Prospective Study of Heart Rate Variability and Mortality in Chronic Heart Failure

Results of the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart)

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Background—Patients with chronic heart failure (CHF) have a continuing high mortality. Autonomic dysfunction may play an important role in the pathophysiology of cardiac death in CHF. UK-HEART examined the value of heart rate variability (HRV) measures as independent predictors of death in CHF.

Methods and Results—In a prospective study powered for mortality, we recruited 433 outpatients 62±9.6 years old with CHF (NYHA functional class I to III; mean ejection fraction, 0.41±0.17). Time-domain HRV indices and conventional prognostic indicators were related to death by multivariate analysis. During 482±161 days of follow-up, cardiothoracic ratio, SDNN, left ventricular end-systolic diameter, and serum sodium were significant predictors of all-cause mortality. The risk ratio for a 41.2-ms decrease in SDNN was 1.62 (95% CI, 1.16 to 2.44). The annual mortality rate for the study population in SDNN subgroups was 5.5% for >100 ms, 12.7% for 50 to 100 ms, and 51.4% for <50 ms. SDNN, creatinine, and serum sodium were related to progressive heart failure death. Cardiothoracic ratio, left ventricular end-diastolic diameter, the presence of nonsustained ventricular tachycardia, and serum potassium were related to sudden cardiac death. A reduction in SDNN was the most powerful predictor of the risk of death due to progressive heart failure.

Conclusions—CHF is associated with autonomic dysfunction, which can be quantified by measuring HRV. A reduction in SDNN identifies patients at high risk of death and is a better predictor of death due to progressive heart failure than other conventional clinical measurements. High-risk subgroups identified by this measurement are candidates for additional therapy after prescription of an ACE inhibitor. (Circulation. 1998;98:1510-1516.)

Key Words: heart rate ■ heart failure ■ mortality

Despite recent advances, chronic heart failure (CHF) is a difficult condition to manage in clinical practice, and mortality remains high. The development of new therapeutic modalities has the potential to reduce mortality, but their general applicability may be limited by problems with toxicity or cost. A large number of variables can be measured in CHF with the aim of identifying higher-risk patients who could be targeted for additional therapeutic interventions. Patients with symptoms and signs at rest are relatively easy to identify by bedside assessment. These patients currently have an annual mortality rate >40% even with optimal medical therapy, but they make up only a small proportion of the general heart failure population. Despite therapy including an ACE inhibitor, ambulant outpatients with CHF still have an average annual mortality rate of 10%. Among ambulant outpatients with CHF, some are at increased risk of early death, but these are difficult to identify by currently available methods of risk stratification.

Patients with CHF have autonomic dysfunction, and this may play an important role in the pathophysiology of cardiac death. Analysis of heart rate variability (HRV) is a reliable and reproducible technique for assessing autonomic activity in patients with cardiovascular disease, but its use as a means of identifying high-risk ambulant outpatients with CHF has not been investigated in an adequately sized prospective study. The primary aim of the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-HEART) was to test the hypothesis that autonomic activity, assessed by measuring HRV, provides independent information on the risk of death in ambulant outpatients with CHF that is clinically useful when added to information available from arrhythmia analysis of ambulatory ECGs.
Methods

Study Design and Organization

The protocol for the UK-HEART study was based on results obtained from previous studies of HRV in CHF and specified a prospective multicenter design with predetermined end points. Patient recruitment and data collection were carried out from clinical cardiology departments in 4 UK centers (Leeds, Nottingham, Doncaster, and Edinburgh) between December 1, 1993, and April 31, 1995. Analysis of ambulatory ECGs and measurement of HRV were carried out in an independent unit with extensive previous experience of HRV analysis (Department of Medical Physics, University of Edinburgh) that did not participate in patient recruitment and was blinded to all other data. When patient follow-up was completed, clinical and HRV data were collated in an independent statistical center and analyzed with prespecified end points and methodology.

