Prognostic value of baroreflex sensitivity testing after acute myocardial infarction

T G Farrell, O Odemuyiwa, Y Bashir, T R Cripps, M Malik, D E Ward, A J Camm

Abstract

Background—Disturbances of autonomic function are recognised in both the acute and convalescent phases of myocardial infarction. Recent studies have suggested that disordered autonomic function, particularly the loss of protective vagal reflexes, is associated with an increased incidence of arrhythmic deaths. The purpose of this study was to compare the value of differing prognostic indicators with measures of autonomic function and to assess the safety of arterial baroreflex testing early after infarction.

Methods—As part of a prospective trial of risk stratification in post-infarction patients arterial baroreflex sensitivity, heart rate variability, long term electrocardiographic recordings, exercise stress testing, and ejection fraction were recorded between days 7 and 10 in 122 patients with acute myocardial infarction.

Results—During a one year follow up period there were 10 arrhythmic events. Baroreflex sensitivity was appreciably reduced in these patients suffering arrhythmic events (1-73 SD 1-49) vs 7-83 (4-5) ms/mm Hg, 95% confidence interval (CI) 4-8 to 7-3, p = 0.0001). Significant correlations were noted with age (r = −0.68, p < 0.001) but not left ventricular function. When baroreflex sensitivity was adjusted for the effects of age and ventricular function baroreflex sensitivity was still considerably reduced in the arrhythmic group (2-1 vs 7-57 ms/mm Hg, p < 0.0001). Depressed baroreflex sensitivity carried the highest relative risk for arrhythmic events (23-1, 95% CI 7-7 to 69-2) and was superior to other prognostic variables including left ventricular function (10-4, 95% CI 3-3 to 32-6) and heart rate variability (10-1, 95% CI 5-6 to 18-1). No major complications were noted with baroreflex testing and in particular no patients developed ischaemic or arrhythmic symptoms during the procedure.

Conclusions—Disordered autonomic function as measured by depressed baroreflex sensitivity or reduced heart rate variability was associated with an increase incidence of arrhythmic events in post-infarction patients. Baroreflex testing can be safely performed in the immediate post-infarction period.

Established methods of risk stratification in post-infarction patients are based on clinical features; exercise stress testing; and the identification of complex ventricular arrhythmias, impaired left ventricular function, and multivessel coronary artery disease. Despite such diverse approaches many problems associated with the identification and treatment of patients at high risk of malignant arrhythmias and sudden death remain unsolved. In an attempt to improve the prediction of arrhythmic events, novel methods of risk stratification including the signal averaged electrocardiogram and programmed ventricular stimulation have been evaluated. More recently, with growing awareness of the key role of neural mechanisms in arrhythmogenesis, attention has been focussed on the prognostic value of autonomic function tests such as heart rate variability analysis and baroreflex sensitivity.

It has long been recognised that pronounced disturbances of autonomic function are seen in the acute phase of myocardial infarction and during the subsequent convalescent period. Evidence from human and animal studies suggests that the preservation of vagal reflexes post-infarction protects against the induction of life threatening ventricular arrhythmias and two groups have now reported on the value of heart rate variability in risk stratification. To date, there has only been one report on the value of arterial baroreflex testing performed one month after myocardial infarction. The purpose of this study was to test the feasibility, safety, and prognostic significance of baroreflex sensitivity testing early after infarction and to compare its value with other novel and established prognostic variables.

Patients and methods

STUDY POPULATION

We studied 122 patients admitted to St George’s Hospital with an acute myocardial infarction. Patients over the age of 70 years or those with coexisting valvar heart disease, insulin dependent diabetes, arterial hypertension (> 160/90 mm Hg), atrial fibrillation, or evidence of sinoatrial disease were excluded. No digitalis or angiotensin converting enzyme inhibitors were used in the study group and beta blockade was stopped at least 48 hours before study. Informed consent was obtained from all patients. The end points in the study were cardiac death and life threatening arrhythmic events including sudden death (Cardiac Arrhythmia Pilot Study definition). Sixty
eight of the patients were also included in another study on autonomic function and the inducibility of arrhythmias at programmed stimulation.\textsuperscript{13}

