Cardiac parasympathetic activity during the early hours of acute myocardial infarction

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SUMMARY Cardiac parasympathetic activity was assessed in 21 patients during the first 24 hours of acute myocardial infarction by measuring abrupt beat by beat changes in RR interval, which are expressed as “RR counts”. Eleven patients had inferior wall infarction and 10 had anterior wall myocardial infarction. The whole recording period was analysed in 11 patients (five inferior and six anterior), and intermittent hourly periods were analysed in all 21 subjects. Mean RR counts were significantly lower in patients with anterior than inferior infarction, and below the normal range. Although mean heart rates were faster in the group with anterior infarction, there was a dissociation between RR counts and mean heart rate that was consistent with RR interval variability being an independent measure of parasympathetic activity.

This study indicates that cardiac parasympathetic activity during acute myocardial infarction can be simply and reliably assessed from continuous electrocardiographic recordings, and it showed significantly lower cardiac parasympathetic activity in patients with anterior infarction.

Autonomic disturbances may be detected early after acute myocardial infarction in man. These vary from patient to patient with either apparent sympathetic or parasympathetic effects predominating at any one time, or both occurring concurrently, particularly during the first few hours. The balance of autonomic activity during this period may be important in determining the extent of subsequent myocardial ischaemic injury and the vulnerability to ventricular fibrillation. In general, patients with inferior myocardial infarction more commonly develop bradycardia and transient hypotension, while those with anterior myocardial infarction may develop a faster heart rate.

Measurement of sympathetic and parasympathetic activity in man after a myocardial infarction poses some difficulties. Heart rate changes alone are insufficiently precise because they reflect not only the overall balance of autonomic activity but also hormonal and other influences. Pharmacological intervention studies are not practicable because the drugs given may alter other reflex responses and make interpretation difficult. Other possible techniques are either invasive or cumbersome.

Recently we described a method for measuring cardiac parasympathetic activity continuously from ambulatory electrocardiographic recordings by analysing abrupt beat by beat changes in RR interval. The aim of the present study was to apply this technique to the assessment of cardiac parasympathetic activity during the early hours of acute myocardial infarction. We studied patients with acute inferior and acute anterior wall myocardial infarction for up to 24 hours after the onset of chest pain.

Patients and methods

Patients We studied 21 patients (16 men and five women, aged 38–69 years) who were admitted to hospital within the first few hours of onset of symptoms of acute myocardial infarction (table 1). The diagnosis of acute myocardial infarction was confirmed by the electrocardiographic changes of Q wave infarction and standard serum creatine kinase activity above the normal range for our laboratory. No patient with a history of diabetes, previous treatment with a B adrenoceptor blocking drug or hypotensive agent, or known previous myocardial infarction was included. Eleven patients had electrocardiographic evidence of inferior wall infarction (inferior group) and 10 of anterior wall infarction (anterior group).
Table 1  Clinical details of patients with acute myocardial infarction (mean (SEM or range )

<table>
<thead>
<tr>
<th>Site of infarction</th>
<th>Inferior</th>
<th>Anterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56-7 (38-69)</td>
<td>59.5 (51-65)</td>
</tr>
<tr>
<td>Peak creatine kinase (units/I)</td>
<td>1748 (213)</td>
<td>2116 (364)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>137 (10)</td>
<td>140 (9)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>86 (6)</td>
<td>88 (5)</td>
</tr>
<tr>
<td>Time of admission after onset of symptoms (h)</td>
<td>4.5 (3-6)</td>
<td>4.8 (3-9)</td>
</tr>
<tr>
<td>Number of admissions between;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0800-1959 h</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>2000-0759 h</td>
<td>4</td>
<td>5</td>
</tr>
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Their results were compared with 24 hour electrocardiographic tape recordings from 58 normal ambulant men aged 18-65 years who had no known disease and were not taking regular medications. Twenty four hour electrocardiographic tapes were also recorded from six young men aged 18-27 years who were confined to bed after trauma with leg or pelvic fractures. The tapes were recorded several days after operation when they were fully conscious.

Electrocardiographic Recording
Electrocardiographic signals were recorded on magnetic tape from routine precordial monitoring electrodes from admission until 24 hours after the onset of pain. A digital recording clock provided a time track on a second channel of the tape recorder. The times of clinical events such as recurrence of chest pain, drug administration, and patient activities were recorded at the bedside.

