JACC Vol. 28, No. 5
November 1, 1996:1183–9

Prognostic Value of Heart Rate Variability During Long-Term Follow-Up in Patients With Mild to Moderate Heart Failure

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Objectives. **We sought to assess the prognostic value of heart rate variability measures, including Poincaré plots, in patients with mild to moderate chronic heart failure.**

Background. **Mortality is high in patients with heart failure, and many of them die suddenly. However, identification of high risk patients, particularly those with an increased risk for sudden death, has remained difficult.**

Methods. **We studied 95 patients with heart failure (mean [±SD] age 60 ± 8 years, left ventricular ejection fraction 0.29 ± 0.09, New York Heart Association functional class II [81%] and III [19%]) during up to 4 years of follow-up. Heart rate variability measures and Poincaré plots were obtained from 24-h Holter recordings.**

Results. **During follow-up, 17 (18%) of the 95 patients died. In 15 patients, death was cardiac related (11 patients experienced sudden death). None of the conventional time and frequency domain measures of heart rate variability were related to survival. In contrast, abnormal Poincaré plots identified a significantly higher risk for all-cause cardiac death (Cox proportional hazards ratio 5.7, 95% confidence interval [CI] 1.6 to 20.6, univariate analysis) and for sudden cardiac death (hazards ratio 6.8, 95% CI 1.5 to 31.4) compared with those with normal Poincaré plots. Patients with abnormal Poincaré plots were shown to have a lower left ventricular ejection fraction (0.26 ± 0.10 vs. 0.31 ± 0.08, $p < 0.05$) and higher plasma norepinephrine concentrations (506 ± 207 pg/ml vs. 411 ± 175 pg/ml, $p < 0.05$). In multivariate analysis, abnormal Poincaré plots still had independent prognostic value, both for all-cause cardiac mortality and for sudden cardiac death (hazards ratio 5.3, 95% CI 1.2 to 17.1, hazards ratio 4.5, 95% CI 1.0 to 27.5, respectively.**

Conclusions. **Heart rate variability analysis, as assessed by Poincaré plots, has independent prognostic value in patients with mild to moderate chronic heart failure and identifies an increased risk for all-cause and sudden cardiac death in these patients.**

(J Am Coll Cardiol 1996;28:1183–9)

Mortality is high in patients with chronic congestive heart failure, and death often occurs suddenly (1). Although a number of measures, such as left ventricular ejection fraction (2,3), plasma norepinephrine (4,5), peak oxygen consumption (3) and ventricular arrhythmias (2), have been associated with all-cause mortality in heart failure, it has remained difficult to identify heart failure patients at an increased risk of sudden cardiac death. Recent studies suggest that death in severe heart failure is often due to progressive pump failure, whereas in less advanced disease, a relatively higher proportion of deaths occur suddenly (6,7). Because these patients usually have only mild symptoms, sudden death is particularly devastating in this group and identification of such patients is therefore important.

In patients with chronic heart failure, abnormal autonomic control has been recognized as a potential explanation for the observed increased mortality (8). Analysis of heart rate variability is a noninvasive means of studying autonomic control of the heart (9–11). 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 (12–16). It has recently been suggested that Poincaré plots, which represent beat to beat variations in heart rate, may provide even better insight into the abnormal autonomic control of the heart (17–20). In patients with early-stage heart failure, the predictive value for sudden death of neither conventional heart rate variability measures nor Poincaré plots has been established.

The purpose of the present study was to examine the

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Manuscript received December 6, 1995; revised manuscript received June 3, 1996, accepted June 11, 1996.

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0735-1097/96/$15.00
PII S0735-1097(96)00279-3

Table 1. Definition of Heart Rate Variability Measures

Variable	Definition
Time domain	
Mean NN (ms)	Mean of all normal to normal RR intervals during 24 h
SDNN (ms)	Standard deviation of all normal to normal RR intervals during 24 h
SDANN (ms)	Standard deviation of all 288 averages during 24 h of normal to normal RR intervals in 5-min segments
pNN50 (%)	Percent of differences between successive normal RR intervals >50 ms
Frequency domain	
Total power (ms^2)	Energy in power spectrum between 0.0033 and 0.40 Hz
Very low frequency power (ms^2)	Energy in power spectrum between 0.0033 and 0.04 Hz
Low frequency power (ms^2)	Energy in power spectrum between 0.04 and 0.15 Hz
High frequency power (ms^2)	Energy in power spectrum between 0.15 and 0.40 Hz

prognostic value of heart rate variability measures, including Poincaré plots, in patients with mild to moderate chronic heart failure during 2 to 4 years of follow-up. The study patients had participated in a recently published multicenter heart failure study in the Netherlands (21).

