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 copy 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,¹ 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.² 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.³

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 of risk trial (UK-HEART).⁴ Lombardi and Mortara question the general applicability of these results, based on the mean ejection fraction of the patients. Our patients were required to have symptoms plus a low ejection fraction or abnormal chest x ray. We did not exclude patients with heart failure and preserved systolic function, and this may have contributed to the relatively high mean ejection fraction. After entry into the study, ejection fraction was calculated from simple M mode echocardiography. This may underestimate the degree of left ventricular impairment in our study population as M mode echocardiography is unreliable in patients with regional wall motion abnormalities (76% of our patients had a previously

documented myocardial infarction). Using a more geometrically appropriate technique to assess left ventricular function would probably 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).^{5,6} Radionuclide angiography provides a better measure of left ventricular function in patients such as those enrolled in UK-HEART. In a substudy of 50 unselected patients enrolled in UK-HEART, mean (SD) radionuclide ejection fraction was 31.5 (12)%, almost identical to that in V-HEFT and SOLVD. Despite its disadvantages most clinicians use simple echocardiography in routine clinical practice, and this was reflected in the protocol for UK-HEART. We are surprised that Lombardi and Mortara did not consider these straightforward issues relating to the M mode derived mean ejection fraction in UK-HEART in their editorial.

The simple take home message from UK-HEART is that ambulant outpatients with mild-moderate cardiac failure (who are difficult to risk stratify using conventional techniques) and an SDNN of < 100 ms (37.8% of our patients) have an unfavourable prognosis (annual mortality rate 16.8%). Patients with an SDNN of > 100 ms have a good prognosis (annual mortality rate 5.5%). In multivariate analysis, SDNN is the most powerful predictor of death from progressive heart failure. This may reflect the presence of major neuroendocrine dysfunction in patients with a low SDNN, which has deleterious effects on ventricular geometry leading to a decline in pump function and progressive heart failure.

In contrast to Lombardi and Mortara, we believe that the results of UK-HEART are eminently applicable to a very large proportion of patients, and that 24 hour electrocardiography with measurement of SDNN has a useful role in the assessment of patients with cardiac failure.

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FOR THE UK-HEART STUDY GROUP

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- 1 Lombardi F, Mortara A. Heart rate variability and cardiac failure. *Heart* 1998;80:213-14.
- 2 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;93:1043-65.
- 3 Nolan J, Flapan AD, Goodfield NE, et al. Measurement of parasympathetic activity from 24-hour ambulatory electrocardiograms and its reproducibility and sensitivity in normal subjects, patients with symptomatic myocardial ischaemia, and patients with diabetes mellitus. *Am J Cardiol* 1996;77:154-8.

- 4 Nolan J, Batin PD, Andrews R, et al. A 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). *Circulation* 1998;98:1510-16.
- 5 Cohn JN, Johnson GR, Shabtai R, et al. 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-5-16.
- 6 The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;325:293-302.

EDITOR,—We read with interest the editorial by Lombardi and Mortara about heart rate variability (HRV) and chronic heart failure (CHF).¹ 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),² 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 after it was 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.² 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,³ leading to a poor determination of the real "at risk" patients as a large number of patients with CHF have 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,⁴ 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.⁵

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

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

	SDNN		p Value	RR of cardiac death (95% CI)
	Survivors	Non-survivors		
Age < 50 (n = 47)	110.5 (48.0)	75.9 (57.5)	0.009	1.036 (1.002-1.072)
Age > 50 (n = 75)	96.0 (32.5)	79.6 (25.0)	0.02	1.027 (1.003-1.053)

p value based on proportional hazards model.

Risk ratios (RR) are calculated for a decrease in SDNN equal to 1 ms.

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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- 1 Lombardi F, Mortara A. Heart rate variability and cardiac failure. *Heart* 1998;80:213–14.
- 2 Nolan J, Batin PD, Andrews R, *et al.* 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). *Circulation* 1998;98:1510–16.
- 3 Ponikowski P, Anker SD, Chua TP, *et al.* Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997;79:1645–50.

- 4 Umetani K, Singer DH, McCraty R, *et al.* Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol* 1998;31:593–601.
- 5 Fauchier L, Babuty D, Cosnay P, *et al.* Heart rate variability in idiopathic dilated cardiomyopathy: characteristics and prognostic value. *J Am Coll Cardiol* 1997;30:1009–14.

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*,³ 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-neural 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.³ 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.³ 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.

- 1 Lombardi F, Mortara A. Heart rate variability and cardiac failure. *Heart* 1998;80:213–14.
- 2 Nolan J, Batin P, Andrews R, *et al.* 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). *Circulation* 1998;98:1510–16.
- 3 Fauchier L, Babuty D, Cosnay P, *et al.* Heart rate variability in idiopathic dilated cardiomyopathy: characteristics and prognostic value. *J Am Coll Cardiol* 1997;30:1009–14.