·0096
VT on Holter ECG (n, %)	37/27·4%	21/38·2%	0·1436
Sodium (mmol . l^{-1})	138·0 ± 3·5	136·5 ± 4·5	0·0155
Potassium (mmol . $^{-1}$)	4·2 ± 0·3	4·2 ± 0·4	0·622
Heart rate variability measures			
Mean NN (ms)	780·3 ± 132·0	762·5 ± 122·3	0·3897
SDNN (ms)	91·3 ± 36·1	69·3 ± 31·7	0·0001
SDANN (ms)	81·1 ± 33·9	61·0 ± 27·2	0·0001
SD (ms)	36·1 ± 18·1	27·7 ± 17·9	0·0041
pNN50 (%)	4·8 ± 7·5	4·5 ± 7·3	0·7900
RMSSD (ms)	22·9 ± 14·9	21·1 ± 13·2	0·4119
Day-time total power (ln (ms^2))	5·7 ± 1·1	5·3 ± 1·1	0·0225
Night-time total power (ln (ms^2))	6·3 ± 1·2	5·7 ± 1·3	0·0015
Day-time low frequency power (ln (ms^2))	4·4 ± 1·5	3·8 ± 1·4	0·0208
Night-time low frequency power (ln (ms^2))	4·9 ± 1·5	4·1 ± 1·6	0·0016
Day-time high frequency power (ln (ms^2))	3·5 ± 1·1	3·4 ± 1·2	0·5610
Night-time high frequency power (ln (ms^2))	4·1 ± 1·2	3·7 ± 1·2	0·0479
Treatments			
Diuretic (n, %)	113/83·7%	51/92·7%	0·1007
Digoxin (n, %)	83/61·5%	36/65·5%	0·6007
Amiodarone (n, %)	48/35·6%	24/43·6%	0·2980

Data are expressed as mean ± SD or number of patients; *P* value is given for comparison between survivors and non-survivors.
CAD=coronary artery disease; NICD=non-ischaemic dilated cardiomyopathy; VT=ventricular tachycardia.

night-time total power (RR : 2·5, 95% CI 1·2–5·4) and night-time low frequency power (RR : 2·2, 95% CI 1·0–4·7).

The multivariate relative risk of mortality in relation to clinical variables is listed in Table 2. The presence of coronary artery disease was retained as an independent predictor for all-cause and sudden death, and a cardio-thoracic ratio ≥60% as an independent predictor for all-cause mortality and progressive heart failure death (RR : 2·56, 95% CI 1·01–6·67). An NYHA class III to IV was significantly associated with progressive heart failure death (RR : 3·44, 95% CI 1·43–8·3). Among heart rate variability parameters, a decrease in SDNN was found to have an independent prognostic value for all-cause mortality and progressive heart failure death (RR : 2·47, 95% CI 1·14–5·35), and a lower daytime low frequency power for sudden death. An SDNN <67 ms increased the risk of all-cause and progressive heart failure death 2·5-fold, and a low frequency power during daytime <3·3 ln (ms^2) increased the risk of sudden death 2·8-fold.

Discussion

The main finding of the present prospective study is that in patients with chronic heart failure, heart rate

variability, as assessed by time domain and spectral analysis, has prognostic value not only for the identification of patients at increased risk for all-cause mortality, but, more importantly, also for sudden death. Among time domain indexes, a lower SDNN is a significant and independent predictor of all-cause mortality and of progressive heart failure death. Among spectral measures, reduced power within the low frequency band during daytime is a significant and independent predictor of sudden death risk. A reduced heart rate variability has been observed consistently in patients with cardiac failure[7–9,11]. In this condition, despite signs of sympathetic activation such as faster heart rates and high levels of circulating catecholamines, heart rate variability measures predominantly reflecting sympathetic modulation of heart rate (SDANN, SD, low frequency) were decreased[6]. Thus, in conditions characterized by a marked and persistent sympathetic activation, the sinus node seems to dramatically diminish its responsiveness to neural inputs[10].