Methods

Study group. Patients aged 18 to 75 years who had functional class II or III chronic heart failure and were clinically stable for at least 2 weeks were eligible for the study, as previously described (21). Chronic heart failure was characterized by clinical signs and symptoms and a radionuclide left ventricular ejection fraction ≤0.45 obtained within the previous 2 months. Patients were excluded from participation if heart failure was due to hemodynamically significant valvular or congenital heart disease, active myocarditis, thyroid disease or hypertrophic obstructive cardiomyopathy. Further exclusion criteria were exercise-limiting angina pectoris, myocardial infarction or a major surgical procedure within the previous 2 months, severe hypertension, atrial fibrillation or flutter, pacemaker therapy, a history of sustained ventricular tachyarrhythmias, chronic obstructive lung disease, severe hepatic or renal disease and insulin-dependent diabetes mellitus.

Baseline measures. At the end of a placebo treatment period of 7 to 10 days, a 24-h ambulatory Holter recording was obtained for analysis of heart rate variability and arrhythmias, and venous blood was collected for determination of plasma neurohormonal concentrations. At baseline, up to 80 mg/day of furosemide was allowed as background therapy, as well as short-acting nitrates. Triamterene was also permitted to control serum potassium levels. Other drugs for treatment of heart failure, including angiotensin-converting enzyme inhibitors, alpha- or beta-adrenergic blocking agents and calcium antagonists, were not allowed. The protocol was approved by the Ethics Committee of each participating center and was conducted in accordance with the revised Declaration of Helsinki. Before entry into the study, all patients gave written informed consent.

Follow-up. The patients were followed for at least 2 years after the baseline measures. Deaths were classified as sudden cardiac death, nonsudden cardiac death or noncardiac death by physicians who had no knowledge of the heart rate variability analyses. Sudden cardiac death was defined using standard criteria (22)—i.e., as unexpected death that occurred within 1 h of new or more serious symptoms, or during sleep or while unobserved, in the absence of increasing angina pectoris or progressive heart failure. During the first 6 months, patients were randomly allocated to double-blind study medication (i.e., digoxin, ibopamine [an orally active dopamine agonist] or placebo) (21). Thereafter, patients were treated by their attending physician and received standard treatment for chronic heart failure. Drug use was scored at the last available date during follow-up.

Neurohormonal levels. Venous blood for the determination of plasma neurohormonal levels was drawn after 30 min of supine rest, in the morning hours between 8 AM and 11 AM. Plasma norepinephrine, aldosterone and renin concentrations were analyzed in a central core laboratory. Plasma norepinephrine (23) and plasma renin (24) concentrations were measured as described previously; plasma aldosterone concentration was measured using a commercially available radioimmunoassay kit (Aldokit, Labservice Benelux, Apeldoorn, The Netherlands).

Analysis of heart rate variability. The 24-h ambulatory Holter recordings were analyzed on a Marquette 8000 Holter system (Marquette Electronics, Inc.) by an experienced analyst (J.H.) and supervised by one physician (J.B.). All heart rate variability analyses were performed without knowledge of the clinical characteristics of the patients. Recordings with more than 15% noise or ectopic beats during 24 h were excluded from the heart rate variability analysis. For the calculation of heart rate variability, the data file of RR intervals was transferred to a personal computer. From the time series of RR intervals, time and frequency domain variables were calculated (Table 1). The variables were computed over consecutive 5-min segments. Segments with more than 15% noise or ectopic beats were excluded from the analysis. Before calculation of the frequency domain variables in the other segments, episodes with noise and ectopic beats were substituted by holding the previous normal to normal interval constant throughout the entire period. Spectral analysis was performed using the discrete Fourier transform algorithm (25–28). Low

