Short-Term Heart Rate Variability Strongly Predicts Sudden Cardiac Death in Chronic Heart Failure Patients

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Background—The predictive value of heart rate variability (HRV) in chronic heart failure (CHF) has never been tested in a comprehensive multivariate model using short-term laboratory recordings designed to avoid the confounding effects of respiration and behavioral factors.

Methods and Results—A multivariate survival model for the identification of sudden (presumably arrhythmic) death was developed with data from 202 consecutive patients referred between 1991 and 1995 with moderate to severe CHF (age 52±9 years, left ventricular ejection fraction 24±7%, New York Heart Association class 2.3±0.7; the derivation sample). Time- and frequency-domain HRV parameters obtained from an 8′ recording of ECG at baseline and during controlled breathing (12 to 15 breaths/min) were challenged against clinical and functional parameters. This model was then validated in 242 consecutive patients referred between 1996 and 2001 (validation sample). In the derivation sample, sudden death was independently predicted by a model that included low-frequency power (LFP) of HRV during controlled breathing ≤13 ms^2 and left ventricular end-diastolic diameter ≥77 mm (relative risk [RR] 3.7, 95% CI 1.5 to 9.3, and RR 2.6, 95% CI 1.0 to 6.3, respectively). The derivation model was also a significant predictor in the validation sample (*P*=0.04). In the validation sample, LFP ≤11 ms^2 during controlled breathing and ≥83 ventricular premature contractions per hour on Holter monitoring were both independent predictors of sudden death (RR 3.0, 95% CI 1.2 to 7.6, and RR 3.7, 95% CI 1.5 to 9.0, respectively).

Conclusions—Reduced short-term LFP during controlled breathing is a powerful predictor of sudden death in patients with CHF that is independent of many other variables. These results refine the identification of patients who may benefit from prophylactic implantation of a cardiac defibrillator. (***Circulation***. 2003;107:565-570.)

Key Words: heart failure ■ prognosis ■ nervous system, autonomic ■ respiration ■ death, sudden

C hronic heart failure (CHF) is associated with major abnormalities of autonomic cardiovascular control. Sympathetic activation is important in the pathogenesis and progression of the clinical syndrome, and raised plasma levels of norepinephrine are markers of severity and adverse prognosis.[1]

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Heart rate variability (HRV) is widely used for quantifying neural cardiac control,[2] and low variability is particularly predictive of death in patients after myocardial infarction.[3] Reduced 24-hour time- and frequency-domain measures of HRV identify CHF patients at increased risk of death,[4–7] but no convincing evidence has been provided for its routine clinical use, perhaps because of methodological as well as technical limitations. Short-term laboratory recordings using controlled breathing avoid artifacts in the low-frequency (LF) range from physical activity and irregular slow breaths.[8–10]

The value of HRV in CHF has been tested mainly for prediction of cardiac mortality or pump dysfunction. Identification of patients at high risk for sudden death, who may benefit from an implantable cardioverter defibrillator (ICD), remains elusive.

We therefore tested the prognostic information from short-term HRV for sudden, presumably arrhythmic death in a large population of patients with moderate to severe CHF, comparing this in a multivariate model that included many clinical and functional risk predictors. We anticipated that the value of short-term HRV would be strengthened during controlled as opposed to spontaneous breathing. On the basis of data

collected between 1991 and 1995 (derivation sample), we derived a multivariate predictive model, which was then validated in patients seen between 1996 and 2001 (validation sample), when treatment changes might have altered the variables used for risk prediction.[11]

Methods

The derivation sample data were from 202 consecutive patients in sinus rhythm with dilated cardiomyopathy referred between July 1991 and December 1995 for evaluation and therapy of CHF, including heart transplantation. The validation sample data were from 242 consecutive patients referred between January 1996 and July 2001. We excluded patients with pulmonary or neurological disease, recent myocardial infarction or cardiac surgery (within the previous 6 months), recently changed therapy (last 2 weeks), or any other disease that limits survival.