**BAROREFLEX SENSITIVITY TESTING**

Baroreflex sensitivity was assessed by a previously described method.\textsuperscript{20} All patients were studied in a fasting and supine state between days 7 and 10 (mean 8.2 days). A right femoral line (French gauge 8) was used to record continuous arterial pressure with simultaneous recording of a single electrocardiogram lead at 25 mm/s. In 11 cases a radial line (French gauge 14) was used. After a period of rest when both blood pressure and heart rate values were stable a bolus of phenylephrine was injected intravenously over 15 seconds via a peripheral vein. An initial test dose of 0.2 mg was given, followed by progressively larger doses until a rise in systolic blood pressure of between 15 and 40 mm Hg was obtained. The test was repeated until at least three recordings were made using the optimum bolus dose. Baroreflex sensitivity was calculated by plotting the beat to beat change in RR interval against the beat to beat change in systolic blood pressure (baseline systolic − preceding systolic blood pressure). A linear regression analysis of these points was performed for the first sustained rise in blood pressure and baroreflex sensitivity was then estimated as the value of the slope from the regression analysis.

Only regression lines with a correlation coefficient greater than 0.8 were accepted for analysis. At least three such slopes were calculated for each patient and the mean of these was taken as the baroreflex sensitivity and expressed in ms/mm Hg. During the procedure patients were asked to breathe at a normal rate and to avoid slow or forced respiration. According to the work of La Rovere et al a baroreflex sensitivity of less than 3–0 ms/mm Hg was considered depressed.\textsuperscript{18} Figure 1 shows examples of normal and depressed baroreflex sensitivity in post-infarction patients.

**ANALYSIS OF 24 HOUR ELECTROCARDIOGRAPHIC RECORDINGS**

All of the Holter tapes in the sample population were analysed using the Marquette 8500 scanner running version 5-7 of the Marquette arrhythmia analysis program allowing detection of normal sinus beats and supraventricular and ventricular extrasystoles. After automatic analysis of the tape, the data file was visually reviewed and edited by three of us (TF, YB, OO). In particular the histogram of normal to normal RR intervals was reviewed and the 20 longest and 20 shortest RR intervals were examined to ensure correct recognition. More than 10 extrasystoles in any one hour was regarded as abnormal on the basis of the MPIS study.\textsuperscript{4}

**HEART RATE VARIABILITY ANALYSIS**

Heart rate variability analysis was performed by running the Marquette heart rate variability analysis program. Four methods of temporal domain analysis were used: the standard deviation (SD RR) and root mean square successive difference (rMSSD) of all normal RR intervals, the percentage of all normal RR intervals exceeding the adjacent RR intervals by greater than 50% (pNN50), and the heart rate variability index were calculated. The method used to derive the heart rate variability index has been previously described\textsuperscript{21} and involves the digitising of the whole 24 hour electrocardiographic recording at an analogue to digital (A:D) sampling rate of 128 Hz and transfer to a personal computer (IBM PC-AT). The frequency distribution of durations of normal to normal RR intervals is constructed and heart rate variability index is expressed in milli-seconds as the baseline width of the distribution curve measured by the method of minimum square difference interpolation. This method is less liable to recording noise and misrecognition artefact.\textsuperscript{21} On the basis of previous research, SDRR of less than 50 ms was considered depressed\textsuperscript{16} and the heart rate variability index was dichotomised at 16 ms (mean minus 1 SD).

**EXERCISE PROTOCOL**

Each patient underwent a symptom limited exercise test before discharge. In most cases this was according to the Bruce protocol although in eight patients a modified Bruce protocol was used. Those patients unable to exercise for reasons such as early post-infarction angina or impaired ventricular function were considered to have a positive test. Exercise testing was considered positive if a patient developed anginal chest pain, ST segment depression of greater than 1.5 mm, a failure of systolic blood pressure to rise by greater than 10%, or inability to complete stage one of the exercise protocol.

**Figure 1** Examples of well preserved baroreflex sensitivity (10.65 ms/mm Hg) and depressed (2.47 ms/mm Hg) in two patients after infarction. Baroreflex sensitivity (BRS) is expressed as gradient of regression line.
Autonomic function and myocardial infarction

ASESSMENT OF SIGNAL AVERAGED ELECTROCARDIOGRAM

This was recorded by a commercially available system (Arrhythmia Research Technology, model 1200EPX) as described elsewhere.22 The high pass filter was set at 25 Hz and 100-200 beats were averaged to achieve a noise level of less than 0·4 μV. Recordings were made at day six or seven in all patients in sinus rhythm. Late potentials were considered to be present if any two of the following criteria were present: filtered QRS complex > 120 ms, root mean square voltage during the last 40 ms of the filtered QRS complex < 25 μV, and duration of the filtered QRS complex of > 40 ms after voltage fell below 40 μV.