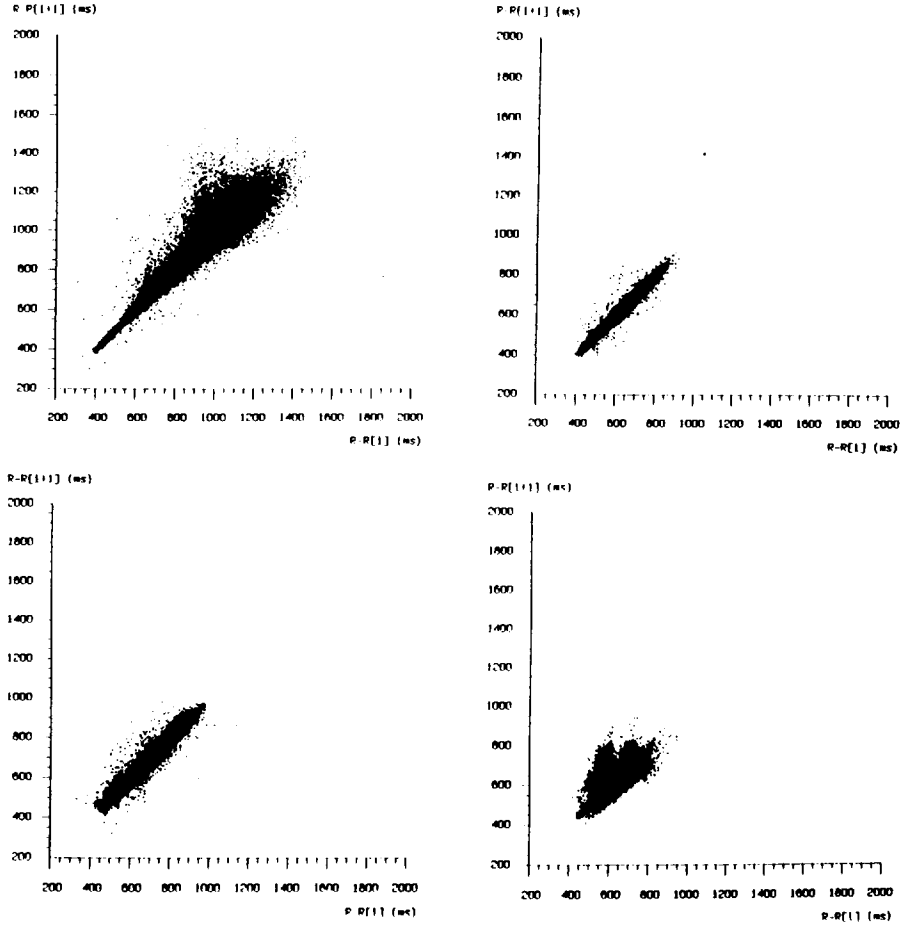


Figure 1. Examples of Poincaré plots. Example of a normal Poincaré plot is shown at the **upper left;** the other three plots are abnormal. **Upper left** plot is from a 50-year old man who was alive after 2.9 years of follow-up. **Lower left** plot ("narrow" pattern) is from a 55-year old man who died suddenly after 132 days of follow-up. **Upper right** plot (also narrow pattern) is from a 68-year old man who died suddenly after 67 days of follow-up. **Lower right** plot ("complex" pattern) is from a 55-year old man who died suddenly after 3.4 years of follow-up. The left ventricular ejection fraction of these patients was 0.25, 0.18, 0.21 and 0.44, respectively. Their plasma norepinephrine concentration was 533, 329, 387 and 427 pg/ml, respectively.

and high frequency power was also expressed in normalized units, analogous to calculations used in autoregressive models. Furthermore, the ratio between low and high frequency power, which is considered a measure of sympathovagal balance, was calculated (11,29).

Poincaré plots. These plots were constructed by plotting each normal to normal RR interval against its subsequent normal to normal RR interval. RR intervals related to ectopic beats or to noise were excluded from the analysis. Poincaré plots were classified as described previously by Woo et al. (18,19). They were considered to be normal when increasing RR interval dispersion was observed with increasing RR intervals (i.e., lower heart rate) (Fig. 1). Two types of abnormal Poincaré plots are generally recognized: "narrow" patterns, with little or no increase in RR interval dispersion at longer RR intervals, and "complex" patterns, with clusters of RR intervals aligning a small core area of RR intervals (Fig. 1).