Our data confirm that a simple and easily measured time-domain index of autonomic activity, SDNN, has independent prognostic value in patients with chronic heart failure and identifies an increased risk for all-cause mortality in these patients. Although heart rate

Table 2   All-cause and sudden death in relation to clinical and heart rate variability measures — univariate and multivariate Cox proportional hazards survival analysis (n=188)

Variables (cut-off value)	All cause death				Sudden death			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Clinical variables								
Age (≥60 years)	1·25	[0·8–2]	—		0·8	[0·4–2]	—	
Aetiology (CAD)	2·5‡	[1·5–4·3]	2·2†	[1·3–3·8]	4·3‡	[1·7–11·1]	4·1†	[1·6–10·5]
NYHA class (III–IV)	2†	[1·3–3·3]			1·4	[0·6–3·3]		
Cardiothoracic ratio (≥60%)	2·5†	[1·4–5]	2·5†	[1·25–5]	2·5*	[1·1–10]	—	
Left ventricular ejection fraction (<30%)	2·2†	[1·2–3·9]	—		3·3*	[1·2–9]	—	
VT on Holter ECG (present)	1·7*	[1–2·9]	—		1·6	[0·7–3·9]	—	
Time domain measures of HRV								
Mean heart rate (>89 beats · min⁻¹)	1·3	[0·8–2·3]	—		1·2	[0·5–2·9]	—	
SDNN (<67 ms)	2·7‡	[1·6–4·6]	2·5‡	[1·5–4·2]	2·1	[0·9–5]	—	
SDANN (<55 ms)	2·5†	[1·4–3·3]	—		2·5*	[1–5]	–	
SD (<30 ms)	2·5†	[1·3–3·3]			1·7	[0·8–5]	—	
pNN50 (<2%)	1·4	[0·8–2·4]	—		1·6	[0·7–3·9]	—	
RMSSD (<14 ms)	1·9*	[1·1–3·4]			2·4*	[1–5·5]	—	
Frequency domain measures of HRV								
Day-time total power (<4·8 ln (ms²))	2*	[1·1–3·4]	—		2·4*	[1–5·6]	—	
Night-time total power (<5·3 ln (ms²))	2·9‡	[1·7–4·9]	—		2·2	[0·9–5·2]	—	
Day-time low frequency power (<3·3 ln (ms²))	2·2‡	[1·3–4·8]	—		3‡	[1·3–7]	2·8*	[1·2–6·8]
Night-time low frequency power (<3·6 ln (ms²))	2·3†	[1·3–4]	—		2·2	[0·9–5·2]	—	
Day-time high frequency power (<2·7 ln (ms²))	1·6	[0·9–2·7]	—		1·6	[0·7–3·7]	—	
Night-time high frequency power (<3·1 ln (ms²))	2·2†	[1·3–3·9]	—		1·7	[0·7–4·2]	—	

*P<0·05; †P<0·01; ‡P<0·001; CAD=coronary artery disease; CI=confidence interval; HRV=heart rate variability; RR=relative risk; VT=ventricular tachycardia.
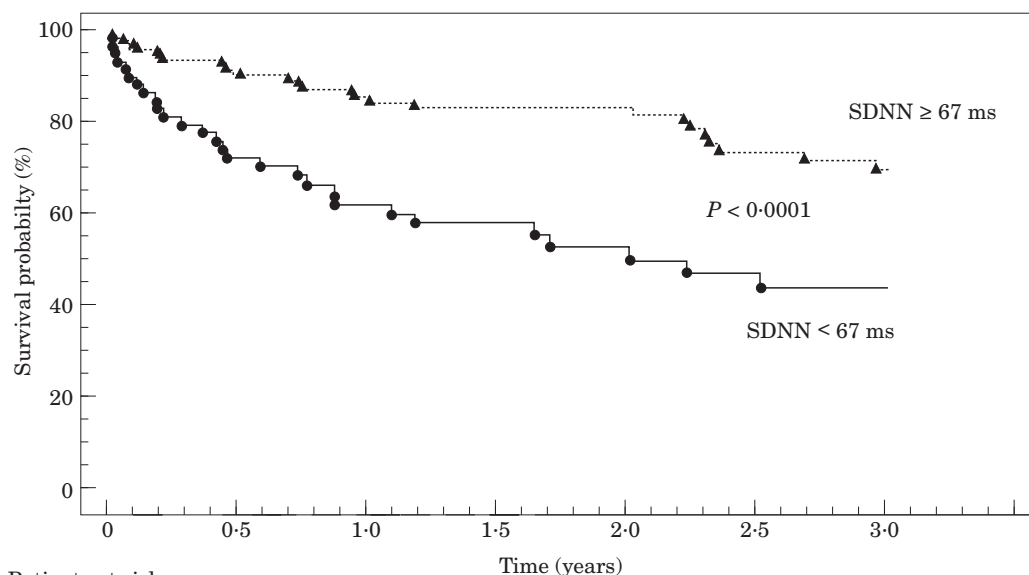