CORONARY ANGIOGRAPHY

Coronary angiography was performed in all patients with a positive exercise test before discharge. The number of coronary arteries with significant stenoses of the luminal diameter (>50%) was noted and patency of the infarct artery according to the Thrombolysis in Myocardial Infarction Trial (TIMI) scale was recorded. Left ventricular ejection fraction was calculated with the Mac angio package (Dodge formula) using the right anterior oblique view. In those patients who did not undergo angiography the ejection fraction was calculated using radionuclide scanning. A left ventricular ejection fraction < 40% was considered abnormal.

STATISTICAL ANALYSIS

Results were compared using the two tailed Student’s t test and the χ² test with Yates’ correction where appropriate. A multiple ANOVA procedure was used to assess the influence of age and left ventricular function on the relation between baroreflex sensitivity and clinical events. Homogeneity of variance was assessed by Cochran’s C test. To test the relation between baroreflex sensitivity and continuous variables simple linear regression was fitted. All results are expressed as mean (SD) with 95% confidence intervals (95% CIs) where appropriate. Statistical significance was assumed for p < 0·05. The standard definitions for sensitivity, specificity, and positive and negative predictive accuracy were used. Relative risk was defined as the ratio event rate in patients with a positive test: event rate in patients with a negative test.

Results

The test group consisted of predominantly men; only five women were included and the mean age of the population was 56 (9·3) years. There was a roughly equal distribution of anterior and inferior infarcts (64 v 58) but a preponderance of Q wave infarcts (82 v 40). Each patient has been followed up for a minimum of one year after infarction and the results presented apply to events occurring in this year. During this time there were 13 deaths and 10 documented life threatening arrhythmic events (five patients died suddenly and five others were readmitted with sustained ventricular arrhythmias).

Twenty four per cent of patients were discharged on oral β blockade. Coronary revascularisation was performed in 22% of patients (angioplasty or coronary vein grafting) and five patients received antiarrhythmic drugs after clinical arrhythmic events.

There were no major complications after baroreflex sensitivity testing. In particular, no patient developed signs or symptoms of myocardial ischaemia or serious ventricular arrhythmias and arterial cannulation of the femoral and radial arteries was not associated with any complications. Minor symptoms were common, however, after administration of phenylephrine, with over 95% of the patients experiencing either transient headaches, and circumoral or facial paraesthesia. In five patients, not reported here, we were unable to obtain satisfactory baroreflex sensitivity recordings. This was due to frequent ventricular extrasystoles during the test (three cases), the development of paroxysmal atrial flutter (one case), and paroxysmal episodes of atrial flutter (one case).

Baroreflex sensitivity for the whole population was 7·39 (4·68) ms/mm Hg and there was a significantly inverse correlation with age (r = -0·68, p < 0·001) (fig 2). No difference was noted in baroreflex sensitivity according to anterior infarction (7·36 (5·05) vs 6·78 (5·12) ms/mm Hg, 95% CI −0·23 to 0·36 NS) or the use of thrombolytic agents (7·98 (3·3) vs 6·78 (3·9) ms/mm Hg, 95% CI −0·9 to 1·5 NS).

BAROREFLEX SENSITIVITY, EJECTION FRACTION, AND CORONARY ARTERY DISEASE

The mean left ventricular ejection fraction in the study group was 51% (14·4%). Baroreflex
sensitivity was not correlated with left ventricular ejection fraction (r = 0.1, NS) (fig. 2). Of the 83 patients catheterised 38 had single vessel disease, 26 had two vessel disease, and 19 three vessel disease. Baroreflex sensitivity was lowest in patients with three vessel disease (4.76 (3.5) mm Hg/min) and this was significantly lower than in patients with single vessel disease (7.66 (5.1) mm Hg/min, 95% CI 0.34 to 5.5, p = 0.02) but not two vessel disease (6.7 (3.86) mm Hg/min, 95% CI 0.3 to 4.1, p = 0.08). Infarct artery patency (TIMI grade 2 or greater) did not appear to affect baroreflex sensitivity (6.87 (4.23) mm Hg/min, 95% CI 1.9 to 2.2) (fig. 3).