Statistical analysis. Data are presented as the mean value ± SD, unless otherwise indicated. For comparison of the baseline data, the Student *t* test, Wilcoxon rank-sum test (for non-normally distributed variables) and the Fisher exact test (for categoric variables) were used. Mean values of heart rate variability measures were calculated for the complete 24-h period. Survival analysis was performed using a Cox proportional hazards model (EGRET package, version 0.26.6). When estimating the association of continuous variables with mortality, the patients were dichotomized by the median value of the examined variable. For the standard deviation of all normal to normal RR intervals during 24 h, we also evaluated the cutoff value of 50 ms, as defined by Kleiger et al. (30) in their study in postinfarction patients. Kaplan-Meier survival curves were calculated for graphic display of survival. For all comparisons, $p < 0.05$ was considered statistically significant.

Results

Baseline measures. Holter recordings for heart rate variability analysis were available in 95 of the 161 patients in the original Dutch Ibopamine Multicenter Trial (DIMT) study group (21). Their mean (±SD) age was 60 ± 8 years and left ventricular ejection fraction 0.29 ± 0.09. Of all the patients, 82 (86%) were men and 13 (14%) were women; 78 patients (82%) were in functional class II and 17 (18%) were in class III. Heart failure was due to coronary artery disease in 71 patients and due to idiopathic dilated cardiomyopathy in 24 patients. At baseline, 53 patients were taking furosemide, at an average dose of 25 ± 17 mg.

Conventional analysis of heart rate variability could be

Table 2. Characteristics at Baseline in Relation to Survival (n = 95)

	Survivors (n = 78)	Nonsurvivors (n = 17)	p Value
Age (yr)	59 ± 7	61 ± 9	NS
Male/female (%)	85/15	94/6	NS
LVEF	0.30 ± 0.09	0.23 ± 0.10	0.009
NYHA functional class II/III (%)	85/15	71/29	NS
Ischemic HF/idiopathic HF (%)	78/21	65/35	NS
Hemodynamic data			
HR (beats/min)	78 ± 12	86 ± 15	0.027
SBP (mm Hg)	131 ± 17	131 ± 19	NS
DBP (mm Hg)	83 ± 9	83 ± 7	NS
Plasma neurohormones			
Norepinephrine (pg/ml)	421 (119–883)	507 (329–1,112)	0.014
Aldosterone (pg/ml)	87 (8–498)	128 (16–373)	NS
Renin (μU/ml)	19 (3–82)	22 (7–58)	NS
Arrhythmias on 24-h Holter ECG			
Ventricular premature beats (h^{-1})	12 (1–780)	26 (1–549)	0.048
Ventricular tachycardia (%)	36	65	0.028
Drug use (%)*			
Diuretics	66	93	0.034
Digoxin	40	60	NS
ACE	45	47	NS
Ibopamine	20	27	NS
Calcium antagonists	9	27	NS
Other vasodilating drugs	20	20	NS
Beta-blockers	21	14	NS
Antiarrhythmic drugs	13	27	NS
Anticoagulants	43	47	NS
Antiplatelet agents	29	40	NS

*Drug use as scored at last follow-up visit. Data presented are mean value ± SD, median (range) or percent of patients. ACE = angiotensin-converting enzyme; DBP = diastolic blood pressure; ECG = electrocardiogram; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure.

performed in 87 of the 95 patients; in 8 patients ectopic beats or noise precluded a reliable analysis. In 6 of these 8 patients, frequent ventricular premature beats precluded heart rate variability analysis. Poincaré plots were available in all 95 patients. They were classified as normal in 57 patients (60%) and as abnormal in the other 38 (40%). Of these 38 abnormal Poincaré plots, 32 showed a narrow pattern and 6 a complex pattern.

Between left ventricular ejection fraction and the heart rate variability measures, only moderate but statistically significant correlations were observed ($r = 0.23$ to 0.36, $p < 0.05$ to 0.01). Furthermore, there were negative correlations between plasma norepinephrine concentration and heart rate variability measures ($r = -0.30$ to -0.41, $p < 0.05$ to 0.001). Patients with abnormal Poincaré plots had a significantly lower left ventricular ejection fraction (0.26 ± 0.10 vs. 0.31 ± 0.08, $p < 0.05$) and a higher plasma norepinephrine concentration (506 ± 207 pg/ml vs. 411 ± 175 pg/ml, $p < 0.05$).