Figure 1 **Kaplan–Meier survival curves for all-cause death in 188 patients with chronic heart failure with ≥67 (n=128) vs <67 ms (n=60) standard deviation of normal RR intervals (SDNN).**

variability is reduced in many patients with chronic heart failure[19–21], first studies have failed to establish a clinical role for this technique, because they contained only a small number of highly selected patients, and have produced conflicting results[12–15,22]. Recently, three studies have proved the prognostic value of SDNN
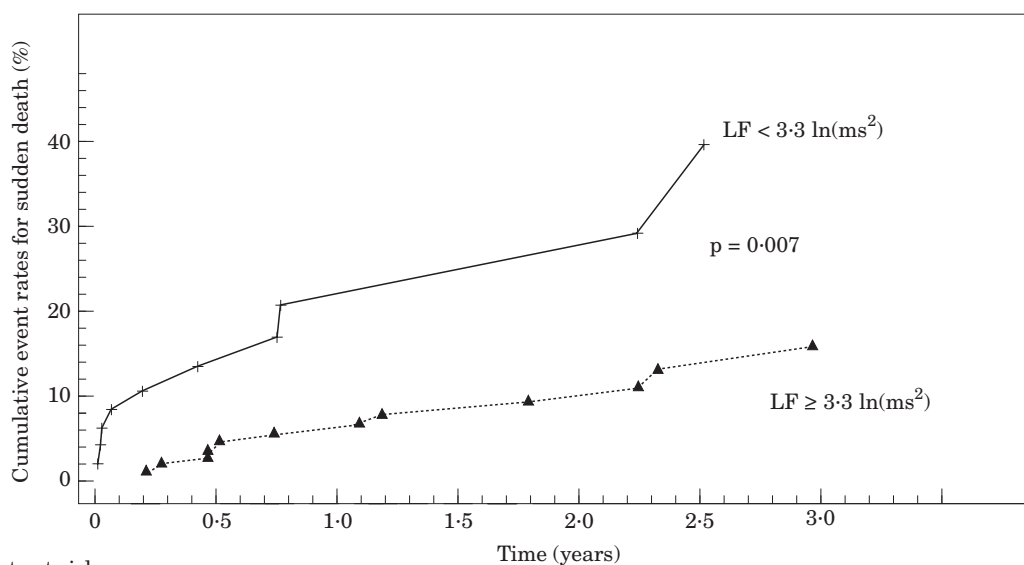
Figure 2 Kaplan–Meier event rates curves for sudden death in 188 patients with chronic heart failure with $\geq 3 \cdot 3$ (n=138) vs $<3 \cdot 3$ ln (ms^2) (n=50) daytime low frequency power.

in congestive heart failure. In a retrospective study of 93 patients with idiopathic dilated cardiomyopathy, Fauchier et al.[18] demonstrated that a depressed SDNN (<100 ms) is an independent predictor of cardiac events (cardiac death or heart transplantation) in multivariate analysis. Studying 102 consecutive patients with congestive heart failure due to ischaemic heart disease or idiopathic dilated cardiomyopathy, Ponikowski et al.[17] found that depressed SDNN (<100 ms), SDANN and low frequency power were independent predictors of cardiac death. In the UK-Heart prospective study[16], including 433 patients with congestive heart failure, due to ischaemic heart disease in 76% of cases, Nolan et al. demonstrated that SDNN, but not RMSSD or pNN50, was significantly associated with all-cause mortality and progressive heart failure death in multivariate analysis. In that study, an SDNN<50 ms identified a smaller subgroup of patients who were at higher risk of death. The reduction of SDNN reflects the summed influence of abnormalities in sympathetic, parasympathetic and renin-angiotensin activities, abnormal chemoreceptor function, changes in respiratory pattern and physical inactivity in congestive heart failure[23–25].

Our data also demonstrate that spectral measures of heart rate variability can predict sudden death. Depressed low frequency power during daytime (<3·3 ln (ms^2)) increased the risk of sudden death 2·8-fold. Confirming the results of the UK-Heart study[16], time-domain measurements of heart rate variability did not predict the risk of sudden death. Previously, in a prospective study of 95 patients with heart failure due to coronary artery disease or idiopathic dilated cardiomyopathy, Brouwer et al.[15] found that abnormal Poincaré plots had independent prognostic value both

for all-cause and sudden death. These relationships between impairment of heart rate variability and sudden death confirm that the autonomic nervous system plays an important role in myocardial electrical instability in chronic heart failure. At the difference of time–domain indices, spectral analysis of heart rate variability allowed a more detailed study of the autonomic environment of the heart and thus can predict sudden death in patients with chronic heart failure or in post infarct patients[26]. Among the spectral measures of heart rate variability, reduced power within the low frequency band predicted sudden death. These low frequency oscillations in heart rate variability are mediated both by the sympathetic and the parasympathetic systems and depend on the intact baroreflex[6]. The decrease in low frequency power in patients with chronic heart failure, despite high levels of sympathetic activation, may be secondary to abnormalities in central autonomic regulation and impairment of beta adrenergic receptor sensitivity[27,28].