Entry Criteria

Ambulant patients of either sex, 18 to 80 years old, with CHF were recruited. The ethical committee at each institution approved the protocol, and all patients gave informed consent. Patients were eligible for the trial if they had stable clinical signs and symptoms of CHF present for at least 3 months classified as NYHA functional class I to III in association with objective evidence of cardiac dysfunction at rest (pulmonary venous congestion, pulmonary edema, or a cardiothoracic ratio >0.55 on at least 1 chest radiograph, or a documented radionuclide or echocardiographic left ventricular ejection fraction <0.45). To avoid possible confounding effects, patients were excluded if they had a comorbid condition known to have an independent effect on autonomic activity (diabetes mellitus, chronic renal failure, a history of alcohol abuse, clinical evidence of autonomic neuropathy, or a recent myocardial infarction), documented constrictive or hypertrophic cardiomyopathy, sustained non-sinus dysrhythmias, atrioventricular conduction defects, or a comorbid noncardiac disease likely to limit survival.

Baseline Data Collection

At the time of recruitment into the study, a case record form detailing the patient’s medical history, medications, and physical examination was completed for all patients. An erect posteroanterior chest radiograph was obtained and the cardiothoracic ratio measured. A venous blood sample was taken at rest for assessment of electrolyte concentration and renal and liver function. Two-dimensional and M-mode echocardiography was performed by a standardized protocol in accordance with the American Society of Echocardiography recommendations. Left ventricular cavity dimensions at end systole and end diastole were measured, and the left ventricular ejection fraction and fractional shortening index were calculated according to standard formulas. Study patients were registered with the UK national death-casting, and Edinburgh) between December 1, 1993, and April 31, 1995. Analysis of ambulatory ECGs and measurement of HRV were carried out in an independent unit with extensive previous experience of HRV analysis (Department of Medical Physics, University of Edinburgh) that did not participate in patient recruitment and was blinded to all other data. When patient follow-up was completed, clinical and HRV data were collated in an independent statistical center and analyzed with prespecified end points and methodology.

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Baseline Data Collection

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patients had ischemic heart disease (76%) and were treated with a diuretic (97%) or ACE inhibitor (82%). Because fewer than 500 evaluable patients were available for analysis, we elected to extend the mean follow-up period to 482±161 days before any analysis was carried out to maintain the power of the study. Follow-up was completed on March 31, 1996, at which time 54 deaths had occurred, giving an annual mortality rate of 9.5% and fulfilling the requirement of the power calculation. There was only a weak relationship between SDNN and left ventricular function (Figure 1, Table 2). A similar pattern was present for sNN50 and rMSSD (r<0.15 for both variables).

Multivariate Predictors of All-Cause Mortality
The SDNN index was significantly associated with all-cause mortality in univariate analysis (SDNN was 116.6±39.3 ms in survivors and 93.4±48.1 ms in patients who died, P<0.0001). Measurements of sNN50 and rMSSD were similar in survivors and patients who died (log sNN50 was 2.93±0.6 and 2.85±0.6, respectively, P=NS; rMSSD was 22±12 and 19±8 ms, respectively, P=NS). In multivariate analysis, only 4 variables (including SDNN) were significantly associated with all-cause mortality (Table 3). When the patients were categorized into their prespecified SDNN subgroups, there was a highly significant difference in mortality associated with different levels of autonomic dysfunction (Figure 2, Table 4).

Categorizing the sNN50 and rMSSD indices into their prespecified subgroups did not improve their predictive value. When patients are categorized into SDNN tertiles, similar results are obtained, with annual mortality rates ranging from 17.9% in the lower tertile (<93 ms, n=142 patients) to 6.2% in the middle tertile (93 to 130 ms, n=143 patients) and 5.5% in the upper tertile (>130 ms, n=146 patients).

Mode of Death and Its Relation to Measured Variables
Of the 54 deaths that occurred, 18 were due to SCD (33%), 23 to progressive heart failure (43%), and 7 to other cardiovascular events (13%), and 6 were noncardiac (11%). The variables that were significant independent predictors of SCD or death due to progressive heart failure in multivariate analysis are listed in Table 5. SDNN was not associated with SCD but was the best independent predictor of death due to progressive heart failure in multivariate analysis.