Analysis of Variation in RR Interval
Continuous Assessment
The 24 hour electrocardiographic tapes were analysed for the presence of ventricular extrasystoles by a pathfinder arrhythmia analyser (Reynolds Medical). Ten patients with more than five extrasystole beats per hour were excluded from this part of the study. Recordings from the remaining patients (five patients from the inferior group and six patients from the anterior group (all men)) were then analysed as previously described. We counted the number of times successive RR intervals differed by more than 50 ms from the preceding RR interval. The electrocardiographic signals were played at 60 times real speed into a QRS wave detector which generated timing pulses. These were passed to a specially designed microcomputer which measured each RR interval. Hourly counts of mean RR interval and RR interval differences in excess of 50 ms were derived and have been called “RR counts (G)”. For the purpose of this analysis only those counts where the RR interval lengthened were used, because previous work has indicated that there are no significant differences between numbers of lengthened and shortened RR counts. The computer was programmed to exclude changes in RR interval that exceeded 300 ms to avoid false counts caused by missed beats and most ectopic complexes. A running oscilloscopic trend plot of successive RR intervals and a display of the electrocardiographic signal being processed allowed the operator to monitor signal quality, adjust trigger threshold to optimise the rejection of noise and artefact, and to identify arrhythmic episodes.

Intermittent Assessment
To obtain information on the patients excluded from the continuous assessment because of ectopic activity, additional analyses of intermittent short periods were performed in all 21 subjects. This was done by replaying QRS trigger pulses through a BBC B microprocessor programmed to measure successive RR intervals. Sampling periods of 400 beats were selected every hour from the tape recorded electrocardiographic signals, avoiding periods with considerable numbers of extrasystoles. Trend plots of RR intervals and beat by beat RR interval differences were displayed for each sampling period (fig 1). Coupling intervals and compensatory pauses associated with extrasystoles were identified by comparison with a simultaneously recorded electrocardiogram and excluded from further analysis. A score of “RR counts (I)” was derived by calculating the number of times within the 400 beat sequence that successive RR interval differences exceeded 50 ms during sinus rhythm. In those patients in whom, because of extrasystoles, less than 400 sinus beats were used to measure “RR counts (I)”, the results were expressed as a proportion of 400 beats. The mean (SD) number of sinus beats used in these patients was 379 (27).

Statistical Analysis
Statistical comparisons between groups were performed by a Wilcoxon rank sum test. A Wilcoxon signed rank test was used to test for significant trends.

Results
Clinical Presentation
There were no significant differences detected between patients with inferior and anterior wall myocardial infarction in age, sex, arterial blood pressure eight hours after onset of symptoms, or peak activity of serum creatine kinase (table 1). All patients received opiates either before or on admission to hospital. Additional opiates were adminis-
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Fig 1 Individual RR interval differences and RR intervals in a patient (a) before, (b) during, and (c) 90 minutes after 0·6 mg intravenous atropine.

tered to 10 patients (five with inferior and five with anterior infarction) for recurrence of chest pain. There were no clear patterns in timing of chest pain or opiate administration, although statistical analysis was not possible. Five patients (three inferior and two anterior infarcts) were treated with intravenous diuretics. Symptoms and signs possibly attributable to vagal activity such as nausea, vomiting, and bradycardias, were commoner in patients with inferior myocardial infarction (n = 7); than in those with anterior myocardial infarction (n = 2); and those that could be attributable to increased sympathetic activity, such as sweating and peripheral vasoconstriction, occurred in two of the patients with anterior infarction.

ANALYSIS OF VARIATION IN RR INTERVAL

RR interval

Table 2 shows the results of RR interval analysis. Patients with anterior myocardial infarction had shorter mean RR intervals (faster heart rates) than patients with inferior infarction on both continuous and intermittent assessments over the recording period. In the smaller number of patients with continuous assessment mean RR intervals did not change significantly in either the inferior or anterior groups between the early (4–9 hours) and late (19–24 hours) periods of recording. In the larger number of patients who had intermittent analysis the mean RR interval lengthened significantly (p < 0·01) in the inferior group towards the end of the 24 hour period.

<table>
<thead>
<tr>
<th>RR interval variation</th>
<th>Mean RR interval (ms)</th>
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<tbody>
<tr>
<td>Over whole 4–24 h period</td>
<td>Early (4–9 h)</td>
</tr>
<tr>
<td>Inferior (n = 11)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Anterior (n = 10)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Difference</td>
<td>p &lt; 0·02</td>
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Intermittent analysis: RR counts (I) (mean counts/400 beats)

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<th>Continuous analysis: RR counts (C) (mean hourly counts)</th>
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<tr>
<td>Inferior (n = 5)</td>
<td>60 (39)</td>
</tr>
<tr>
<td>Anterior (n = 6)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Difference</td>
<td>p &lt; 0·01</td>
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counts (I) in fig 2 show that with anterior infarction
counts are low throughout, whereas with inferior
infarction counts are higher and significantly so at
most points during the 24 hour recording period.
Figure 3 shows the value for RR counts (C) obtained
in 58 ambulant men, together with counts for six
young men who were in bed recovering from trauma
but who were otherwise normal. When RR counts
(C) in the myocardial infarction patients were com-
pared with these normal values (fig 4), those with
inferior myocardial infarction fell within the normal
range whereas those with anterior myocardial in-
farction had reduced counts.

