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

Maria Teresa La Rovere, MD; Gian Domenico Pinna, MS; Roberto Maestri, MD; Soccorso Capomolla, MD; Oreste Febo, MD; Roberto Ferrari, MD; Mariella Franchini, MD; Marco Gnemmi, MD; Cristina Opasich, MD; Pier Giorgio Riccardi, MD; Egidio Traversi, MD; Franco Cobelli, MD

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-lead 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 \( \leq 13 \text{ ms}^2 \) and left ventricular end-diastolic diameter \( \geq 77 \text{ mm} \) (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 \( \leq 11 \text{ ms}^2 \) during controlled breathing and \( \leq 83 \) 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

Chronic 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

See p 514

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

Received August 19, 2002; revision received October 28, 2002; accepted October 28, 2002.

From Divisione di Cardiologia e Bioingegneria (M.T.L.R., G.D.P., R.M., S.C., O.F., M.F., M.G., P.G.R., E.T., F.C.), Fondazione Salvatore Maugeri, IRCCS Istituto Scientifico di Montescano, Pavia, Italy; Dipartimento di Cardiologia (A.M.), Policlinico di Monza, Monza, Italy; Centro di Fisiopatologia Cardiovascolare (R.F.), Fondazione Salvatore Maugeri, IRCCS Istituto Scientifico di Gussago, Brescia, and Università di Ferrara, Italy; and Divisione di Cardiologia (C.O.), Fondazione Salvatore Maugeri, IRCCS Istituto Scientifico di Pavia, Italy.

Correspondence to Maria Teresa La Rovere, MD, Istituto Scientifico di Montescano, Fondazione Salvatore Maugeri, IRCCS, 27040 Montescano (PV), Italy. E-mail mtlarovere@fsm.it

© 2003 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000047275.25795.17
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 implan-
tation. 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) record-
nings 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 demo-
graphic, clinical, functional, and HRV parameters recorded at base-
line were entered in a dedicated database.

The end point of survival analysis was sudden (presumably
arhythmic) 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 VO2)
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 χ2 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 regres-
sion 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 χ2 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
decreased 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Derivation Sample (n=202)</th>
<th>Validation Sample (n=242)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>54 (13)</td>
<td>54 (12)</td>
<td>0.64</td>
</tr>
<tr>
<td>Male, %</td>
<td>87</td>
<td>83</td>
<td>0.31</td>
</tr>
<tr>
<td>NYHA class II to III, %</td>
<td>88</td>
<td>88</td>
<td>0.32</td>
</tr>
<tr>
<td>Cause, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>49</td>
<td>46</td>
<td>0.31</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>45</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Valvular</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Echocardiographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23 (8)</td>
<td>27 (11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESSD, mm</td>
<td>62 (14)</td>
<td>59 (16)</td>
<td>0.007</td>
</tr>
<tr>
<td>LVESDD, mm</td>
<td>72 (12)</td>
<td>69 (13)</td>
<td>0.02</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>115 (55)</td>
<td>139 (65)</td>
<td>0.011</td>
</tr>
<tr>
<td>Mitral regurgitation grade 3 to 4, %</td>
<td>36</td>
<td>34</td>
<td>0.22</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VO2, mL·kg⁻¹·min⁻¹</td>
<td>14 (6)</td>
<td>15 (6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Holter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPCs/h, n</td>
<td>15 (48)</td>
<td>15 (63)</td>
<td>0.96</td>
</tr>
<tr>
<td>NSVT, %</td>
<td>38</td>
<td>39</td>
<td>0.85</td>
</tr>
<tr>
<td>QRS duration ≥120 ms, %</td>
<td>45</td>
<td>40</td>
<td>0.23</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>49 (23)</td>
<td>46 (17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.19 (0.32)</td>
<td>1.05 (0.30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>139 (5)</td>
<td>140 (4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>4.3 (0.4)</td>
<td>4.4 (0.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Bilirubin, mg/dL</td>
<td>1.0 (0.48)</td>
<td>0.7 (0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HRV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline RR interval, ms</td>
<td>823 (211)</td>
<td>834 (218)</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline SD, ms</td>
<td>21 (17)</td>
<td>21 (19)</td>
<td>0.94</td>
</tr>
<tr>
<td>Baseline LF power, ms²</td>
<td>30 (101)</td>
<td>45 (96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline HF power, ms²</td>
<td>32 (65)</td>
<td>40 (82)</td>
<td>0.06</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.08 (1.56)</td>
<td>1.41 (2.03)</td>
<td>0.02</td>
</tr>
<tr>
<td>Controlled-breathing R-R interval, ms</td>
<td>833 (206)</td>
<td>839 (271)</td>
<td>0.02</td>
</tr>
<tr>
<td>Controlled-breathing SD, ms</td>
<td>18 (15)</td>
<td>17 (14)</td>
<td>0.63</td>
</tr>
<tr>
<td>Controlled-breathing LF power, ms²</td>
<td>28 (92)</td>
<td>41 (90)</td>
<td>0.04</td>
</tr>
<tr>
<td>Controlled-breathing HF power, ms²</td>
<td>43 (108)</td>
<td>55 (112)</td>
<td>0.41</td>
</tr>
<tr>
<td>Therapy, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors/AT₁ receptor antagonist</td>
<td>90</td>
<td>99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>96</td>
<td>85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrates</td>
<td>56</td>
<td>45</td>
<td>0.02</td>
</tr>
<tr>
<td>Digoxin</td>
<td>78</td>
<td>56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>6</td>
<td>31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>29</td>
<td>22</td>
<td>0.09</td>
</tr>
</tbody>
</table>