Discussion
For the first time in a large, prospective, and appropriately powered study, reduced HRV has been demonstrated to be an independent predictor of death in ambulant outpatients with CHF. The results of UK-HEART provide novel insights into the pathophysiology of CHF and may help clinicians to risk-stratify outpatients with CHF using a small number of simple, widely available measurements. Risk stratification may become increasingly important as new therapeutic approaches are developed for CHF patients already treated with an ACE inhibitor.

The protocol for UK-HEART was designed to reflect current clinical practice in the management of patients with CHF. Our aim was to recruit a wide spectrum of ambulant outpatients with CHF. The results of UK-HEART provide novel insights into the pathophysiology of CHF and may help clinicians to risk-stratify outpatients with CHF using a small number of simple, widely available measurements. Risk stratification may become increasingly important as new therapeutic approaches are developed for CHF patients already treated with an ACE inhibitor.
to the relatively high ejection fraction. The baseline characteristics and annual mortality rate of our study population are otherwise very similar to both V-HeFT and SOLVD.3,19 Radionuclide angiography provides a better index of baseline left ventricular function in patients such as those enrolled in UK-HEART and would probably have produced a lower mean ejection fraction for our study group. Despite its disadvantages, most clinicians use simple echocardiography in preference to radionuclide angiography in routine day-to-day clinical practice, and this is reflected in the protocol of UK-HEART.

In keeping with previous small and primarily retrospective studies, the data from UK-HEART confirm that measurements of left ventricular cavity dimensions from M-mode echocardiograms, serum sodium, and the cardiothoracic ratio provide independent prognostic information in multivariate analysis of a large, prospective study.6,7 Patients who manifest echocardiographic or radiological cardiac enlargement or who have hyponatremia should be considered to be at increased risk of premature death. We did not test the value of measured peak oxygen consumption or catecholamine assays, because they are not routinely available to many clinicians.

Although HRV is reduced in many patients with CHF,8,9 previous studies have failed to establish a clinical role for the technique, because they contain only small numbers of highly selected atypical patients and have produced conflicting results.20–23 Our data indicate that SDNN, rMSSD, and sNN50 are decreased in patients with CHF. The mechanisms responsible for reduced HRV in CHF are complex. The sNN50 and rMSSD indices reflect the modulating effect of changes in parasympathetic activity.11,14 The reduction in these indices in UK-HEART confirms the findings of previous small studies9,10 and indicates that a reciprocal reduction in parasympathetic activity accompanies the well-described sympathetic activation that occurs in CHF. The SDNN index is modulated predominantly by low-frequency cyclical changes that have only recently been studied in detail. These low-frequency changes in part reflect thermoregulatory mechanisms, fluctuation in activity of the renin-angiotensin system, and the function of peripheral chemoreceptors.24–26 Recently, Mortara et al27 and Bernardi et al28 investigated other mechanisms responsible for low-frequency HRV, demonstrating that both respiratory pattern and physical activity are important modulators of these slow cyclical changes in heart rate and therefore, by inference, of the SDNN index. The reduction in SDNN that we have demonstrated reflects the summed influence of abnormalities in sympathetic, parasympathetic, and renin-angiotensin activity; abnormal chemoreceptor function; changes in respiratory pattern; and physical inactivity in CHF.24–28 Abnormal breathing patterns and physical inactivity are common in CHF, and concerns have been raised as to whether this will limit the prognostic utility of HRV analysis in this patient group.27,28 The data from UK-HEART confirm that HRV analysis remains useful in CHF and that it is not necessary to control for the effects of respiratory pattern.

### TABLE 3. Statistically Significant Multivariate Predictors of All-Cause Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>Wald $\chi^2$</th>
<th>$P^*$</th>
<th>Risk Ratio of Death (95% CI)*</th>
<th>SD of Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.52±0.06</td>
<td>0.57±0.06</td>
<td>11.9</td>
<td>0.0006</td>
<td>1.62 (1.23–2.14)</td>
<td>6.5%</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>116.6±39.3</td>
<td>93.4±48.1</td>
<td>8.0</td>
<td>0.005</td>
<td>1.62 (1.16–2.44)</td>
<td>41.2 ms</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>50±12</td>
<td>57±11</td>
<td>8.0</td>
<td>0.005</td>
<td>1.69 (1.18–2.44)</td>
<td>12 mm</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>140.0±2.7</td>
<td>138.0±4.3</td>
<td>6.3</td>
<td>0.012</td>
<td>1.42 (1.08–1.87)</td>
<td>3.0 mmol/L</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1. Risk ratios are calculated for an increase in CTR or LVESD or a decrease in SDNN or sodium. Values are mean±SD.

