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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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.[1,2] 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.[3–6] 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.[3,4] Despite therapy including an ACE inhibitor, ambulant outpatients with CHF still have an average annual mortality rate of 10%.[7] 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.[3,7]

Patients with CHF have autonomic dysfunction,[8–10] 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,[11,12] 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,

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chest radiographs, simple echocardiograms, and routinely available biochemical measurements.

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.[8,9] 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.[8,9,12,13] 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[14] 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 concomitant 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 nonsinus 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 baseline clinical and demographic data 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-reporting scheme (Office of Population Censuses and Surveys), who notified the steering committee of all deaths. All events reported to the steering committee were evaluated by at least 2 senior physicians. Death certificates, autopsy findings, and hospital and general practitioners' records were reviewed, and each event was categorized on the basis of definitions used in previous studies of mortality in CHF.[6,15] The mode of death was classified as (1) sudden cardiac death (SCD) if it occurred within 1 hour of a change in symptoms or if it occurred during sleep or while unobserved, if circumstantial evidence pointed to death from cardiovascular causes in the absence of clinical or postmortem evidence of acute myocardial infarction or increasing heart failure; (2) progressive heart failure if death occurred after a documented period of symptomatic or hemodynamic deterioration; (3) other cardiovascular death if it did not occur suddenly and was not associated with progressive heart failure; or (4) noncardiovascular death.

Ambulatory ECGs: Arrhythmia and HRV Analysis

Twenty-four-hour ambulatory ECGs were obtained in all subjects during normal, unrestricted out-of-hospital activity with a miniature tape recorder (Tracker, Reynolds Medical Ltd) with a crystal-generated time reference track that allows correction for recording and replay speed errors to within 0.5% (a feature essential for accurate measurement of HRV). Twenty-four-hour ambulatory ECGs were replayed through a Pathfinder arrhythmia analyzer (Reynolds Medical Ltd) to document the presence of ventricular arrhythmias (>10 ventricular ectopic beats per hour, or the occurrence of couplets or runs of nonsustained ventricular tachycardia, defined as 3 or more consecutive ventricular ectopic beats at a rate >120 bpm), which may be associated with an adverse outcome in CHF,[3,4,6] and to facilitate accurate HRV measurement. Ambulatory ECGs <16 hours in duration or with $<90\%$ of the recording suitable for analysis were excluded to avoid confounding effects due to circadian variations in HRV. After initial arrhythmia analysis and editing, the remaining normal-to-normal RR intervals in suitable recordings were measured, and time-domain analysis of HRV was carried out according to published guidelines.[16] For the purposes of this study, 3 different HRV indices were measured: (1) the SD of all normal-to-normal RR intervals in the entire 24-hour recording (SDNN), an index of the total amount of HRV present in the 24-hour recording period, which is modulated by multiple factors; (2) the number of increases in successive normal-to-normal RR intervals >50 ms in the 24-hour recording (sNN50), an index of parasympathetic activity; and (3) the square root of the mean of the squares of the differences between adjacent normal-to-normal RR intervals in the 24-hour recording (rMSSD), a complementary index of parasympathetic activity.

Sample Size and Statistical Analysis

We have previously found a log SD of 0.6 for between-subject sNN50 in ambulant outpatients with CHF.[12,13] Assuming that patients with mild to moderate CHF have an annual mortality of 10%,[7] a 90% power to detect a 2-fold difference in HRV in survivors compared with nonsurvivors at the 5% level of significance would occur with recruitment of 500 patients followed up for 12 months. Descriptive group data are presented as mean$\pm$SD unless otherwise stated. The Cox proportional hazards regression model was used to determine which measurements were significantly related to mortality during the follow-up period, with the multivariate model used to adjust for the effect of covariates. For the HRV measurements, prespecified values were used to investigate the effect of categorizing variables. Previous studies have demonstrated a relationship between HRV measured early after acute myocardial infarction and outcome[17,18] using values of (1) SDNN of >100 ms, 50 to 100 ms, and <50 ms; (2) sNN50 of >200, 200 to 100, and <100; and (3) rMSSD of >20 ms, 10 to 20 ms, and <10 ms, and we therefore elected to investigate the utility of those dichotomy points in the CHF population. In addition, we studied the use of alternative dichotomy points by investigating mortality in patients divided into tertiles according to SDNN values. Where appropriate, Kaplan-Meier cumulative mortality curves were plotted for HRV subgroups to display trends in mortality over time, and risk ratios were calculated for categorized variables. Survival curves were compared by the log-rank test.

