Prognostic Significance of Early Short-Term Measurements of Heart Rate Variability Following Acute Myocardial Infarction

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This study of 164 subjects demonstrates that short-term (5-minute) recordings of heart rate variability, performed within 48 hours of admission, identify those who survive acute myocardial infarction but have an adverse prognosis. ©2004 by Excerpta Medica, Inc. (Am J Cardiol 2004;94:1275–1278)

Cardiac autonomic control is profoundly deranged after acute myocardial infarction (AMI), with evidence of impaired vagal control and high levels of sympathetic activity. The extent of this derangement, in particular subnormal vagal activity, can be assessed by the measurement of baroreflex sensitivity and heart rate variability (HRV). There is considerable evidence to show that low levels of these markers of cardiac autonomic control are strongly and independently associated with an adverse prognosis.1 It is currently widely believed that abnormal cardiac autonomic control after AMI is not merely a consequence of the infarct but actively and deleteriously influences the clinical course of the disease. The predictive value of HRV has been exclusively derived from a 24-hour Holter electrocardiogram, which is slow and expensive to record and analyze.2 Isolated short-term (5-minute) recordings may be of use, but data for their predictive value are scarce and have been derived largely through the post hoc selection of suitable fragments of 24-hour recordings.3 The aim of this study was to determine the prognostic significance of short-term recordings of HRV soon after AMI.

Subjects were recruited from among patients admitted to coronary care units at 3 hospitals in the United Kingdom between 1998 and 2000. This was a substudy of a double-blind, placebo-controlled comparison of the effect of early (<48 hours) and late (at 5 days) angiotensin-converting enzyme (ACE) inhibition with ramipril on short-term HRV. Data presented in this report are derived from HRV recordings taken before the study drug was administered. Patients were eligible if they presented ≤48 hours of AMI in sinus rhythm. AMI was diagnosed according to criteria of the World Health Organization.4 Patients were excluded if they had established autonomic dysfunction, had a noncardiac disease likely to influence mortality rate, had a permanent pacemaker, were already treated with ACE inhibitors, or treatment with ACE inhibitors was contraindicated. Patients who were being treated with β-adrenoceptor antagonists before admission were eligible for inclusion provided that there was no change to drug dose after admission but before HRV was examined. No patients began taking β-adrenoceptor antagonists after admission but before HRV could be examined. All patients were discharged on an ACE inhibitor. All patients gave their written informed consent before entry into the ramipril study, which was approved by the local clinical research ethics committees. The substudy, which did not involve further patient contact, received separate approval.

Studies were performed ≤48 hours of admission, with subjects in the semi-supine position after a 2-hour fast and ≥30 minutes of rest in bed. Studies were performed on the admitting ward at the bedside.

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Blood pressure was measured with automated oscillometric sphygmomanometers after this rest period. HRV was examined according to previously published methods. Subjects were studied during free respiration, and recordings of ≥256 consecutive RR intervals were made on each occasion. A respiratory signal was obtained, displayed, and recorded from 2 electrodes attached to the chest wall to monitor changes in impedance with respiration.

HRV analysis was performed according to previously published methods. Standard time-domain measures were calculated, including mean NN interval, SD of NN-interval values (an index that expresses overall variability), percent successive NN-interval differences >50 ms, and root-mean-square of successive NN-interval differences. Percent successive NN-interval differences >50 ms and root-mean-square of successive NN-interval differences are measures of high-frequency (“beat-to-beat”) variation mediated principally by the vagus nerve. Frequency-domain analysis was performed on stationary RR-interval series by using autoregressive modeling, as previously described. Stationarity of the time series was tested by calculation of the mean and variance of the first and last 128 beats of each recording period to verify a difference of <10% in the values for each time series. The mean was subtracted from each point in the RR-interval series, and power spectral analysis was performed with Burg’s algorithm. The power of each underlying frequency was quantified by decomposing the total variability signal with the method of Zetterburg, thus enabling determination of spectral powers at low frequency (centered at ~0.1 Hz) and at high frequency (corresponding to the observed respiratory frequency) expressed in absolute and normalized units ([power/total power] × 100%)

All patients were flagged at entry through the National Health Service Central Registry, and notification was received of date and cause of death. Completed follow-up data were available for the cohort. Baseline demographic and clinical characteristics were compared with unpaired t test and Fisher’s exact test. Variables of markedly non-normal distribution (e.g., peak creatinine kinase) were appropriately transformed before analysis. The association of the selected HRV measurements and other variables with prognosis was assessed with univariate and multivariate Cox’s regression analyses. Survival curves were constructed by the Kaplan-Meier method. A 2-tailed p value <0.05 was considered statistically significant.

One hundred sixty-four subjects were recruited from among patients admitted to the coronary care units at 3 hospitals in the United Kingdom from 1998 to 2000. HRV analysis could not be performed in 27 patients after recruitment because of an excess ectopic beats or poor-quality electrocardiographic data in the samples collected. Subjects in whom HRV analysis could not be performed were less likely to smoke (19 vs 20% nonsmokers, p = 0.05) and had higher peak levels of creatinine kinase (2,591 ± 420 vs 1,821 ± 119 U/L, p = 0.02), but there were no other differences from the group in whom HRV was analyzed. Over a median follow-up of 32 months (range 25 to 50), 21 subjects (13%) died of cardiovascular disease, and 2 subjects were in the group whose HRV analysis could not be performed. Therefore, HRV data were available for 137 subjects, 19 of whom had died by the census date.