*P value based on Cox proportional hazards model. Risk ratios are calculated for a change in each variable equal to the SD of the variable around its sample mean value.

### TABLE 4. All-Cause Mortality in SDNN Subgroups

<table>
<thead>
<tr>
<th>SDNN Subgroup</th>
<th>No. of patients died/no. of patients in group</th>
<th>Annual mortality rate, %</th>
<th>Risk ratio of death (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 ms</td>
<td>11/24</td>
<td>51.4</td>
<td>9.4 (4.1–20.6)</td>
</tr>
<tr>
<td>50–100 ms</td>
<td>23/139</td>
<td>12.7</td>
<td>2.4 (1.2–4.5)</td>
</tr>
<tr>
<td>&gt;100 ms</td>
<td>20/268</td>
<td>5.5</td>
<td>[24–28]</td>
</tr>
</tbody>
</table>

Risk ratios refer to relative risk of death compared with patients with an SDNN of >100 ms.
or physical activity when measurements are used for prognostic purposes.

Our data also demonstrate that a simple and easily measured time-domain index of autonomic activity, SDNN, is a significant predictor of all-cause mortality and remains significant even after other common variables available to clinicians have been controlled for. In UK-HEART, an SDNN of >100 ms was associated with a relatively good prognosis. In contrast, an SDNN of <100 ms (37.8% of our group) is associated with a less favorable prognosis and an annual mortality rate of 16.8%. The prognostic value of SDNN measured early after acute myocardial infarction has been investigated previously; almost 74% of postinfarction patients have a SDNN of <100 ms, with an annual mortality rate of 7%. Using a value of <100 ms to categorize our patients with symptomatic CHF identifies a smaller subgroup of patients who are at appreciably higher risk of death, suggesting that measurement of SDNN may be of greater value for risk stratification of CHF patients than for postinfarction patients.

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. The results should therefore be viewed with caution, but they do provide insights into the relationships between autonomic activity and mode of death in CHF. Radiographic or echocardiographic cardiac enlargement, the presence of nonsustained ventricular tachycardia, and a reduction in serum potassium are all independently related to the occurrence of SCD. These findings confirm retrospective data from V-HeFT and GE-SICA, in which patients with complex ventricular arrhythmias had a greater degree of left ventricular impairment and an increased risk of SCD. The relationship between serum potassium and SCD may relate to facilitation of ventricular tachyarrhythmias in hypokalemic patients. Although the autonomic nervous system plays an important role in regulating myocardial electrical stability, time-domain measurements of HRV did not predict SCD in UK-HEART. The relationship between tonic autonomic activity, autonomic reflexes, arrhythmia substrates, myocardial electrical stability, and SCD in CHF has not been well defined. Although the time-domain indices that we studied are not related to SCD, a more detailed study of the autonomic environment of the heart using techniques such as spectral analysis or measurement of baroreceptor sensitivity, which do predict SCD in postinfarct patients, may be of value. It may prove difficult, however, to identify CHF patients at risk of SCD by use of techniques for detecting myocardial electrical instability, because many of these patients die of bradyarrhythmias, electromechanical dissociation, or other mechanisms unrelated to ventricular tachyarrhythmias.