Results

Patient Recruitment and Follow-Up

A total of 529 patients were recruited. Five ambulatory ECGs were lost in transit to the analysis center. Of the remaining 524 patients, 28 were excluded because of technical problems that precluded analysis of the ambulatory ECGs, and 63 were excluded because of the presence of unsuspected sustained arrhythmias or conduction defects. The baseline characteristics and group mean HRV measurements of the remaining 433 eligible patients are detailed in Table 1. The majority of

TABLE 1. Patient Characteristics and Group Mean HRV Measurements

	Mean±SD
Age, y	62.0±9.6
NYHA grade	2.3±0.5
Frusemide dose, mg	71.5±68.9
LVESD, mm	50±12
LVEDD, mm	62±9
LVEF	0.41±0.17
FSI	0.19±0.10
Serum sodium, mmol/L	139.8±3.0
Cardiothoracic ratio	0.53±0.06
Heart rate, bpm	74.4±11.6
sNN50, $\log_{10}$	3.2±3.3
rMSSD, ms	21.5±12.3
SDNN, ms	113.4±41.2

LVESD indicates left ventricular end-systolic diameter; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; and FSI, fractional shortening index. Values are mean±SD.

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

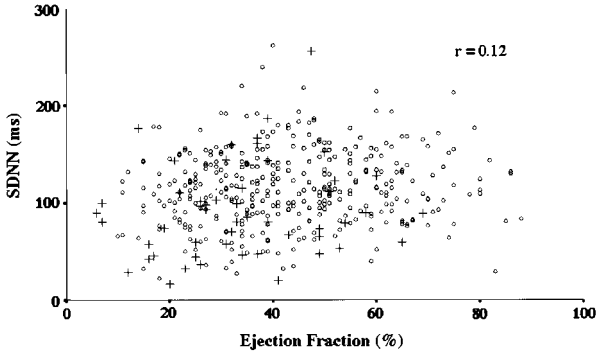

Figure 1. Relation between left ventricular function and HRV. Ejection fraction plotted against SDNN. Open circles indicate survivors; crosses, nonsurvivors.

TABLE 2. Relation Between Left Ventricular Function and HRV

Ejection Fraction	SDNN, ms
<0.34	105±38
0.34–0.5	116±46
>0.5	117±34

SDNN values for tertiles of ejection fraction (mean±SD for SDNN).

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 mild to moderate symptoms treated with optimal contemporary drug therapy and characterized according to simple, widely available clinical techniques. The mean ejection fraction of 0.41±0.17 in UK-HEART probably underestimates the degree of left ventricular impairment present in our study population, because M-mode echocardiography is unreliable in a proportion of patients with regional wall motion abnormalities. In addition, our entry criteria allowed some patients with heart failure and normal systolic function to enter the study, and this may also have contributed

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

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

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.

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 studies[9,10] 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 al[27] and Bernardi et al[28] 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

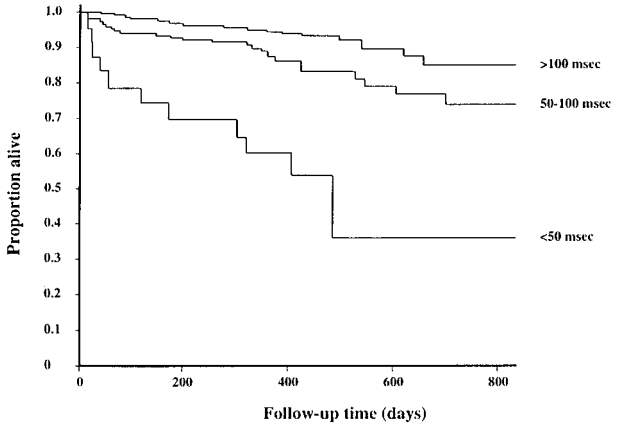

Figure 2. Kaplan-Meier survival curves in patients categorized into SDNN subgroups. $P<0.0001$ for difference in survival.

TABLE 4. All-Cause Mortality in SDNN Subgroups

	SDNN <50 ms	SDNN 50–100 ms	SDNN >100 ms
No. of patients died/no. of patients in group	11/24	23/139	20/268
Annual mortality rate, %	51.4	12.7	5.5
Risk ratio of death (95% CI)	9.4 (4.1–20.6)	2.4 (1.2–4.5)	...

Risk ratios refer to relative risk of death compared with patients with an SDNN of >100 ms.

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

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

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.

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 an SDNN of <100 ms, with an annual mortality rate of 7%.[17] 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 GESICA, in which patients with complex ventricular arrhythmias had a greater degree of left ventricular impairment and an increased risk of SCD.[3,29] 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,[30,31] 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.[32]

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

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,[33] 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[34,35] and may be of most value in patients with nonsustained ventricular tachycardia. A number of strategies are now available to favorably influence HRV in patients with CHF. Digoxin, β-blockers, centrally acting sympathetic inhibitors, low-dose transdermal scopolamine, and exercise training increase HRV (including SDNN).[36–40] Recent data indicate that β-blockers and digoxin prevent death due to progressive heart failure, and this effect may be mediated in part by the beneficial effect that these agents have on neuroendocrine function.[41–43] Patients with an SDNN $<$100 ms are at considerable risk of death due to progressive heart failure and may have the most to gain from the prescription of additional drug therapy or the provision of an exercise training program.

