LETTERS TO THE EDITOR

Scope
Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation
Letters should be:
• not more than 600 words and six references in length
• typed in double spacing (fax copies and paper copies only)
• signed by all authors
They may contain short tables or a small figure. Please send a copy of your letter on disk. Full instructions to authors appear in the January 1999 issue of Heart (page 104).

Heart rate variability and cardiac failure

EDITOR,—We read the recent important editorial by Lombardi and Mortara with interest, and we would like to comment on several points raised.

As the authors state, spectral analysis of short term recordings of heart rate variability (HRV) is of limited value in patients with cardiac failure. Long term recordings in patients with cardiac failure contain a large amount of noise, artefact, ectopic activity, and non-stationary heart rate fluctuations, and spectral measurements are unreliable under these circumstances. We believe that studies of HRV in patients with cardiac failure are most reliable when confined to time domain techniques, which are highly reproducible in patients with cardiac disease.

We believe that most early studies of HRV and risk stratification were small, retrospective, inadequately sized, and most of the patients enrolled had very severe cardiac failure. These patients can be risk stratified by a physician using simple bedside clinical assessment and a stethoscope. The incremental prognostic value provided by additional investigations, such as analysis of HRV, is very limited in patients whose mortality rate may exceed 50% per annum.

The only adequately sized prospective study to evaluate time domain measures of HRV in cardiac failure is the United Kingdom heart failure evaluation and assessment (UK-HEART). Lombardi and Mortara question the general applicability of HRV and risk stratification in patients with cardiac failure, whereas interest in the prognostic value of HRV in CHF has increased as patients with myocardial infarction. For the first time, a large prospective study, UK-HEART, demonstrated that a reduction in standard deviation of normal RR interval (SDNN) was an independent predictor of death in outpatients with CHF. Moreover, SDNN was a better predictor of death due to progressive heart failure than other conventional clinical measurements. Lombardi and Mortara pointed out that most of the studies demonstrating the prognostic value of HRV in CHF used a cut off value of about 100 ms for risk stratification, leading to a poor discrimination of "at risk" patients as a large number of patients with CHF had an SDNN below 100 ms.

The interest of measuring HRV in CHF could therefore be in its negative predictive value, determining patients at low risk of cardiac events. As the therapeutic implications of decreased HRV remain speculative, one may not consider that a high positive predictive value is of more interest than a high negative predictive value. In UK-HEART it was confirmed that patients with "very preserved" HRV (SDNN > 100 ms) had a low annual mortality rate, whereas the few patients with "very decreased" HRV (SDNN < 50 ms) had a high risk of death.

A possible confounding parameter when measuring HRV in patients with CHF is age. HRV decreases with increasing age, whereas the incidence of CHF increases as patients get older. However, there are no data about the prognostic value of HRV in CHF according to age. In a previous study, we found that analysis of HRV allows better identification of patients with IDC at high risk of cardiac death or heart transplantation.

We present our experience of the role of age in the prognostic value of HRV in CHF patients. Time domain analysis of HRV on 24


Table 1 Relative risk of cardiac death according to age for a decrease in SDNN

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>SDNN Survivors (ms)</th>
<th>SDNN Non-survivors (ms)</th>
<th>p Value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50</td>
<td>110.5 (48.0)</td>
<td>75.9 (57.5)</td>
<td>0.009</td>
<td>1.036 (1.002-1.072)</td>
</tr>
<tr>
<td>Age &gt; 50</td>
<td>98.0 (32.5)</td>
<td>79.6 (26.0)</td>
<td>0.02</td>
<td>1.027 (1.003-1.053)</td>
</tr>
</tbody>
</table>

p value based on proportional hazards model.

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nearly have produced a lower mean ejection fraction.

Apart from ejection fraction, the baseline characteristics and mortality rate of our study population are very similar to V-HEFT (vasodilator in heart failure trials) and SOLVD (studies of left ventricular failure). Lombardi and Mortara question the general applicability of HRV (HRV) and chronic heart failure (CHF). We would like to add some comments in light of the recent publication of the UK heart failure evaluation and assessment of risk trial (UK-HEART), and in view of our experience of patients with idiopathic dilated cardiomyopathy (IDC).