Baroreflex Sensitivity and Exercise Testing
In 71 patients the exercise test was considered positive. The mean peak heart rate at exercise for the whole group was 136 (18.2) beats/min, mean exercise duration was 6:26 (2:12) min, and the mean workload achieved was 7:18 (2:51) MET. Baroreflex sensitivity appeared to be significantly lower in those patients with a positive exercise test (6.39 (4.0) mm Hg/min, 95% CI 0.7 to 4.0, p = 0.01) and weak but significant correlations were noted between baroreflex sensitivity and workload expressed in METs (r = 0.34, p < 0.0002), exercise duration (r = 0.33, p < 0.0003), and the peak heart rate achieved at exercise (r = 0.23, p = 0.02).

Baroreflex Sensitivity, 24 Hour Electrocardiographic Recordings and the Signal Averaged Electrocardiogram
Frequent ventricular extrasystoles (> 10/h) were noted on long term electrocardiographic recordings in 37 patients and in these patients baroreflex sensitivity was significantly lower (5.9 (5.01) mm Hg/min, 95% CI 0.3 to 3.9, p = 0.04). In 28 patients repetitive ventricular forms were noted but baroreflex sensitivity though lower was not significantly so (6.07 (5.57) mm Hg/min, 95% CI 0.4 to 3.7, p = 0.07). The signal averaged electrocardiogram was considered positive in 22 patients but again no difference was noted in baroreflex sensitivity (7.5 (5.9) mm Hg/min, 95% CI 2.2 to 4.2, NS).

Relation of Baroreflex Sensitivity to Test Variables
In the study population the mean change in systolic blood pressure was 28.5 (range 15 to 36) mm Hg, and the mean dose of phenylephrine used was 0.32 mg. No correlation was noted between baroreflex sensitivity and test variables such as the dose of phenylephrine used (r = 0.04) or the subsequent rise in systolic blood pressure (r = 0.014) but there was a weak correlation between baroreflex sensitivity and the resting heart rate or RR interval (r = 0.282, p = 0.001). We found a significant correlation between baroreflex sensitivity and the maximum change in RR interval (r = 0.513, p = 0.001), but this was not as strong as might have been expected. In several patients, abrupt rather than gradual changes in heart rate occurred during the phenylephrine test (fig. 4).

Heart Rate Variability and Baroreflex Sensitivity
For the whole study group the mean value of the SDRR was 100 (40) ms, heart rate variability index was 26.76 (10.33) ms, rMSSD was 29.41 (14.66) ms, pNN50 was 6.76 (8.7), and the mean RR interval was 845 (144) ms. As heart rate variability and baroreflex sensitivity are reputed measures of vagal tone, it might be expected that strong correlations would exist between these measures. In fact no correlation was noted between any temporal measure of heart rate variability (SDRR, rMSSD, pNN50, or the heart rate variability index) and
Autonomic function and myocardial infarction

Autonomic function with phenylephrine

Figure 4 Plot of relation between baroreflex sensitivity (BRS) and variables associated with phenylephrine test including resting RR interval, change in systolic blood pressure, dose of phenylephrine used, and change in maximum RR interval.

Figure 5 Column graph (mean (SD)) of BRS according to clinical events. Arrhythmic events include sudden deaths and ventricular fibrillation.

Baroreflex sensitivity. A weak correlation was noted, however, between the maximum RR interval change during baroreflex testing and the pNN50 index (r = 0.35, p = 0.04).

Baroreflex testing and events

Baroreflex sensitivity was appreciably depressed in those patients (n = 10) suffering arrhythmic events including sudden death (1.75 (1.49) v 7.89 (4.53) ms/mm Hg, 95% CI 4.8 to 7.3, p = 0.0001) (fig 5). A MANOVA procedure was performed to assess the effects of age and left ventricular function on the relation between baroreflex sensitivity and arrhythmic events. After allowing for these possible influences, baroreflex sensitivity was still significantly reduced in patients suffering arrhythmic events (2.1 v 7.57 ms/mm Hg, p < 0.0001). Although age had a significant influence on the relation between baroreflex sensitivity and arrhythmic events (r value = 6.07, p < 0.0001), no such relation was noted for left ventricular function (r value = 1.650, NS) (table 1).