Our data, associated with the recent results of UK-Heart, in relation to mode of death suggest that 24-h ECG monitoring may be useful in guiding the prescription of additional therapy for patients with chronic heart failure. Patients with lower SDNN are at considerable risk of death due to progressive heart failure and may have the most to gain from prescription of digoxin, beta-blockers or the provision of an exercise training programme which all increase SDNN[29–31]. Recent data indicate that beta-blockers and digoxin prevent death due to progressive heart failure, and this effect may be mediated in part by the beneficial effect that these agents have on neuroendocrine function[32–34]. Patients with depressed low frequency power during the daytime had an increased risk of sudden death; treatment should be

reviewed to decrease this risk. Hypokalaemia should be corrected. Beta-blockers, amiodarone and perhaps angiotensin II receptor antagonists seem to be promising for the prevention of sudden death in congestive heart failure[32,35,36]. As an alternative therapy, implantable defibrillators should be reasonably considered[37].

Study limitations

There are several limitations to our study. Although we studied a large population of patients with chronic heart failure over a mean follow-up of 22 months, our data relating to mode of death are based on relatively small numbers of events, and many deaths in heart failure patients are difficult to classify with certainty. These results should therefore be viewed with caution, but they do provide insights into the relationships between autonomic activity and mode of death in congestive heart failure.

The exclusion, by design, of patients with several clinical conditions potentially associated with a higher mortality, particularly patients with recent myocardial infarction or insulin-dependent diabetes mellitus, that influence heart rate variability measures, may add bias to our results. However, a reduction of heart rate variability as a marker of a poor prognosis is already established in these populations, our results can probably also be applied to patients with congestive heart failure with these conditions.

The treatment of our patients with congestive heart failure with digoxin, angiotensin-converting enzyme inhibitors and amiodarone potentially influence heart rate variability[38] and should also be addressed. However, since the medical regimen of survivors and non-survivors did not differ, we may assume that treatment has not affected our results.

Our results and the data from UK-Heart[16] confirm that 24-h heart rate variability analysis remains useful in chronic heart failure and that it is not necessary to control the effects of respiratory pattern or physical activity when measurements are used for prognostic purposes. The fact that results in the daytime period had a better prognostic value underlines the interest of 24-h ambulatory recordings in unrestricted activity patients.

In conclusion, our results confirm the value of time domain measures of heart rate variability in chronic heart failure, that a decrease in SDNN is one of the most important prognostic markers for all-cause mortality, and demonstrate the importance of frequency analysis of heart rate variability in this disease. Depressed low frequency power during daytime <3·3 ln (ms^2) identifies patients at risk of sudden death.

References

[1] Ho KKL, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: The Framingham Study. J Am Coll Cardiol 1993; 22 (Suppl): 6A–13A.

[2] Galinier M, Vialette JC, Fourcade J et al. QT interval dispersion as a predictor of arrhythmic events in congestive heart failure. Importance of aetiology. Eur Heart J 1998; 19: 1054–62.

[3] Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L, for the CONSENSUS Trial Study Group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990; 82: 1730–6.

[4] Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. Circulation 1993; 87 (Suppl VI): VI-40–48.

[5] Hirsch AT, Dzau VJ, Creager MA. Baroreceptor function in congestive heart failure: effect on neurohumoral activation and regional vascular resistance. Circulation 1987; 75 (Suppl IV): IV-36–48.

[6] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996; 93: 1043–65.

[7] Saul JP, Arai Y, Berger RD, Lilly LS, Colucci WS, Cohen RJ. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. Am J Cardiol 1988; 61: 1292–9.

[8] Casolo G, Balli E, Taddei T, Amuhasi J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. Am J Cardiol 1989; 64: 1162–7.

[9] Binkley PF, Nunziata E, Hass GJ, Nelson SD, Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. J Am Coll Cardiol 1991; 18: 464–72.

[10] Kienzle MG, Ferguson DW, Birkett CL, Myers GA, Berg WJ, Mariano J. Clinical, hemodynamical and sympathetic neural correlates of heart rate variability in congestive heart failure. Am J Cardiol 1992; 69: 761–7.

[11] Szabo BM, Van Veldhuisen DJ, Brouwer J, Haaksma J, Lie KI. Relation between severity of disease and impairment of heart rate variability parameters in patients with chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol 1995; 76: 713–6.