In UK-HEART, a reduction in SDNN was the best independent predictor of death due to progressive heart failure. The SDNN index is modulated by multiple mechanisms, and a low SDNN in CHF reflects the presence of a major degree of physiological dysfunction. The SDNN index is not strongly related to simple measurements of left ventricular systolic function in UK-HEART. It is therefore possible to have evidence of widespread dysfunction in cardiovascular regulatory mechanisms leading to a reduction in SDNN, despite apparently well-compensated CHF. Persistent neuroendocrine dysfunction with reflex activation of the renin-angiotensin and sympathetic systems may aggravate remodeling of the ventricle, leading to progressive heart failure in patients with a low SDNN, and this may explain the relationship that we have demonstrated. The sNN50 and rMSSD

### TABLE 5. Statistically Significant Multivariate Predictors of SCD or Death Due to Progressive Heart Failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>Wald $\chi^2$</th>
<th>$P^*$</th>
<th>Risk Ratio (95% CI)</th>
<th>SD of Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.53 ± 0.06</td>
<td>0.59 ± 0.07</td>
<td>6.7</td>
<td>0.010</td>
<td>1.87 (1.16–3.00)</td>
<td>6.5%</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>62 ± 10</td>
<td>70 ± 10</td>
<td>5.8</td>
<td>0.016</td>
<td>1.92 (1.13–3.27)</td>
<td>9.5</td>
</tr>
<tr>
<td>NSVT, %</td>
<td>33.7</td>
<td>70.6</td>
<td>5.4</td>
<td>0.020</td>
<td>3.71 (1.23–11.22)</td>
<td>...</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.4 ± 0.5</td>
<td>4.1 ± 0.6</td>
<td>4.3</td>
<td>0.039</td>
<td>1.64 (1.03–2.63)</td>
<td>0.49 mmol/L</td>
</tr>
<tr>
<td>Death due to progressive heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>115.5 ± 40.1</td>
<td>74.0 ± 39.1</td>
<td>12.1</td>
<td>0.0005</td>
<td>2.54 (1.50–4.30)</td>
<td>41.2</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>116.7 ± 35.9</td>
<td>158.7 ± 72.6</td>
<td>9.7</td>
<td>0.002</td>
<td>1.50 (1.16–1.93)</td>
<td>40.0</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>139.9 ± 2.8</td>
<td>137.1 ± 5.2</td>
<td>7.3</td>
<td>0.007</td>
<td>1.59 (1.13–2.22)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percentage of population positive for specified variable as indicated. Risk ratios are calculated for an increase in cardiothoracic ratio, left ventricular end-diastolic dimension (LVEDD), or creatinine, a decrease in potassium or sodium, or for nonsustained ventricular tachycardia (NSVT) present versus nonsustained ventricular tachycardia absent.

*P value based on Cox proportional hazards model. Risk ratios are calculated for a change in each variable equal to the SD of the variable around its sample mean value.
indices measure activity in only 1 component of the interlinked regulatory systems that are deranged in CHF, and this may explain their inability to predict SCD or progressive heart failure.

Our data in relation to mode of death suggest that 24-hour ambulatory ECG may be useful in guiding the prescription of additional therapy for patients with symptomatic CHF who are already established on a diuretic and ACE inhibitor. The occurrence of unsuspected supraventricular tachyarrhythmias or conduction defects is associated with an adverse prognosis, and these patients may benefit from antithrombotic therapy or pacemaker implantation. Patients with nonsustained ventricular tachycardia are at increased risk of sudden death, and their treatment should be reviewed to optimize cardiac performance and eliminate hypokalemia. Angiotensin II receptor antagonists, amiodarone, and implantable defibrillators all have promise for the prevention of SCD in CHF, and the treatment should be reviewed to optimize cardiac performance and eliminate hypokalemia. Angiotensin II receptor antagonists, amiodarone, and implantable defibrillators all have promise for the prevention of SCD in CHF.

In conclusion, the results of UK-HEART demonstrate that 24-hour ambulatory ECG with measurement of SDNN and arrhythmias provides important prognostic information when combined with a small number of other simple measurements in symptomatic CHF. An SDNN of <100 ms, particularly when associated with renal impairment or hyponatremia, identifies patients at increased risk of death due to progressive heart failure. The presence of nonsustained ventricular tachycardia, particularly when it is associated with radiological or echocardiographic cardiac enlargement or hypokalemia, identifies patients at risk of SCD. Prospective studies are necessary to determine whether these simple measurements can be used to guide cost-effective use of therapeutic interventions designed to prevent progression of heart failure and premature death.

Acknowledgments

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References

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