These patients were from a larger database of 904 patients; 26% were excluded because of atrial fibrillation or pacemaker implantation. From the remaining 669 patients in sinus rhythm, a further 138 were excluded, mainly because they were clinically unstable. Of 531 patients who underwent autonomic testing, 87 were not included because of poor-quality recordings (short duration of controlled breathing, high number of ectopic beats, or large artifacts). Thus, 444 patients represented the population under study.

All patients gave informed consent. The local ethics committee approved the study.

HRV Study and Analysis

Studies were performed in the morning after 30 minutes of supine rest. ECG and lung volume (inductance plethysmography) recordings were obtained, first during 8 minutes of spontaneous respiration and then during 8 minutes of controlled breathing at 12 to 15 breaths/min. R-R time series were derived from the ECG with a resolution of 1 ms. A selection was then made of a 5-minute section free from artifacts or marked sudden changes in respiration or R-R interval for each recording condition.[12] Linear detrending was then applied.[12]

Time-domain analysis included measurement of the mean R-R interval and its standard deviation. Spectral analysis was performed by the autoregressive approach (Burg algorithm) with spectral decomposition and was verified with the classic Blackman-Tukey method.[13] The power in the LF band (0.04 to 0.15 Hz) and high-frequency (HF) band (0.15 to 0.45 Hz)[2] was computed by summing all spectral components with their central frequency within each band but excluding components with <10% of the overall power in the band.

Study Variables and Follow-Up Data

Within 1 week of the HRV study, all patients underwent 2D echocardiography, cardiopulmonary exercise testing, 24-hour Holter recording, and routine blood tests. In a subset of 131 patients (from the derivation sample), blood samples were collected for plasma noradrenaline assay.[14]

During follow-up, patients were periodically reevaluated and hospitalized if clinically unstable. The date and mode of death were accurately investigated. Time-to-event information and demographic, clinical, functional, and HRV parameters recorded at baseline were entered in a dedicated database.

The end point of survival analysis was sudden (presumably arrhythmic) death, defined as death occurring within 1 hour of onset of symptoms in a previously medically stable patient, death during sleep, unwitnessed death occurring within 1 hour of the patient last being seen alive, or appropriate and documented ICD discharge for fast ventricular tachycardia or ventricular fibrillation.

Statistical Analysis

To derive a prognostic model from the derivation sample, continuous variables characterized by higher risk at lower values (eg, peak $\dot{V}O_2$) were dichotomized according to a cutoff between the 20th and 50th

percentiles, whereas those characterized by higher risk at higher values (eg, the number of ventricular premature contractions) were dichotomized according to a cutoff point selected between the 50th and 80th percentiles. The optimal cutoff point was identified by the highest χ^2 value in the Cox regression model.

Significant univariate predictors in the same compartment of variables (eg, echocardiographic, HRV) were analyzed jointly in a multivariate Cox model to identify the subset containing independent prognostic information. All selected variables were then used as candidates for the final survival model. Kaplan-Meier survival curves were compared with the log-rank test.

To validate the model, the prognostic equation obtained from the derivation sample was applied to patients of the validation sample, after having categorized the prognostic variables according to the derivation cutoff points. Survival curves were then estimated for these validation patients.

Finally, "optimized" cutoff points were computed in the validation sample de novo to derive a corresponding multivariate Cox regression model as in the derivation sample. This identified the prognostic model best suited for the cohort of subjects followed up during the most recent years (1996 to 2001) of the overall study period (1991 to 2001). We expected that improvements in their general treatment (particularly greater use of ACE inhibition and β-blockade) might affect the prognostic model of sudden death.

Because of skewness in the distribution of some variables, descriptive statistics are given as median (interquartile range). Comparisons between groups were performed by the Mann-Whitney U test or χ^2 test. A probability value <0.05 was considered significant.

Results

The baseline characteristics of the derivation and validation samples are separately reported in Table 1. Patients in the validation sample were significantly less sick than patients in the derivation sample. In Table 1, therapy is reported as optimized therapy at entry to follow-up. As anticipated, use of β-blockers was higher in the validation sample. During follow-up, use of β-blockers in this group increased to 48%; therefore, β-blocker treatment at entry and during follow-up was tested in survival analysis.