The usefulness of HRV for risk stratification of cardiac events in CHF has indeed been debated for several years and it has largely accepted in patients after myocardial infarction. For the first time, a large prospective study, UK-HEART, demonstrated that a reduction in standard deviation of normal RR interval (SDNN) was an independent predictor of death in outpatients with CHF. Moreover, SDNN was a better predictor of death due to progressive heart failure than other conventional clinical measurements. Lombardi and Mortara pointed out that most of the studies demonstrating the prognostic value of HRV in CHF used a cut off value of about 100 ms for risk stratification, leading to a poor discrimination of "at risk" patients as a large number of patients with CHF had an SDNN below 100 ms.

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hour ECG recording was assessed in 122 patients with IDC (WHO criteria; mean age 50 years; range 18–72; 94 men; mean (SD) left ventricular ejection fraction 34 (12)%). Patients had conventional treatment with angiotensin converting enzyme (ACE) inhibitors, diuretics, and digoxin. With a mean (SD) follow up of 54 (39) months, 18 patients died from cardiac causes. Using multivariate analysis (proportional hazard model) only reduced SDNN* (p = 0.003), increased mean pulmonary artery pressure (p = 0.04), and ventricular tachycardia during 24 hour ECG recording (p = 0.04) predicted cardiac death. Relative risk for cardiac death was calculated for a decrease in SDNN in two groups of patients aged < 50 (n = 47) or > 50 (n = 75) (table 1). For a decrease in SDNN of 1 ms, relative risk was one third higher in patients aged < 50 compared to patients aged > 50.

The fact that a decrease in HRV is a more powerful predictor of risk in young patients is of particular interest, as these patients probably have the most to gain from additional drug treatment, an exercise programme, or both, or for whom heart transplantation could be considered. The usefulness of HRV for such implication remains to be evaluated in large studies.

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These letters were shown to the authors, who reply as follows:

We read with interest the letter by Nolan and Fox on behalf of the UK-HEART study group concerning our recent editorial.1 Whereas there is a general agreement on the interpretation of previous studies and on the limits of spectral analysis of short term recordings, these authors suggest that the results of UK-HEART2 were not adequately interpreted.

The reason for such apparent discrepancy may be the fact that the results of UK-HEART were published in full only in October 1998 and therefore well after the acceptance of our editorial. Nevertheless, we were aware of the importance of this prospective study and quoted and discussed the results that had been published in abstract form. The complete results of UK-HEART indicate that a reduced SDNN identifies a group of ambulant outpatients with mild–moderate heart failure with an unfavourable prognosis because of the progression of the disease. However, it is noteworthy that these data, as reported in our editorial, may be not applicable to patients with a more severe impairment of ventricular function. The possibility, suggested by Nolan and Fox, of an overestimation of the value of ejection fraction by the methods used in their study does not facilitate an appropriate appraisal of the severity of the disease. Indeed, according to the figure recently published on Circulation,4 nearly 25% of the patients enrolled in UK-HEART had a left ventricular ejection fraction > 50%.

An additional point that deserves further investigation is why a reduced SDNN is unable to identify cardiac failure patients who are victims of sudden cardiac death. Moreover, the finding that a cut off value of 100 ms was effective in stratifying mortality risk of these patients is likely to reflect, in our opinion, the design of the study, which was based on ambulant outpatients rather than those restricted to hospital. This cut off is higher than the value reported to stratify patients with a recent myocardial infarction in the post-thrombolysis era and suggests a possible significant influence of non-neutral factors in the determination of HRV parameters in chronic heart failure.

Fauchier et al provide interesting comments on the possible clinical utility of a high negative predictive value of preserved HRV (SDNN > 100 ms) to identify a subgroup cardiac failure patients at low risk.1 Unfortunately, good clinical indicators of favourable outcome have been extensively reported in the literature, while the identification of high risk patients remains the most challenging and important objective. As to the adjunctive role of aging in determining a reduction in HRV parameters, we are in agreement with Fauchier et al’s observation that age has to be considered when determining the prognostic role of HRV. The results described in the letter (table 1) suggest that reduced HRV may be a more powerful predictor of cardiac death in younger rather than in older patients; however, a significant difference between the two relative risks is, at the moment, not proved and needs to be confirmed in larger studies. Nevertheless, the correlation between reduction in HRV and increased cardiac mortality described by Fauchier et al leaves unsolved the question of why a depressed HRV is unable to identify cardiac failure patients at risk for sudden cardiac death.