When we confined the analysis to patients suffering sudden death (n = 5), baroreflex sensitivity was still significantly lower (2.34 (1.9) v 7.54 (4.67), 95% CI 1.1 to 9.3, p = 0.001). When all cause cardiac mortality (n = 13) was considered, baroreflex sensitivity was lower but not significantly so (5.9 (3.78) v 7.49 (4.79), 95% CI 1.14 to 4.3, NS).

Comparison of baroreflex sensitivity, heart rate variability, and other prognostic variables in the prediction of arrhythmic events

The heart rate variability index (15.6 (6.5) v 27.8 (10.1) ms, 95% CI 9.8 to 15.4, p = 0.001), pNN50 (2.7 (2.94) v 7.2 (9.0)%, 95% CI 2.0 to 6.7, p = 0.005), and SDRR (60 (24) v 101 (37) ms, 95% CI 15 to 67, p = 0.001) were all significantly lower in patients suffering arrhythmic events. For all cause mortality only the heart rate variability index was significantly reduced (20.1 (7.6) v 27.6 (10.4) ms, 95% CI 1.6 to 14.3, p = 0.007). Table 2 summarises the results of investigations in patients suffering differing clinical events and table 3 gives the prognostic value of baroreflex sensitivity compared with differing measures of heart rate variability and other established prognostic variables. It can be seen that depressed baroreflex sensitivity is a superior predictor of arrhythmic risk compared with any other variable.

Discussion

Several studies have now drawn attention to the disturbances of autonomic tone that occur in both the acute and recovery phases of myocardial infarction. More recently the role of heart rate variability, a non-invasive index of parasympathetic activity, in risk stratification has been examined in two large studies. These have led to the hypothesis that the impairment or loss of vagal reflexes may predispose to arrhythmic events or sudden deaths. As the arterial baroreceptors are predominantly responsible for changes in heart rate it has been suggested that baroreflex sen-

Table 1 Results of MANOVA analysis

<table>
<thead>
<tr>
<th></th>
<th>Adjusted BRS means for the effects of age and LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted mean (ms/mm Hg)</td>
</tr>
<tr>
<td></td>
<td>Observed mean (ms/mm Hg)</td>
</tr>
<tr>
<td>DF</td>
<td>F Value</td>
</tr>
<tr>
<td>Arhythmic event</td>
<td>1</td>
</tr>
<tr>
<td>Covariates</td>
<td>2</td>
</tr>
<tr>
<td>Constants</td>
<td>1</td>
</tr>
<tr>
<td>No arrhythmic event</td>
<td>1</td>
</tr>
</tbody>
</table>

Regression for covariates: LVEF r = -1.650; age r = -6.097; p = 0.0001.
DF, degrees of freedom; LVEF, left ventricular ejection fraction; BRS, baroreflex sensitivity.
Table 2 Summary of investigations according to clinical events

<table>
<thead>
<tr>
<th>Event</th>
<th>BRS (ms/mm Hg; mean (SD))</th>
<th>HRV SDRR (ms; mean (SD))</th>
<th>HRV index (ms; mean (SD))</th>
<th>LVEF% (mean (SD))</th>
<th>ETT (% positive)</th>
<th>SAECG (% positive)</th>
<th>VE10 (% positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3 (1.9)± 7.5 (4.7)**</td>
<td>65 (26)± 99 (38)**</td>
<td>17.9 (7.5)± 27.2 (10.3)**</td>
<td>33 (10.6)± 51.5 (14.1)**</td>
<td>80 ± 58</td>
<td>60 ± 16</td>
<td>80 ± 28</td>
<td></td>
</tr>
<tr>
<td>Arrhythmic events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.8 (1.5)± 7.9 (4.5)**</td>
<td>60 (24)± 101 (37)**</td>
<td>15.6 (6.5)± 27.6 (10.1)**</td>
<td>33 (9.4)± 52 (14)**</td>
<td>80 ± 57</td>
<td>70 ± 13</td>
<td>80 ± 25</td>
<td></td>
</tr>
<tr>
<td>Cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.9 (3.8)± 7.5 (4.8)</td>
<td>75 (39)± 100 (37)</td>
<td>20.1 (7.6)± 27.6 (10.4)**</td>
<td>41 (18)± 52 (15.7)**</td>
<td>69 ± 58</td>
<td>31 ± 17</td>
<td>54 ± 28</td>
<td></td>
</tr>
</tbody>
</table>

BRS, baroreflex sensitivity; HRV, heart rate variability; LVEF, left ventricular ejection fraction; ETT, exercise tolerance test; SAECG, signal averaged electrocardiogram; VE10, greater than 10 extrastoles in any hour on long term electrocardiographic recording.