Mortality Data and Survival Analysis

After 3 years' follow-up, total mortality was 37% in the derivation sample and 22% in the validation sample. Sudden death occurred in 19 patients (9.4%) in the derivation sample and 20 (8%) in the validation sample.

Sudden Death Predictors in the Derivation Sample

All variables are listed in Table 1; Table 2 shows univariate predictors of sudden death in the derivation sample. In the final multivariate model, only LF power during controlled breathing and left ventricular end-diastolic diameter emerged as independent predictors of sudden death (Table 3).

Figure 1 shows the survival curves in the derivation sample dichotomized by reduced or preserved LF power during controlled breathing. The 3-year rate of sudden death was 23% for patients with markedly reduced LF power and declined to 7% in those with better-preserved LF power. Plasma noradrenaline levels measured in a subset of 131 patients were significantly higher in those with reduced LF power (425 ± 224 versus 334 ± 182 pg/mL, $P=0.036$).

Sudden Death Predictors in the Validation Sample

When the model equation obtained from the derivation sample was fitted to the validation sample, it was still found

TABLE 1. Baseline Clinical and Test Characteristics in the Derivation and Validation Samples

Variables	Derivation Sample (n=202)	Validation Sample (n=242)	P
Clinical			
Age, y	54 (13)	54 (12)	0.64
Male, %	87	83	0.31
NYHA class II to III, %	88	88	0.32
Cause, %			
Ischemic	49	46	0.31
Idiopathic	45	45	
Valvular	4	4	
Other	2	5	
Echocardiographic			
LVEF, %	23 (8)	27 (11)	<0.0001
LVESD, mm	62 (14)	59 (16)	0.007
LVEDD, mm	72 (12)	69 (13)	0.02
Deceleration time, ms	115 (55)	135 (65)	0.011
Mitral regurgitation grade 3 to 4, %	36	34	0.22
Cardiopulmonary exercise testing			
Peak $\dot{V}O_2$, mL·kg^{-1}·min^{-1}	14 (6)	15 (6)	0.11
Holter			
VPCs/h, n	15 (48)	15 (63)	0.96
NSVT, %	38	39	0.85
QRS duration ≥120 ms, %	45	40	0.23
Blood chemistry			
BUN, mg/dL	49 (23)	46 (17)	0.01
Creatinine, mg/dL	1.19 (0.32)	1.05 (0.30)	<0.0001
Sodium, mEq/L	139 (5)	140 (4)	<0.0001
Potassium, mEq/L	4.3 (0.4)	4.4 (0.5)	0.11
Bilirubin, mg/dL	1.0 (0.48)	0.7 (0.5)	<0.0001
HRV			
Baseline RR interval, ms	823 (211)	834 (218)	0.05
Baseline SD, ms	21 (17)	21 (19)	0.94
Baseline LF power, ms^2	30 (101)	45 (96)	0.01
Baseline HF power, ms^2	32 (65)	40 (82)	0.06
LF/HF	1.08 (1.56)	1.41 (2.03)	0.02
Controlled-breathing R-R interval, ms	833 (206)	839 (271)	0.02
Controlled-breathing SD, ms	18 (15)	17 (14)	0.63
Controlled-breathing LF power, ms^2	28 (92)	41 (90)	0.04
Controlled-breathing HF power, ms^2	43 (108)	55 (112)	0.41
Therapy, %			
ACE inhibitors/AT$_1$ receptor antagonist	90	99	<0.001
Diuretics	96	85	<0.001
Nitrates	56	45	0.02
Digoxin	78	56	<0.001
β-Blockers	6	31	<0.001
Amiodarone	29	22	0.09

NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; VPCs/h, ventricular premature contractions/hour; NSVT, nonsustained ventricular tachycardia; and BUN, blood urea nitrogen.

Values are median (interquartile range [75th percentile−25th percentile]).