We were able to obtain technically adequate ambulatory ECGs capable of providing potentially useful prognostic information in 94.7% of our study population. This diagnostic yield could be increased by repeating studies in the small number of patients with technical problems that arose during the recording period. Although our study population is selected to exclude diabetics and patients with a recent myocardial infarction, the value of reduced HRV as a marker of a poor prognosis is already established in these populations. By inference, our results can also be applied to CHF patients with these conditions. Facilities for ambulatory monitoring and technical staff trained in arrhythmia analysis are available in most cardiology departments in developed countries. Low-cost, commercially available software that will reliably measure SDNN in a tape that has undergone an initial conventional arrhythmia analysis is now available. Although more complex time- and frequency-domain measurements of HRV are available that provide more physiological information than the SDNN index, our data indicate that this simple HRV index provides potentially useful clinical information. If prospective intervention studies confirm that targeted additional therapy is beneficial in CHF, measurement of SDNN may become an essential part of routine clinical evaluation. The dichotomy limits that we chose to evaluate the effect of categorizing the HRV indices were an a priori requirement of the UK-HEART protocol. We have also provided information on mortality in SDNN tertiles to demonstrate that choosing other dichotomy points would not significantly alter our results. It is apparent from Figure 1 that a large proportion of all deaths in our study group occurred in patients with the combination of a low ejection fraction and a low SDNN. Risk stratification can be improved by using several variables in combination and choosing optimal dichotomy points for these variables,[44] and the SDNN index may be of most value when combined with the other simple prognostic measures evaluated in UK-HEART.

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.

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References

1. Sanderson J. The sword of Damocles. *Lancet*. 1996;348:2–3.
2. Cohn JN. The management of chronic heart failure. *N Engl J Med*. 1996;335:490–498.
3. Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, Smith R, Fletcher R. Ejection fraction, peak oxygen consumption, cardiothoracic ratio, ventricular arrhythmias and plasma norepinephrine as determinants of prognosis in heart failure. *Circulation*. 1993;87(suppl VI):VI-5–VI-16.
4. Johnson G, Carson P, Francis GS, Cohn JN. Influence of prerandomization (baseline) variables on mortality and on the reduction of mortality by Enalapril: Veterans Affairs Cooperative Study on Vasodilator Therapy of Heart Failure (V-HeFT II). *Circulation*. 1993;87(suppl VI):VI-32–VI-39.
5. Rector TS, Cohn JN. Prognosis in congestive heart failure. *Annu Rev Med*. 1994;45:341–350.
6. Cleland JGF, Dargie HJ, Ford I. Mortality in heart failure: clinical variables of prognostic value. *Br Heart J*. 1987;58:572–582.
7. Carson P, Johnson G, Fletcher R, Cohn J. Mild systolic dysfunction in heart failure (left ventricular ejection fraction $>$35%): baseline characteristics, prognosis and response to therapy in the Vasodilator in Heart Failure Trials (V-HeFT). *J Am Coll Cardiol*. 1996;27:642–649.
8. Nolan J. *Studies of the Parasympathetic Nervous System in Chronic Heart Failure* [MD thesis]. Leeds, UK: University of Leeds; 1996.
9. Nolan J, Flapan AD, Capewell S, MacDonald T, Neilson JMM, Ewing DJ. Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. *Br Heart J*. 1992;67:482–486.
10. Tuininga YS, van Veldhuisen DJ, Brouwer J, Haaksma J, Crijus HJGM, Man in 't Veld AJ, Lie KI. Heart rate variability in left ventricular