*P = 0.05; †P = 0.046; ‡P = 0.049; ††P = 0.02; ‡‡P = 0.007; ‡‡‡P = 0.001; ‡‡‡‡P = 0.0001.

Table 3 Comparison of different prognostic variables in the prediction of arrhythmic events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive accuracy (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise test positive</td>
<td>80</td>
<td>42.9</td>
<td>11</td>
<td>2.9 (1-8.9)</td>
</tr>
<tr>
<td>Late potentials</td>
<td>70</td>
<td>84.7</td>
<td>28</td>
<td>0.9 (3-2.29)</td>
</tr>
<tr>
<td>Ventricular ectopy &gt; 10h</td>
<td>80</td>
<td>75</td>
<td>22</td>
<td>20.6 (11-37.1)</td>
</tr>
<tr>
<td>Repetitive forms</td>
<td>80</td>
<td>82.1</td>
<td>28.6</td>
<td>13.4 (4-3.4-7)</td>
</tr>
<tr>
<td>HRV SD RR &lt; 50 ms</td>
<td>60</td>
<td>94</td>
<td>55</td>
<td>10.4 (5-6-18)</td>
</tr>
<tr>
<td>HRV index &lt; 16 ms</td>
<td>50</td>
<td>88.4</td>
<td>27.7</td>
<td>5.77 (3.0-11.1)</td>
</tr>
<tr>
<td>BRS &lt; 3.0 ms/mm Hg</td>
<td>80</td>
<td>97</td>
<td>44</td>
<td>23.1 (7-7.4-92)</td>
</tr>
<tr>
<td>LVEF &lt; 40%</td>
<td>80</td>
<td>76.8</td>
<td>25.5</td>
<td>10.4 (3-3.3-26)</td>
</tr>
</tbody>
</table>

BRS, baroreflex sensitivity; LVEF, left ventricular ejection fraction; HRV, heart rate variability; SD RR, standard deviation of normal RR intervals.

sivity testing may provide a more sensitive and accurate assessment of autonomic function in patients after infarction. An earlier study from this department showed that depressed baroreflex sensitivity is associated with an increased induction of ventricular arrhythmias at programmed ventricular stimulation.13 This finding is supported by the work of Schwartz and colleagues with a canine post-infarction model.14 15

The present study adds to an increasing body of evidence supporting a link between disorder autonomic function and sudden death. La Rovere et al have previously reported on the prognostic significance of baroreflex sensitivity testing in a smaller group of patients tested one month after myocardial infarction16 and a strong correlation was noted between depressed baroreflex sensitivity and cardiovascular mortality but our present study is the first to have compared the value of baroreflex sensitivity and heart rate variability testing soon after infarction. This is particularly important as many arrhythmic events and sudden deaths occur in the immediate weeks after discharge.17 By delaying the investigation, many events will be missed, consequently biasing the value of the test.

BAROREFLEX SENSITIVITY TESTING: TECHNICAL CONSIDERATIONS

Of particular importance is the finding that the phenylephrine method of baroreflex sensitivity assessment is safe and well tolerated in the immediate post-infarction period, although many patients did suffer transient minor side effects. Until recently the method was labour intensive and involved intra-arterial cannulation, consequently restricting its use in clinical practice. The development of reliable, non-invasive blood pressure monitoring by infrared photoplethysmography coupled with on line methods of analysis has largely solved these problems.

Baroreflex sensitivity seems to be independent of test related variables in the post-infarction population apart from a weak correlation with the resting RR interval.18 19 Whereas these findings are similar to those of La Rovere et al they are at variance with previous studies in non-infarct patients.20 Also, several patients in the present study had abrupt rather than the gradual changes in heart rate normally seen after the phenylephrine baroreflex test. These findings may represent further indirect evidence that the autonomic control of heart rate is disturbed after infarction. Care must be taken in extrapolating the results of baroreflex sensitivity testing in a controlled laboratory setting to a physiological state involving physical activity and ischaemic challenges. The baroreflex is not static, but instead exhibits dynamic resetting of its threshold, set point, and gain.21 Other autonomic reflex arcs may also be important. For example, in the canine experiments performed by Schwartz and colleagues, those animals not liable to arrhythmias during ischaemic challenges not only exhibited well preserved baroreflex sensitivity but also pronounced heart rate changes during the ischaemic challenge, thought to be mediated by the Von Bezold-Jarisch reflex.14