TABLE 2. Significant Univariate Association of Risk Variables With Arrhythmic Mortality in the Derivation Sample

| Variables (Cutoff Value)	χ^2	P	RR (95% CI)
Echocardiographic			
LVEF (≤21%)	4.2	0.04	2.6 (1.1–6.5)
LVEDD (≥77 mm)	5.1	0.02	2.8 (1.1–6.9)
Holter monitoring			
VPCs (≥86/h)	3.7	0.05	2.3 (1.0–5.3)
Blood chemistry			
BUN (≥57 mg/dL)	4.7	0.03	2.6 (1.1–6.9)
Bilirubin (≥1.03 mg/dL)	4.2	0.05	2.7 (1.0–7.2)
HRV			
Baseline SD (≤21 ms)	7.3	0.007	4.6 (1.5–13.9)
Baseline LF power (≤11 ms^2)	5.9	0.01	3.1 (1.2–7.6)
Baseline LF/HF (≤0.37)	7.5	0.006	3.6 (1.4–9.0)
Controlled-breathing LF power (≤13 ms^2)	8.1	0.004	3.8 (1.5–9.4)

Abbreviations as in Table 1.

to provide a significant prediction ($P=0.037$). However, only reduced LF power during controlled breathing predicted sudden death (relative risk [RR] 2.8, 95% CI 1.2 to 6.8, $P=0.02$; Figure 2), whereas an increased left ventricular end-diastolic diameter did not (RR 1.7, 95% CI 0.7 to 4.5, $P=0.3$). We analyzed the effect of improved medical therapy on the autonomic measures. Although LF power showed a marginally significant increase ($P=0.045$), there was a large overlap between the 2 groups (25th and 75th percentiles, 7 and 99 versus 13 and 103 ms^2 in the derivation and validation samples, respectively).

Tables 4 and 5 show the univariate and multivariate predictors when survival analysis was run de novo in the validation sample. Ventricular premature contractions per hour and β-blocker use during follow-up emerged as significant univariate predictors of sudden death; the use of β-blockers was associated with a 64% reduction in the risk of sudden death. However, in multivariate analysis, only ventricular premature contractions per hour and LF power during controlled respiration remained as independent predictors. Survival curves for patients identified on the basis of LF power and ventricular premature contractions per hour are shown in Figure 3. The combination of preserved LF power and fewer ventricular premature contractions per hour defined a large subset of patients (62% of the entire population) with a low 3-year sudden death rate of 3%, which was significantly lower than that in the remaining patients (23%). The positive predictive value was 18% and the negative predictive value 97%, with a sensitivity and specificity of 80% and 67%, respectively.

TABLE 3. Multivariate Prognostic Model for Sudden Death in the Derivation Sample

Variables (Cutoff Value)	χ^2	P	RR (95% CI)
Controlled-breathing LF power (≤13 ms^2)	7.8	0.005	3.7 (1.5–9.3)
LVEDD (≥77 mm)	4.1	0.042	2.6 (1.0–6.3)

LVEDD indicates left ventricular end-diastolic diameter.
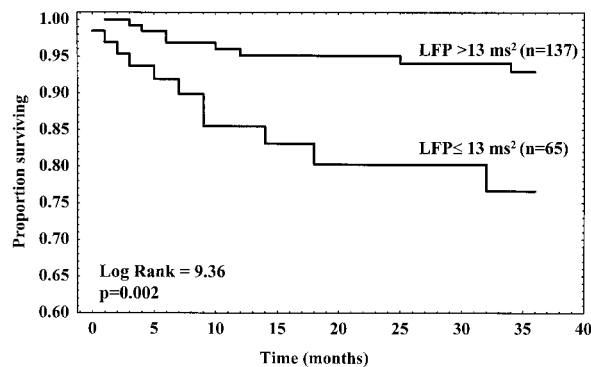
Figure 1. Kaplan-Meier survival curves for sudden cardiac death in derivation sample. Mortality was significantly higher for patients with markedly depressed LF power (LFP) during controlled breathing (LFP $\leq$13 ms^2) than for patients with preserved LFP.