Follow-up. The records for all 95 patients were available for follow-up. During follow-up, 17 patients died. In two patients, the cause of death was noncardiac (one bronchial carcinoma, one cerebrovascular accident). Fifteen patients died from cardiac reasons; there were 11 sudden deaths and 4 other cardiac deaths (3 progressive heart failure, 1 fatal myocardial infarction). The duration of follow-up ranged from 2.0 to 3.9 years for surviving patients (mean 2.6) and from 8 days to 3.4 years for the patients who died (mean 1.5). The baseline characteristics for survivors and nonsurvivors are listed in Table 2. Left ventricular ejection fraction was significantly lower in the group of nonsurvivors. Heart rate, plasma norepinephrine concentration and number of ventricular premature heartbeats were all higher and the presence of ventricular tachycardias was more common in the group of nonsurvivors. Furthermore, patients who died were using diuretics significantly more often than those who survived. There were no other differences in drug use between the two groups. Also, biochemical measures (serum sodium and potassium not tabulated) showed no significant differences between survivors and nonsurvivors.

Survival analysis. In Table 3, the univariate relative risk of mortality in relation to clinical variables is listed. In patients with a low left ventricular ejection fraction, the relative risk of cardiac death and sudden death was significantly higher in patients with relatively preserved left ventricular ejection fraction (Cox proportional hazards ratio 4.3 and 4.9, respectively). Ventricular arrhythmias were related to all-cause cardiac

Table 3. All-Cause, Cardiac and Sudden Death in Relation to Clinical and Heart Rate Variability Measures—Univariate Cox Proportional Hazards Survival Analysis (n = 95)

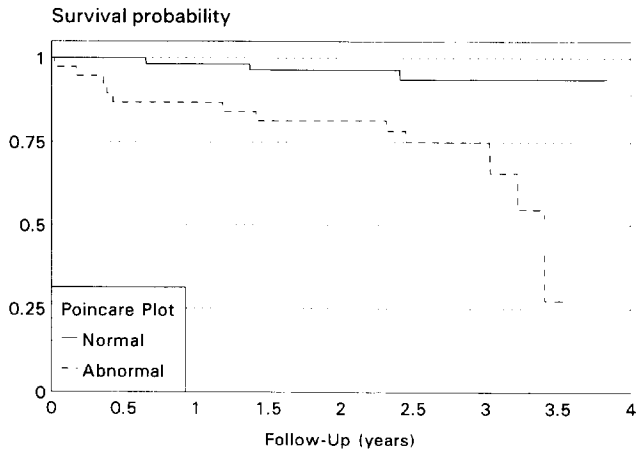
Variable (cutoff value)	Cardiac Death		Sudden Death	
	RR	95% CI	RR	95% CI
Clinical variables				
LVEF (<0.30)	4.3*	1.2–15.3	4.9*	1.0–22.5
Plasma norepinephrine (>435 pg/ml)	2.1	0.7–6.3	1.9	0.6–6.4
Ventricular premature beats (>20/h)	4.0*	1.1–14.3	4.3	0.9–20.4
Ventricular tachycardia (present)	3.0*	1.0–8.9	2.7	0.8–9.1
Time domain measures of heart rate variability				
Mean NN interval (<750 ms)	1.1	0.4–2.9	1.1	0.3–3.6
SDNN (<110 ms)	1.2	0.4–3.5	2.0	0.5–8.0
SDNN (<50 ms)†	3.6	0.5–27.8	5.4	0.7–43.4
SDANN (<100 ms)	1.2	0.4–3.5	1.3	0.3–4.7
pNN50 (<2.0%)	2.2	0.8–6.5	3.0	0.8–11.2
Frequency domain measures of heart rate variability				
Total power (<2,500 ms^2)	1.7	0.6–4.8	2.0	0.6–6.8
Very low frequency power (<1,500 ms^2)	1.3	0.4–4.4	1.3	0.4–4.4
Low frequency power (<300 ms^2)	1.6	0.6–4.4	1.8	0.5–6.2
High frequency power (<100 ms^2)	1.7	0.6–4.6	1.3	0.4–4.3
Poincaré plot (abnormal)	5.7‡	1.6–20.6	6.8*	1.5–31.4