dysfunction and heart failure: effects and implications of drug treatment. *Br Heart J*. 1994;72:509–513.
11. Batin PD, Nolan J. Assessment of autonomic function: reflex testing or variability analysis? *J Amb Mon*. 1996; 9: 255–273.
12. Nolan J, Flapan AD, Goodefield NE, Prescott RJ, Bloomfield P, Neilson JMM, Ewing DJ. Measurement of parasympathetic activity from 24-hour ambulatory electrocardiograms and its reproducibility and sensitivity in normal subjects, patients with symptomatic myocardial ischemia, and patients with diabetes mellitus. *Am J Cardiol*. 1996;77:154–158.
13. Nolan J, Flapan AD, Reid J, Neilson JMM, Bloomfield P, Ewing DJ. Cardiac parasympathetic activity in severe uncomplicated coronary artery disease. *Br Heart J*. 1994;71:515–520.
14. The Task Force on Heart Failure at the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J*. 1995;16: 741–751.
15. Greene H, Richardson D, Barker A, Roden D, Capone R, Echt D, Friedman L, Gillespie M, Hallstrom A, Verter J, and the CAPS Investigators. Classification of deaths after myocardial infarction as arrhythmic or non-arrhythmic. *Am J Cardiol*. 1989;63:1–6.
16. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation*. 1996;93:1043–1065.
17. Kleiger RE, Miller JP, Bigger JT Jr, Moss MJ, and the Multicentre Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987;59:256–262.
18. Zuanetti G, Neilson JMM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post–myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Circulation*. 1996;94:432–436.
19. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293–302.
20. Szabo BM, van Veldhuisen DJ, van der Veer N, Brouwer J, De Graeff PA, Crijus HJ Prognostic value of heart rate variability in chronic congestive heart failure secondary to idiopathic or ischaemic dilated cardiomyopathy. *Am J Cardiol*. 1997;79:978–980.
21. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, Haaksman J, Dijk A, Visser KR, Buosma F, Dunselman PH, Lie KI. Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. *J Am Coll Cardiol*. 1996;28:1183–1189.
22. Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, Webb-Peploe K, Harrington D, Banasiak W, Wrabeck K, Coats AJ. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1997;79:1645–1650.
23. Binder T, Freys B, Porenta G, Heinz G, Wutte M, Kreiner G, Gossinger H, Schmidinger H, Pacher R, Weber H. Prognostic value of heart rate variability in patients awaiting cardiac transplantation. *Pacing Clin Electrophysiol*. 1992;15:2215–2220.
24. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation*. 1991;84: 482–492.
25. Parati G, Saul JP, Di Rieuzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation: a critical appraisal. *Hypertension*. 1995;25:1276–1286.
26. Ponikowski P, Chua TP, Amadi AA, Piepoli M, Harrington D, Volterani M, Colombo R, Mazzuero G, Giordani A, Coats AJS. Detection and significance of a discrete very low frequency rhythm in RR interval variability in chronic congestive heart failure. *Am J Cardiol*. 1996;77: 1320–1326.
27. Mortara A, Sleight P, Pinna GD, Maestri R, Prpa A, La Rouvere MT, Cobelli F, Tavazzi L. Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. *Circulation*. 1997;96:246–252.
28. Bernadi L, Valle F, Coco M, Calciati A, Sleight P. Physical activity influences heart rate variability and very-low-frequency components in Holter electrocardiograms. *Cardiovasc Res*. 1996;32:234–237.
29. Doval HC, Nul DR, Grancelli HO, Varini SD, Soifer S, Corrado G, Dubner S, Scapin O, Perrone SV. Non-sustained ventricular tachycardia in severe heart failure: independent marker of increased mortality due to sudden death. *Circulation*. 1996;94:3198–3203.
30. Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation*. 1992;85:163–171.
31. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet*. 1998;351:478–484.
32. Luu M, Stevenson W, Stevenson L, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation*. 1989;80:1675–1680.
33. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. *Circulation*. 1991;84: 40–48.
34. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Shaveley DB, Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet*. 1997;349:747–752.
35. Moss AJ, Hall WJ, Cannon DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M, for the Multicentre Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med*. 1996;335:1933–1940.
36. Pousset F, Copie X, Lechat P, Jaillon P, Boissel JP, Hetzel M, Fillette F, Remme W, Guize L, Le Heuzey JY. Effects of bisoprolol on heart rate variability in heart failure. *Am J Cardiol*. 1996;77:612–617.
37. La Rovere MT, Mortara A, Pantaleo P, Maestri R, Cobelli F, Tavazzi L. Scopolamine improves autonomic balance in advanced congestive heart failure. *Circulation*. 1994;90:838–843.
38. Adamopoulos S, Ponikowski P, Cerquetani E, Piepoli M, Rosano G, Sleight P, Coats A. Circadian pattern of heart rate variability in chronic heart failure patients: effects of physical training. *Eur Heart J*. 1995;16: 1380–1386.
39. You-huaz Z, You-cheng S, Zuu Z, Xian-qi Y. Sympathetic inhibition with clonidine improves autonomic balance in congestive heart failure. *Int J Cardiol*. 1997;59:139–144.
40. Slatton ML, Irani WN, Hall SA, Marcoux LG, Page RL, Grayburn PA, Eichhorn EJ. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? *J Am Coll Cardiol*. 1997;29: 1206–1213.
41. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH, for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349–1355.
42. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet*. 1997;349: 375–380.
43. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336: 525–533.
44. Redwood SK, Odemuyiwa O, Hnatkova K, Staunton A, Poloniecki J, Camm AJ, Malik M. Selection of dichotomy limits for multifactorial prediction of arrhythmic events and mortality in survivors of acute myocardial infarction. *Eur Heart J*. 1997;18:1278–1287.