BAROREFLEX SENSITIVITY AND CLINICAL CORRELATES

An important observation was the lack of correlation between baroreflex sensitivity and left ventricular ejection fraction, which has been noted previously.18 This may at first seem surprising but reports of a relation between baroreflex sensitivity and ventricular function are confined to studies of congestive heart
Autonomic function and myocardial infarction

failure, a condition that was absent in our patients at the time of testing. Left ventricular dysfunction may also manifest itself as abnormalities in wall motion and the resulting difference in wall stress might result in increased afferent sympathetic activity (particularly in anterior infarction where sympathetic fibres predominate). Although it has been suggested that baroreflex sensitivity may correlate better with regional wall motion abnormalities rather than a global index of ventricular function, a small pilot study has failed to support this hypothesis.

Our finding that baroreflex sensitivity was lower in patients with a positive exercise test may be related to the classification of some tests as positive on the basis of poor exercise tolerance or haemodynamic response, particularly as there was a weak but significant correlation between baroreflex sensitivity and exercise duration/workload. Unlike La Rovere et al we did not find significant differences in baroreflex sensitivity according to infarct site or the presence of Q waves, although there are theoretical reasons why such differences may exist. The distribution of chemoreceptors and pressure receptors favours the inferoposterior region whereas parasympathetic fibres predominate in the subendocardial layer. The precise anatomical location of infarcts and quantification into transmural and subendocardial infarcts on electrocardiographic criteria is known to be inaccurate, however, and previous studies have produced conflicting results. Webb et al found autonomic function to be significantly more depressed in anterior infarcts whereas La Rovere et al noted the reverse.

The finding of a more pronounced depression of baroreflex sensitivity in patients with multivessel disease is also in agreement with previous studies of both baroreflex sensitivity and heart rate variability after infarction. No clear explanation for this finding is available, but multivessel coronary artery disease might be associated with more extensive myocardial damage or ischaemia, resulting in destruction of ventricular chemo and baro receptors and alterations of afferent parasympathetic transmission.

BAROREFLEX SENSITIVITY AND HEART RATE VARIABILITY

The lack of correlation between temporal measures of heart rate variability and baroreflex sensitivity is not unexpected as it has been suggested that baroreflex sensitivity and heart rate variability may examine different but complementary components of the parasympathetic nervous system. Consequently the prognostic value of these two parameters differs considerably. In this study, baroreflex sensitivity was significantly reduced only in those patients with arrhythmic events, whereas the heart rate variability index was significantly reduced when either arrhythmic events or cardiac mortality was analysed. Bigger et al have studied the relation between baroreflex sensitivity and frequency domain analysis of heart rate variability in 32 patients after infarction. They found only a moderate correlation between baroreflex sensitivity and the high frequency component of the normal RR interval power spectrum but they concluded that the association was not strong enough to make baroreflex sensitivity testing redundant. It should be stressed that reduced heart rate variability does not necessarily predict reduced baroreflex sensitivity and important information may be obtained from both tests. Temporal measures of heart rate variability may represent primary tonal vagal activity whereas baroreflex sensitivity represents the maximum response of the autonomic nervous system to barostress, which may be of particular importance in protecting myocardial electrical stability. This finding may account for the disparity between heart rate variability and baroreflex sensitivity in our study. The pNN50 index has been reported to be the most sensitive heart rate variability measure of parasympathetic tone and might have been expected to correlate with baroreflex sensitivity. Although it did not, there was a significant correlation between the pNN50 and the maximum change in RR intervals on baroreflex sensitivity testing.

BAROREFLEX SENSITIVITY AND ARRHYTHMIC RISK

The striking feature of our study is that baroreflex sensitivity testing was a very strong marker of arrhythmic risk. Patients with depressed baroreflex sensitivity (< 3.0 ms/mm Hg) had a relative risk for arrhythmic events during follow up of 23.1, superior to any other variable including the different measures of heart rate variability and conventional investigations. In particular baroreflex sensitivity was a much better indicator of arrhythmic propensity than impaired left ventricular function (relative risk 10.4) or frequent ventricular extrasystoles (relative risk 20.6). It is of note that baroreflex sensitivity was reduced in patients with frequent ventricular extrasystoles and repetitive forms on long term electrocardiographic recordings, markers of arrhythmic potential.