Effect of atropine
The abrupt variation in RR interval was probably
mediated by the vagus nerve. This is suggested by its
disappearance after intravenous atropine. Figure 1
shows the effect of atropine in a patient with acute
inferior myocardial infarction. Before atropine, the
RR interval was around 1200 ms and there was
considerable RR interval variation. After 0.6 mg
intravenous atropine the mean RR interval shortened
to 600 ms and RR interval variation was abolished.
One and a half hours later there was again consider-
able RR interval variation although the mean RR
interval itself remained unchanged at 600 ms.

Discussion
We studied the technique of non-invasive assessment
of cardiac parasympathetic activity from abrupt beat
by beat RR interval changes during the early hours of
acute myocardial infarction. Such RR interval
changes were less frequent in patients with anterior
than inferior myocardial infarction independent of
underlying heart rate. Individual RR interval pat-
terns were, however, variable from patient to patient.
In some, the RR interval changed irregularly
throughout the period of recording; in others, the
trace of RR interval was smooth and regular for
prolonged periods, suggesting consistently low or
absent cardiac efferent vagal activity throughout the
period of recording; in yet others, regular and
irregular periods were present at variable times.

Previous work in humans has shown that abrupt
changes in RR interval such as those occurring at the
start of muscular exercise, standing up and lying
down, are mediated by the vagus nerve. Variation
in RR interval is abolished in animals by cutting the
vagus nerve, and also in man by giving atropine but
is unaffected by β adrenoceptor blockade. Patients
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with transplanted hearts and diabetic patients with evidence from the cardiovascular reflex of vagal damage have almost no variation in RR interval. In addition, animal studies suggest that the degree of respiratory sinus arrhythmia is directly related to vagal efferent traffic. Thus we feel that RR interval variation, as assessed by our method of measuring RR interval differences, provides a useful index of cardiac parasympathetic activity, which can be recorded and measured over prolonged periods. The parasympathetic mediation of variation in RR interval is further suggested by our observations with atropine. The return of variation in RR interval in our patient with myocardial infarction 90 minutes after he was given atropine was not accompanied by a slowing in heart rate, which suggests that control of variation in heart rate might be mediated separately from that of prevailing heart rate. While the exact relation between prevailing heart rate and heart rate variation is complex, we have previously shown in healthy people and diabetic patients that variation in heart rate does not parallel prevailing heart rate and that some people with high heart rates also had high heart rate variation.

No obvious factors seemed to determine the episodic and irregular timing of these presumed parasympathetically mediated changes. They probably reflect changes in automatic reflex responses, which are influenced by numerous factors including central stimuli and multiple cardiac, respiratory, and baroreceptor afferent stimuli. Asynchrony of vagal afferent and sinoatrial nodal pacemaker activity may also contribute. Responses may be further modulated by intracardiac sympathetic-parasympathetic interactions involving nerve terminals, postsynaptic, and cellular mechanisms and sino-atrial chromaffin cells.

The lower counts in our patients with anterior infarction cannot be attributed to bed rest alone because healthy people confined to bed for other reasons had counts within our expected range for healthy ambulant people (fig 3). Furthermore, in so far as can be judged from this small series, differences in counts were not accounted for by diurnal change, the drugs administered, or clinical features. A possible mechanism for reduced variation in RR interval during anterior infarction is the higher density of parasympathetic innervation to the posterior and inferior left ventricular walls and known preponderance of parasympathetically mediated reflex activity during ischaemia or infarction of these regions. Such dependence of autonomic responses upon site of infarction was shown experimentally after acute coronary occlusions in the cat or dog. Differential responses attributable to the preferential location of vagal afferents in the inferior and posteroinferior regions of the left ventricular wall can mediate depressor reflexes during the periods of acute ischaemic injury very similar to those seen in humans. Associated infarction of the right ventricle, which may accompany acute infarction of the inferior left ventricular wall, can stimulate right atrial and ventricular cardiac receptors and initiate a vagally mediated cardioinhibitory Bezold-Jarisch reflex. An alternative possibility is that differences in "counts" between patients with anterior and inferior infarction may result from enhanced vagal responses after ischaemia of the sinoatrial node associated with occlusion of the right coronary artery.

In conclusion, this study showed that differing degrees of cardiac parasympathetic activity can occur in individual patients during the first 24 hours after onset of symptoms of acute myocardial infarction that may not be manifest by heart rate changes alone, with significantly lower activity in anterior infarction than in inferior infarction. These observations raise the possibility of predicting neurogenically triggered serious cardiac arrhythmias. Transient autonomic imbalances are associated with enhanced electrical instability of the heart and there is evidence to suggest that transient changes in parasympathetic activity may precede episodes of ventricular fibrillation. Assessment of heart rate variability may also be of prognostic value in the months after acute myocardial infarction.

We thank Dr R J Prescott and Mrs C C A McIntyre for statistical advice. This study was supported by the British Heart Foundation and the Wellcome Trust.

References