Baseline demographic characteristics are presented according to follow-up status in Table 1. Subjects who died were older, had a higher rate of hypertension, a lower body mass index, and lower left ventricular ejection fraction than did those who survived. Clinical characteristics of the index event are presented in Table 2. Most subjects presented with cardiac disease for the first time and received thrombolysis for acute infarction (87%). Most of those recruited into the
This study provides evidence that decreases in time-domain (mean NN interval and SD of NN-interval values) and frequency-domain (total power) indexes of HRV assessed by short-term recordings carry prognostic significance after AMI. Decreased HRV was associated with a threefold increase in risk of cardiac death on univariate analysis. The predictive value of HRV that had been assessed using short-term recordings was maintained despite performance of HRV assessment at an early stage after AMI.

Previous studies of the predictive value of short-term recordings of HRV have been largely restricted to retrospective analysis of clean periods extracted from longer 24-hour monitors. Malik and Camm\(^7\) compared the predictive value of 1-hour segments of 24-hour recordings with that of a complete 24-hour recording.

### TABLE 4 Univariate Cox’s Regression Analysis Comparing Survival Rate, Heart Rate Variability, and Baseline Variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% CI)</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>1.06/yr (1.01-1.10/yr)</td>
<td>0.008†</td>
</tr>
<tr>
<td>Women</td>
<td>0.45 (~0.19-1.06)</td>
<td>0.07²</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>0.82/unit (0.69-0.98)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Log10 (peak creatine kinase)</td>
<td>1.23 (0.73-2.07)</td>
<td>0.44</td>
</tr>
<tr>
<td>Anterior wall AMI</td>
<td>1.97 (0.79-4.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (&lt;35%)</td>
<td>9.9 (3.4-28.4)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Lowest quartile NN interval</td>
<td>3.8 (1.5-9.3)</td>
<td>0.004¹</td>
</tr>
<tr>
<td>Lowest quartile SDNN</td>
<td>3.1 (1.2-7.5)</td>
<td>0.015*</td>
</tr>
<tr>
<td>Lowest quartile rMSSD</td>
<td>1.8 (0.6-4.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Lowest quartile low frequency (nu)</td>
<td>0.61 (0.18-2.14)</td>
<td>0.44</td>
</tr>
<tr>
<td>Lowest quartile high frequency (nu)</td>
<td>1.8 (0.7-4.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Lowest quartile total power</td>
<td>2.8 (1.1-7.3)</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

†p < 0.05

¹p < 0.01

95% CI = 95% confidence interval; other abbreviations as in Table 3.

In 20 subjects who had serious cardiac events and 20 subjects who had no complication at 6 months. The 1-hour HRV recordings were capable of stratifying subjects according to increased risk, but the level of risk attributable changed according to the time of the hour taken for each patient. Bigger et al\(^8\) reported that spectral HRV from recording periods lasting from 2 to 15 minutes randomly selected from 24-hour Holter electrocardiograms predicted mortality rate after AMI. In these 2 studies, the predictive power of the shorter recordings was lower than that of the longer recordings. This finding was repeated by Fei et al\(^3\) who compared the predictive value of SD of NN-interval values taken from 5-minute segments with that of the HRV index taken from the same 24-hour recordings. Two other recent small studies have examined the prognostic utility of short-term HRV assessment after AMI. Vaage-Nilsen et al\(^9\) found that the SD of NN-interval values <30 ms from a 5-minute period of HRV assessment selected from a 48-hour Holter monitor recorded 1 week after AMI, age >60 years, and Holter evidence of ongoing myocardial ischemia were independent predictors of mortality rate in a group of 54 subjects followed for 9 years. In a study by Kautzner et al\(^10\) of 48 survivors of acute AMI, the SD of NN-interval values measured during a 30-minute recording 5 days after AMI was lower in 5 patients who died than in the remaining survivors at 1 year. Our findings are consistent with results from these studies in demonstrating the prognostic utility of short-term HRV assessment after AMI. The univariate relative risk identified in our study for low-quartile mean NN interval, SD of NN-interval values, and total power is of lower magnitude than that found by others who used full 24-hour recordings.\(^1\) Other studies that assessed short-term recordings are consistent in demonstrating a lower absolute level of risk compared with long-term recordings, although independent prognostic significance is maintained.\(^3,7\) Short-term recordings therefore remain adequate as a screening tool to identify high-risk subjects soon after infarction.

Short-term HRV assessment has several advantages over assessment based on 24-hour Holter elec-
trocardiographic monitoring. First, practical advantages include the ability to study more patients over a shorter duration. This decreases the significant amount of complicated monitoring and analytic equipment required to provide 24-hour Holter recordings in all patients after AMI. Second, theoretical advantages exist in providing “cleaner” short-term assessment of HRV after AMI. HRV is mainly a reflection of the influence of the autonomic nervous system on the sinus node of the heart. Heart rate alters with many of the changes in demand on the cardiovascular system that are related to changes in respiration, posture, and physical or mental activity. These changes are induced by the control systems that coordinate the total pattern of activity in the patient. Ideally, some information should be available on this total pattern of activity before HRV can be interpreted appropriately. However, total activity is likely to be highly variable across patients studied over 24 hours at different times after AMI (24-hour monitors have been applied from discharge, from 5 days after admission, and ≤4 weeks after discharge).1,2,8,12 Short-term recordings enable studies to be performed under more controlled, static conditions. This in turn should decrease the confounding effects of other activities on comparisons of intra- and interindividual results.13-16