Discussion

Mortality in CHF remains high despite advances in pharmacological treatment.[11] Better identification of patients who could benefit from an ICD would greatly help in their management. Several prognostic models for individual risk have been developed, both invasive and noninvasive.[15] However, specific prediction of sudden death remains a challenge.

The results of the present study add to previously known risk factors by showing that short-term analysis of HRV has independent prognostic value apart from that of clinical and functional variables, including QRS duration[16] and the use of β-blockers.[11] Predictive models often perform less well when applied to a new set of patients, but reduced short-term HRV (particularly in the LF band) remained a significant predictor in the validation study population, even though total mortality and sudden death rates were lower. Preserved LF power and a low ventricular premature contraction rate identify a large number of patients at relatively low risk who may not merit more aggressive treatment.

Prognostic Value of HRV in CHF Patients

A number of earlier studies of HRV have shown significant prognostic information in chronic CHF. The United Kingdom Heart Failure Evaluation and Assessment of Risk Trial[6] (in
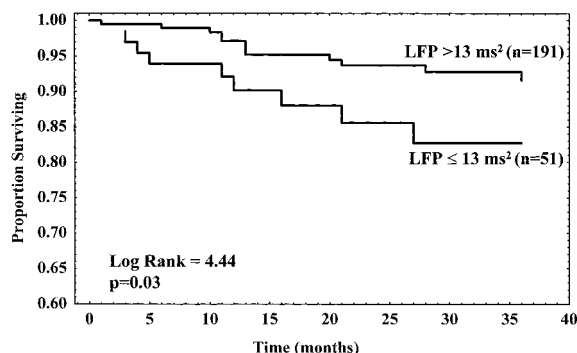
Figure 2. Kaplan-Meier survival curves for sudden cardiac death in validation sample. Although less impressive than in Figure 1, mortality was significantly higher for patients with markedly depressed LF power (LFP) during controlled breathing (LFP $\leq$13 ms^2) than for patients with preserved LFP.

TABLE 4. Significant Univariate Association of Risk Variables With Arrhythmic Mortality in the Validation Sample

Variables (Cutoff Value)	χ^2	P	RR (95% CI)
Holter monitoring			
VPCs/h ($\geq$83)	6.8	0.009	4.9 (1.5–16.0)
Blood chemistry			
Sodium ($\leq$138 mEq/L)	3.5	0.062	2.3 (1.0–5.6)
Bilirubin ($\geq$0.74 mg/dL)	3.8	0.049	2.7 (1.0–7.6)
HRV			
Baseline R-R interval ($\leq$715 ms)	3.7	0.055	2.4 (1.0–5.7)
Baseline SD ($\leq$15 ms)	5.7	0.017	2.8 (1.2–6.7)
Baseline LF/HF ($\leq$0.43)	5.6	0.019	3.0 (1.2–7.4)
Controlled-breathing LF power ($\leq$11 ms^2)	7.1	0.008	3.2 (1.4–7.7)
Controlled-breathing HF power ($\leq$27 ms^2)	5.6	0.017	2.8 (1.2–6.7)
Therapy			
β-Blockers during follow-up	5.3	0.02	0.3 (0.1–0.8)

Abbreviations as in Table 1.

433 outpatients) found that reduced SDNN (SD of the normal-to-normal R-R interval) from 24-hour Holter ECG predicted death from progressive heart failure but failed to predict sudden cardiac death.

It might be expected that increased sympathetic activity would be accompanied by a relative predominance of LF oscillations in frequency-domain analysis of HRV.[17] However, both increased[18] and reduced[5] LF power were found to be associated with an increased risk of cardiac death. Recent data from Galinier et al[7] showed that reduced daytime LF power from 24-hour Holter recording independently and significantly predicted sudden death, although very few other parameters were included in the analysis.

In the present study, reduced LF power (particularly during controlled breathing) independently predicted sudden, presumably arrhythmic death in a multivariate model testing the majority of the recognized pathological determinants of CHF in both the derivation and validation series. In CHF patients, abnormal breathing patterns may play a confounding role that is abolished by controlled respiration[9] or O$_2$ administration.[19] Moreover, even in the absence of a sustained abnormal breathing pattern, tidal volume in CHF patients is often quite irregular, thus affecting HRV assessment. Our data show that a simple bedside ECG recording of <10 minutes' duration obtained during controlled breathing provides additional important prognostic information. Importantly, the predictive value was unaffected by the significant improvement of CHF patients that resulted from optimal medical therapy.