[12] Binder T, Freys N, Porenta G et al. Prognostic value of heart rate variability in patients awaiting cardiac transplantation. Pacing Clin Electrophysiol 1992; 15: 2215–20.

[13] Mortara A, La Rovere MT, Sigorini MG et al. Can power spectral analysis of heart rate variability identify a high risk subgroup of congestive heart failure patients with excessive sympathetic activation? A pilot study before and after heart transplantation. Br Heart J 1994; 71: 422–30.

[14] Fei L, Keeling PJ, Gill JS et al. Heart rate variability and its relation to ventricular arrhythmias in congestive heart failure. Br Heart J 1994; 71: 322–8.

[15] Brouwer J, Van Veldhuisen DJ, Man in't Vedl AJ et al. for the Dutch Ibopamine Multicenter Trial Study Group. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. J Am Coll Cardiol 1996; 28: 1183–9.

[16] Nolan J, Batin PD, Andrews R et al. Prospective study of heart rate variability and mortality in chronic heart failure. Results of the United Kingsom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart). Circulation 1998; 98: 1510–6.

[17] Ponikowski P, Anker SD, Chua TP *et al*. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1997; 79: 1645–50.

[18] Fauchier L, Babuty D, Cosnay P, Autret ML, Fauchier JP. Heart rate variability in idiopathic dilated cardiomyopathy: characteristics and prognostic value. J Am Coll Cardiol 1997; 30: 1009–14.

[19] Gibelin P, Dadoun-Dybal M, Morand P. Variabilité de la fréquence cardiaque dans l'insuffisance cardiaque chronique: influence de la gravité et de l'étiologie. Arch Mal Coeur 1994; 87: 1207–11.

[20] Nolan J, Flapan AD, Capewell S, MacDonald T, Neilson JMM, Ewing DJ. Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. Br Heart J 1992; 67: 482–6.

[21] Tanabe T, Iwamoto T, Fusegawa Y, Yoshioka K, Shiina Y. Alterations of sympathovagal balance in patients with hypertrophic and dilated cardiomyopathies assessed by spectral analysis of RR interval variability. Eur Heart J 1995; 16: 799–807.

[22] Szabo BM, Van Veldhuisen DJ, Van der Veer N, Brouwer J, De Graeff PA, Crijus HJ. Prognostic value of heart rate variability in chronic congestive heart failure secondary to idiopathic of ischaemic dilated cardiomyopathy. Am J Cardiol 1997; 79: 978–80.

[23] Parati G, Saul JP, Di Rieuzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation: a critical appraisal. Hypertension 1995; 25: 1276–86.

[24] Mortara A, Sleight P, Pinna GD *et al*. Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. Circulation 1997; 96: 246–52.

[25] Bernadi L, Valle F, Coco M, Calciati A, Sleight P. Physical activity influences heart rate variability and very-low-frequency components in Holter electrocardiograms. Cardiovasc Res 1996; 32: 234–7.

[26] Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992; 85: 163–71.

[27] Van de Borne P, Montano N, Pagani M, Oren R, Somers VK. Absence of low frequency variability of sympathetic nerve activity in severe heart failure. Circulation 1997; 95: 1449–54.

[28] Cooley RL, Montano N, Cogliati C *et al*. Evidence for a central origin of the low-frequency oscillation in RR-interval variability. Circulation 1998; 98: 556–61.

[29] Pousset F, Copie X, Lechart P *et al*. Effects of bisoprolol on heart rate variability in heart failure. Am J Cardiol 1996; 77: 612–7.

[30] Slatton ML, Irani WN, Hall SA *et al*. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? J Am Coll Cardiol 1997; 29: 1206–13.

[31] Adamopoulos S, Ponikowski P, Cerquetani E *et al*. Circadian pattern of heart rate variability in chronic heart failure patients: effects of physical training. Eur Heart J 1995; 16: 1380–6.

[32] Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH, for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996; 334: 1349–55.

[33] Australia/New Zealand Heart Failure Research Collaborative Group. Randomised placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet 1997; 349: 375–80.

[34] The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336: 525–33.

[35] Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomised trials. Lancet 1997; 350: 1417–24.

[36] Pitt B, Segal R, Martinez FA *et al*. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997; 349: 747–52.

[37] Moss AJ, Hall WJ, Cannon DS *et al*. for the Multicentre Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996; 335: 1933–40.

[38] Tuininga YS, Van Veldhuisen DJ, Brouwer J *et al*. Heart rate variability in left ventricular dysfunction and heart failure: effects and implications of drug treatment. Br Heart J 1994; 72: 509–13.