*$p < 0.05$. †Cutoff value as used by Kleiger et al. (30). For all other variables, the median value was used as cutoff value. Ventricular tachycardia was classified as present or absent (n = 39 and n = 56, respectively), and Poincaré plots as abnormal or normal (n = 38 and n = 57, respectively). ‡$p < 0.01$. CI = confidence interval; RR = relative risk (hazards ratio from the Cox proportional hazards analysis); other abbreviations as in Tables 1 and 2.

death but not to sudden death. Other clinical variables, including the neurohormones measured, only revealed trends for an association with increased mortality, which reached no statistical significance (Table 3). The frequency domain measures of heart rate variability, expressed in normalized units, and the ratio of low-to-high frequency power also showed only nonsignificant trends for a relation with increased mortality (not tabulated).

Poincaré plots were the only heart rate variability measure that identified an increased risk for mortality, both for all-cause cardiac death and sudden death (Table 3, Fig. 2). Of the 38 patients with abnormal Poincaré plots, 12 (32%) died of a cardiac cause, and 9 of these patients died suddenly. Of the 57 patients with normal Poincaré plots, 3 (5%) died during follow-up, and 2 of these deaths were sudden.

Figure 2. Kaplan-Meier survival curves for cardiac death in patients with normal versus abnormal Poincaré plots (Cox proportional hazards ratio 5.7, 95% CI 1.6 to 20.6, $p < 0.05$).



When dividing all patients with abnormal Poincaré plots into narrow (n = 32) and complex (n = 6), the hazards ratio for cardiac death was 5.2 in patients with a narrow Poincaré plot and 8.8 in patients with a complex Poincaré plot (95% confidence interval [CI] 1.4 to 19.2 and 1.7 to 44.7, respectively). The hazards ratio for sudden cardiac death was 5.4 in patients with a narrow Poincaré plot and 13.5 in patients with a complex Poincaré plot (95% CI 1.1 to 27.0 and 2.2 to 82.9, respectively).

In multivariate survival analysis, abnormal Poincaré plots were found to have prognostic value independent of left ventricular ejection fraction, plasma norepinephrine, ventricular premature beats and presence of ventricular tachycardia (Table 4). The hazards ratio, based on abnormal Poincaré plots, for cardiac death and sudden death was 4.5 and 5.3, respectively.

Discussion

The main finding of the present study is that in the early stages of heart failure, heart rate variability, as assessed by Poincaré plots, has prognostic value not only for the identification of patients at increased risk for all-cause cardiac mortality, but, more importantly, also for sudden cardiac death. Although the presence of an abnormal Poincaré plot is associated with a lower left ventricular ejection fraction and a higher plasma norepinephrine concentration, it was also found to have independent prognostic value when using multivariate

Table 4. All-Cause, Cardiac and Sudden Death in Relation to Clinical and Heart Rate Variability Measures—Multivariate Cox Proportional Hazards Survival Analysis (n = 95)

Variable (cutoff value)	Cardiac Death		Sudden Death	
	RR	95% CI	RR	95% CI
LVEF (<0.30)	3.7	0.7–18.0	6.2	0.7–53.5
Plasma norepinephrine (>450 pg/ml)	1.1	0.3–3.4	1.3	0.2–7.4
Ventricular premature beats (>20/h)	3.4	0.9–12.9	4.0	0.8–19.7
Ventricular tachycardia (present)	1.6	0.5–5.7	1.4	0.3–5.8
Poincaré plot (abnormal)	4.5*	1.2–17.1	5.3*	1.0–27.5

*$p < 0.05$. The median value of the variables was used as the cutoff value. Ventricular tachycardia was classified as present or absent (n = 39 and n = 56, respectively), and Poincaré plots as abnormal or normal (n = 38 and n = 57, respectively). Abbreviations as in Tables 2 and 3.

analysis. The predictive value of an abnormal Poincaré plot therefore seems to be unrelated to other, well known risk factors in patients with heart failure (1–7).