TABLE 5. Multivariate Prognostic Model for Sudden Death in the Validation Sample

Variables (Cutoff Value)	χ^2	P	RR (95% CI)
VPCs/h ($\geq$83)	7.9	0.005	3.7 (1.5–9.0)
Controlled-breathing LF power ($\leq$11 ms^2)	5.7	0.017	3.0 (1.2–7.6)

VPCs indicates ventricular premature contractions.
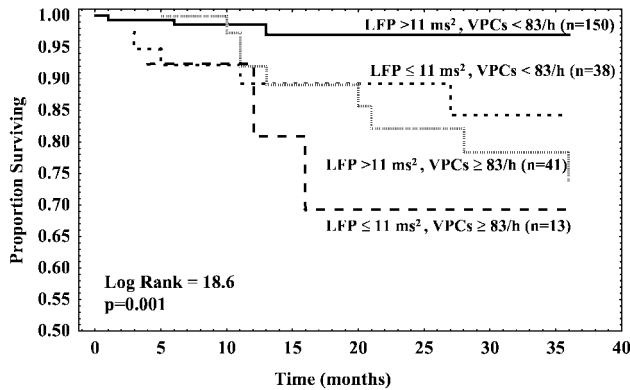
Figure 3. Kaplan-Meier survival curves for sudden cardiac death in validation sample on basis of optimized survival analysis. Mortality was 3% for patients with preserved LF power (LFP) during controlled breathing (LFP >11 ms^2) and fewer ventricular premature contractions per hour (VPCs/h <83), and it differed significantly from that of patients with other combinations of risk predictors.

Reduced LF Power as a Marker of Sympathetic Overactivity

In severe CHF, despite the clear evidence of high resting sympathetic drive provided by elevated plasma catecholamines,[1] R-R interval variability is reduced, and LF power has been found to be paradoxically reduced or abolished,[20–23] which contradicts the idea of the LF/HF ratio as an index of sympathovagal balance. Reduced LF power during extreme sympathoexcitation might be due to (1) reduced responsiveness of the sinus node,[21] (2) loss of oscillatory behavior during overwhelming chronic sympathetic overactivity,[20] (3) a central abnormality in autonomic modulation,[22,23] or (4) the effect of an impaired baroreflex.[24] However, because variability in the LF band is also vagally mediated, a role for parasympathetic withdrawal (possibly due to low baroreflex sensitivity) cannot be excluded[25]; the spectral patterns observed in advanced CHF patients are similar to those observed during progressive atropine blockade. Both vagomimetic drugs[26] and β-blockers[27] improve autonomic balance in CHF patients. In the subset of patients in whom plasma catecholamines were assessed, peripheral noradrenaline was significantly higher in the presence of markedly reduced LF power, in agreement with the finding that markedly increased sympathetic discharge in CHF is correlated with reduced LF power,[22,23] thus providing the link with an increased risk for sudden death.

Clinical Implications and Conclusions

Simple bedside autonomic markers, in conjunction with clinical and functional variables that are routinely collected in the evaluation of patients with advanced CHF, can help to identify patients at increased risk for sudden death who could benefit from more aggressive antiarrhythmic therapy. The Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II Study[28] showed a 30% reduction in the risk of death due to any cause in patients with ischemic cardiomyopathy who had been randomized to ICD implantation. In the present study population, the cause of CHF did not predict sudden death. There is a clear need to identify patients who

do not require an ICD. The presence of frequent ventricular premature contractions per hour and/or reduced LF power identified a group of patients (38% of the entire population) with a 3-year sudden death rate of 23%. Importantly, it also defined a larger population at very low risk, with a 3-year sudden death rate of 3%. We therefore suggest that short-term HRV recordings should be routine in CHF patients.

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