It is well recognised that the electrical stability of the myocardium is influenced by both divisions of the autonomic nervous system. Sympathetic or adrenergic stimulation is known to reduce ventricular refractoriness and fibrillation threshold and to increase the propensity to arrhythmias; it may also produce afterdepolarisations and triggered activity. Vagal stimulation opposes these effects, prolonging ventricular refractoriness and reducing the effects of adrenergic stimulation. Indeed, the inhibitory effects of vagal stimulation are more pronounced in the setting of adrenergic stimulation than in isolated stimuli. Normally, afferent nerve transmission from the arterial baroreceptors to the higher centres results in inhibition of the sympathetic outflow while concomitantly increasing efferent parasympathetic activity. Myocardial infarction may interfere with this mechanism in several ways. Denervation of the myocardium as a consequence of infarction may produce several effects: areas of myocardium may become supersensitive to catecholamines and the de-
Table 4  Summary of investigations in patients with arrhythmic events

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Event</th>
<th>BRS  (ms/mm Hg)</th>
<th>HRV SD RR  (ms)</th>
<th>HRV index  (ms)</th>
<th>LVEF%</th>
<th>ETT</th>
<th>SAECCG</th>
<th>VE10</th>
<th>CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VT</td>
<td>1-42</td>
<td>32</td>
<td>170</td>
<td>22</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>VT</td>
<td>2-32</td>
<td>35</td>
<td>8-6</td>
<td>45</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>VT</td>
<td>0-36</td>
<td>34</td>
<td>9-2</td>
<td>41</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>SD</td>
<td>4-6</td>
<td>67</td>
<td>17-3</td>
<td>47</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>SD</td>
<td>3-2</td>
<td>12-4</td>
<td>39</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>SD</td>
<td>0-3</td>
<td>68</td>
<td>18-7</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>SD</td>
<td>2-4</td>
<td>90</td>
<td>29-9</td>
<td>26</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>SD</td>
<td>0-5</td>
<td>11-0</td>
<td>16-5</td>
<td>35</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>VT</td>
<td>0-7</td>
<td>45</td>
<td>16-5</td>
<td>27</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>VT</td>
<td>1-1</td>
<td>77</td>
<td>27-0</td>
<td>27</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

BRS, baroreflex sensitivity; HRV, heart rate variability; LVEF%, left ventricular ejection fraction; ETT, exercise tolerance test; SAECCG, signal averaged electrocardiogram; VE10, greater than 10 extra systoles in any one hour on long term electrocardiographic recording; CAD, number of diseased arteries; VT, representation with sustained ventricular arrhythmias; SD, sudden or arrhythmic death; +, positive; −, negative.

Table 4 gives details of each arrhythmic event and shows that conventional risk factors would have failed to identify several cases. Not all patients had impaired ventricular function or multivessel disease and markers of electrical instability were absent in several cases. Autonomic function and in particular baroreflex sensitivity was considerably reduced in all patients. Although patient 4 had a baroreflex sensitivity of 4-6 ms/mm Hg, this was still well below the group mean and would be considered low for a 36 year old man. Whether baroreflex sensitivity is an independent predictor of arrhythmic propensity will require further investigation involving a larger group of patients. When adjusted for age and ventricular function baroreflex sensitivity was still significantly lower in the arrhythmic group, however. It is hoped that a large multicentre trial (Autonomic Tone and Reflexes After Myocardial Infarction, ATRAMI) will answer these questions.

Conclusion
This paper draws attention to the association between autonomic tone, arrhythmic risk and death after infarction. Baroreflex sensitivity assessment is safe and can be performed soon after infarction. It provides different but complimentary data to heart rate variability and in our present study the prognostic value of baroreflex sensitivity appears to be independent of the effects of age and left ventricular function. Its precise value as an independent predictor of arrhythmic events and its relation to other prognostic variables will require further investigation. Such studies, including the ATRAMI trial, are in progress.

23 Eckberg DL. Baroreflex inhibition of the human sinus node: importance of stimulus intensity, duration and rate of...
Autonomic function and myocardial infarction