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 ms² 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 2. Significant Univariate Association of Risk Variables With Arrhythmic Mortality in the Derivation Sample

<table>
<thead>
<tr>
<th>Variables (Cutoff Value)</th>
<th>χ²</th>
<th>P</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (≥21%)</td>
<td>4.2</td>
<td>0.04</td>
<td>2.6 (1.1–6.5)</td>
</tr>
<tr>
<td>LVESDD (≥77 mm)</td>
<td>5.1</td>
<td>0.02</td>
<td>2.8 (1.1–6.9)</td>
</tr>
<tr>
<td>Holter monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPCs (≥86/h)</td>
<td>3.7</td>
<td>0.05</td>
<td>2.3 (1.0–5.3)</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (≥57 mg/dL)</td>
<td>4.7</td>
<td>0.03</td>
<td>2.6 (1.1–6.9)</td>
</tr>
<tr>
<td>Bilirubin (≥1.03 mg/dL)</td>
<td>4.2</td>
<td>0.05</td>
<td>2.7 (1.0–7.2)</td>
</tr>
<tr>
<td>HRV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline SD (≥21 ms)</td>
<td>7.3</td>
<td>0.007</td>
<td>4.6 (1.5–13.9)</td>
</tr>
<tr>
<td>Baseline LF power (≤11 ms²)</td>
<td>5.9</td>
<td>0.01</td>
<td>3.1 (1.2–7.6)</td>
</tr>
<tr>
<td>Baseline LF/HF (≤0.37)</td>
<td>7.5</td>
<td>0.006</td>
<td>3.6 (1.4–9.0)</td>
</tr>
<tr>
<td>Controlled-breathing LF power (≤13 ms²)</td>
<td>8.1</td>
<td>0.004</td>
<td>3.8 (1.5–9.4)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

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

<table>
<thead>
<tr>
<th>Variables (Cutoff Value)</th>
<th>χ²</th>
<th>P</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled-breathing LF power (≤13 ms²)</td>
<td>7.8</td>
<td>0.005</td>
<td>3.7 (1.5–9.3)</td>
</tr>
<tr>
<td>LVESDD (≥77 mm)</td>
<td>4.1</td>
<td>0.042</td>
<td>2.6 (1.0–6.3)</td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic diameter.
functional variables, including QRS duration and the use of independent prognostic value apart from that of clinical and risk factors by showing that short-term analysis of HRV has ever, specific prediction of sudden death remains a challenge.