A number of variables have been associated with all-cause cardiac mortality in patients with chronic heart failure (1–7), but attempts to identify risk factors for sudden death have been disappointing so far. Recently, increased QT dispersion was found to be associated with an increased risk of sudden death in chronic heart failure (31). Furthermore, it has been suggested that relatively fast and long runs of ventricular tachycardia might also be related to sudden death (32). Plasma norepinephrine concentration has overall prognostic value in patients with heart failure, but it has not been shown to be related to an increased risk for sudden death (1,4,6,33). In the present study, left ventricular ejection fraction and ventricular arrhythmias were also related to cardiac mortality in univariate analysis, but only Poincaré plots remained associated with both all-cause cardiac death and sudden cardiac death in the multivariate analysis. The prognostic value of a single measure of plasma norepinephrine concentration was less powerful than that of an abnormal Poincaré plot. This finding may be explained by the fact that whereas Poincaré plots reflect autonomic control during 24 h, plasma norepinephrine is only an instantaneous assessment of sympathetic activity.

In patients with advanced heart failure, Woo et al. (20) reported that complex Poincaré plots are associated with a higher risk of sudden death when compared with a narrow Poincaré plot (20). In their study, patients with more severe heart failure were examined, and all patients were found to have abnormal Poincaré plots. Our data indicate a lower incidence (45%) of abnormal Poincaré plots in patients in the early stages of heart failure. When these patients are further divided, mortality appears to be higher in patients with a complex Poincaré plot as compared with those with a narrow Poincaré plot. Although the number of patients in these subgroups is small, it may therefore be hypothesized that complex Poincaré plots reflect a more severe disturbance of the autonomic control of the heart, which is apparently more often found in patients with severe heart failure (17).

Study limitations. In our study, the conventional time and frequency domain measures of heart rate variability did not have significant prognostic value. However, in postmyocardial infarction patients (30), and also in patients with severe heart failure (34), several heart rate variability measures were reported to have significant value in assessing prognosis. The low prognostic value of conventional heart rate variability measures in our study may be explained in part by the relative low mortality in this patient group with mild heart failure. Furthermore, frequency domain measures of heart rate variability cannot always be calculated reliably in patients with heart failure because the incidence of ventricular premature complexes may be high. In our study, a reliable heart rate variability analysis could not be performed in eight patients (8%) for this reason. These patients with frequent premature ventricular complexes, however, were also at a higher risk of mortality (Table 3). Finally, it was already pointed out by Woo et al. (19) that complex Poincaré plots, which are apparently more often observed in patients with severe heart failure, are associated with increased beat to beat variability, which hampers recognition of patients at a higher risk using conventional measures of heart rate variability.

A further limitation of our study is that patients were not randomized by use of drugs during follow-up. Also, during the first 6 months of the study, patients received different study medications (digoxin, ibopamine or placebo). After the first 6 months of the study, the addition of other drugs by the treating physician may have influenced mortality during follow-up. However, baseline measures were performed using equal conditions for all patients. Furthermore, the use of drugs, except for diuretics, during follow-up was equal in survivors and nonsurvivors. We therefore believe that these effects are limited. It should also be realized that at the time this study was initiated, angiotensin-converting enzyme inhibition had not yet become standard treatment in patients with heart failure. Therefore, only 46% of the patients received treatment with an angiotensin-converting enzyme inhibitor during follow-up.

Clinical implications. Our data indicate that in the early stages of heart failure, heart rate variability, as assessed by Poincaré plots, has independent prognostic value. It may therefore provide a noninvasive clinical guide to prognosis in chronic heart failure and possibly in other cardiac disorders. Poincaré plots provide information on autonomic control of the heart, which is less readily recognized by other techniques.

Autonomic imbalance has been recognized to evolve early in the development of heart failure and probably plays a major role in progression of the disease (35). This rather unknown technique of constructing Poincaré plots can be performed easily in patients with heart failure also. Further improvement may, however, be achieved by better quantification of the abnormalities in heart rate fluctuations that are observed in patients with chronic heart failure. In addition, our findings were obtained in a relatively small patient group. Therefore, our results need confirmation in larger patient groups to reliably establish the predictive value of an abnormal Poincaré plot in clinical practice.

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