Discussion

Mortality in CHF remains high despite advances in pharmacological treatment. 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. 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 and the use of β-blockers. 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 (in

### 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 >13 ms²) than for patients with preserved LFP.

### 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 >13 ms²) than for patients with preserved LFP.

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. However, both increased and reduced LF power were found to be associated with an increased risk of cardiac death. Recent data from Galinier et al. 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 or O₂ administration. 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 4. Significant Univariate Association of Risk Variables With Arrhythmic Mortality in the Validation Sample

<table>
<thead>
<tr>
<th>Variables (Cutoff Value)</th>
<th>χ²</th>
<th>P</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPCs/h (≥83)</td>
<td>6.8</td>
<td>0.009</td>
<td>4.9 (1.5–16.0)</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium (≥138 mEq/L)</td>
<td>3.5</td>
<td>0.062</td>
<td>2.3 (1.0–5.6)</td>
</tr>
<tr>
<td>Bilirubin (≥0.74 mg/dL)</td>
<td>3.8</td>
<td>0.049</td>
<td>2.7 (1.0–7.6)</td>
</tr>
<tr>
<td>HRV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline R-R interval</td>
<td>3.7</td>
<td>0.055</td>
<td>2.4 (1.0–5.7)</td>
</tr>
<tr>
<td>Baseline SD (≥15 ms)</td>
<td>5.7</td>
<td>0.017</td>
<td>2.8 (1.2–6.7)</td>
</tr>
<tr>
<td>Baseline LF/HF (≤0.43)</td>
<td>5.6</td>
<td>0.019</td>
<td>3.0 (1.2–7.4)</td>
</tr>
<tr>
<td>Controlled-breathing LF power (≥11 ms²)</td>
<td>7.1</td>
<td>0.008</td>
<td>3.2 (1.4–7.7)</td>
</tr>
<tr>
<td>Controlled-breathing HF power (≥27 ms²)</td>
<td>5.6</td>
<td>0.017</td>
<td>2.8 (1.2–6.7)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers during follow-up</td>
<td>5.3</td>
<td>0.02</td>
<td>0.3 (0.1–0.8)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

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

<table>
<thead>
<tr>
<th>Variables (Cutoff Value)</th>
<th>χ²</th>
<th>P</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holter monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPCs/h (≥83)</td>
<td>7.9</td>
<td>0.005</td>
<td>3.7 (1.5–9.0)</td>
</tr>
<tr>
<td>Controlled-breathing LF power (≥11 ms²)</td>
<td>5.7</td>
<td>0.017</td>
<td>3.0 (1.2–7.6)</td>
</tr>
</tbody>
</table>

VPCs indicates ventricular premature contractions.
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, R-R interval variability is reduced, and LF power has been found to be paradoxically reduced or abolished, 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, (2) loss of oscillatory behavior during overwhelming chronic sympathetic overactivity, (3) a central abnormality in autonomic modulation, or (4) the effect of an impaired baroreflex. 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; the spectral patterns observed in advanced CHF patients are similar to those observed during progressive atropine blockade. Both vagoamimetic drugs and β-blockers 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, 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 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.

Acknowledgments

We thank Pinuccia Estini, Cristina Pastorelli, Alexander Prpa, and Fernanda Scavi for their expert technical assistance. We express our special gratitude to Prof Luigi Tavazzi for his helpful criticism, support, and motivation in the realization of our heart failure unit and its database and to Prof Peter Sleight for reviewing the final results and manuscript.

References


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

Maria Teresa La Rovere, Gian Domenico Pinna, Roberto Maestri, Andrea Mortara, Soccorso Capomolla, Oreste Febo, Roberto Ferrari, Mariella Franchini, Marco Gnemmi, Cristina Opasich, Pier Giorgio Riccardi, Egidio Traversi and Franco Cobelli

_Circulation_. 2003;107:565-570; originally published online January 13, 2003;
doi: 10.1161/01.CIR.0000047275.25795.17

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/4/565

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/