Cardiac parasympathetic activity in severe uncomplicated coronary artery disease

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Abstract

Background—Previous studies have suggested that coronary artery disease is independently associated with reduced cardiac parasympathetic activity, and that this is important in its pathophysiology. These studies included many patients with complications that might be responsible for the reported autonomic abnormalities.

Objective—To measure cardiac parasympathetic activity in patients with uncomplicated coronary artery disease.

Patients and methods—44 patients of mean (SD) age 56 (8) with severe uncomplicated coronary artery disease (symptoms uncontrolled on maximal medical treatment; > 70% coronary stenosis at angiography; normal ejection fraction; no evidence of previous infarction, diabetes, or hypertension). Heart rate variability was measured from 24 hour ambulatory electrocardiograms by counting the number of times successive RR intervals exceeded the preceding RR interval by > 50 ms, a previously validated sensitive and specific index of cardiac parasympathetic activity.

Results—Mean (range) of counts were: waking 112 (range 6–501)/h, sleeping 198 (0–812)/h, and total 3912 (151–14 454)/24 h. These mean results were unremarkable, and < 10% of patients fell below the lower 95% confidence interval for waking, sleeping, or total 24 hour counts in normal people. There was no relation between the severity of coronary artery disease or the use of concurrent antianginal drug treatment and cardiac parasympathetic activity.

Conclusion—In contrast with previous reports no evidence of a specific independent association between coronary artery disease and reduced cardiac parasympathetic activity was found. The results of previous studies may reflect the inclusion of patients with complications and not the direct effect of coronary artery disease itself.

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The autonomic nervous system plays an important part in the pathophysiology of patients with ischaemic heart disease. Acute myocardial infarction and impaired left ventricular function due to ischaemic heart disease are associated with abnormal autonomic function. Hypertension, which commonly occurs in patients with coronary artery disease, is also independently associated with autonomic dysfunction.

Several studies suggest that coronary artery disease may be independently associated with a specific impairment of cardiac parasympathetic activity that occurs without sympathetic dysfunction. Also, it has been suggested that the magnitude of parasympathetic dysfunction may be proportional to the severity of coronary artery disease, with the maximal impairment occurring in patients with three vessel disease. All of these studies, however, contained a substantial proportion of patients with complications relating to their coronary artery disease or associated disorders such as diabetes or hypertension. The abnormalities detected may therefore have been due predominantly to the effect of these other factors and not to an independent effect of coronary artery disease.

The principal aim of our study was to examine the hypothesis that coronary artery disease is associated with a specific independent impairment of cardiac parasympathetic activity by studying patients with symptomatic severe but uncomplicated coronary artery disease. We used our time domain technique of heart rate variability analysis. We also investigated the effect of severity of coronary artery disease and concurrent administration of antianginal drug treatment on cardiac parasympathetic activity.

Patients and methods

PATIENT SELECTION

Ambulant outpatients with severe angina pectoris were selected for our study. All patients had symptoms of at least three months duration that were uncontrolled despite optimal medical treatment (New York Heart Association functional class III or IV due to disabling angina). As part of their clinical assessment all patients underwent cardiac catheterisation with a view to possible myocardial revascularisation. The presence of exercise induced cardiac ischaemia was confirmed where possible by Bruce protocol treadmill exercise tests.

Patients with previously documented myocardial infarction, valvar heart disease, hypertension, diabetes mellitus, renal failure, a history of excess alcohol consumption, clinical evidence of autonomic neuropathy, or clinical signs of heart failure were excluded.
Resting 12 lead electrocardiograms were obtained and patients with pathological Q waves, atrial arrhythmias, or conduction defects were also excluded. The only drugs allowed in the study were \( \beta \) blockers, calcium antagonists, or long acting nitrates prescribed for the treatment of angina. No changes were made to drug treatment during the course of the study.

**ASSESSMENT OF ANGIOGRAPHIC SEVERITY OF CORONARY ARTERY DISEASE AND LEFT VENTRICULAR FUNCTION**

Left sided cardiac catheterisation and selective coronary arteriography were performed with a standard Judkins technique. The angiograms were reviewed by a consultant cardiac radiologist (JR) who was unaware of the results of the heart rate variability analysis. The coronary arteries and their branches were divided into 15 segments, according to the Ad Hoc Committee on Grading of Coronary Arterial Disease of the American Heart Association, and only the luminal narrowing in segments 1–3 for the right coronary artery, segments 6 and 7 for the left anterior descending artery, segments 11 and 12 for the circumflex artery, and segment 5 for the left main coronary artery were used in the final assessment. By confining the analysis to these segments alone, only patients with significant obstructive lesions in the main epicardial coronary arteries were included. Stenoses were considered to be significant if a > 70% luminal narrowing was present.

Left ventricular end diastolic pressure was measured during catheterisation and the ejection fraction was calculated from the cineangiograms by the area-length method.

**ANALYSIS OF HEART RATE VARIABILITY**

Twenty four hour electrocardiograms were obtained with a miniature tape recorder (Tracker, Reynolds Medical) during normal ambulant out of hospital activities within seven days of cardiac catheterisation. Each patient kept a diary and noted times of going to bed and rising.

Tapes were replayed through a Pathfinder arrhythmia analyser (Reynolds Medical) at 120 times the original recording speed. Heart rate variability was then assessed by a time domain method, that is valid even in the presence of frequent extrasystolic beats. Briefly each RR interval is measured and successive beat by beat RR interval differences calculated. Each time an RR interval exceeds the preceding RR interval by more than 50 ms a count is registered and a cumulative total is built up. The results are presented as total 24 h RR counts, mean hourly waking and sleeping RR counts, and mean waking and sleeping heart rates. We have previously discussed in detail the theoretical basis of our method, which is a reproducible, sensitive, and specific index of cardiac parasympathetic activity. Counts in study patients have been compared with age related 95% confidence intervals (95% CIs) obtained from a previous study of 77 normal people.

**STATISTICAL ANALYSIS**

As RR counts are not normally distributed, a logarithmic transformation was applied and standard parametric statistical techniques used on the transformed values. Count rates are expressed as geometric mean and range. All other measures are expressed as arithmetic mean (SD). Differences between groups were evaluated by analysis of variance and an unpaired Student’s \( t \) test.

**Results**

**PATIENTS CHARACTERISTICS**

Fifty five patients with coronary artery disease were studied. Tapes from 11 patients were excluded because of frequent supraventricular extrasystoles, or technical problems with tape quality. Forty four patients with a mean (SD) age 56 (8) were therefore included in our study, and the table shows their characteristics. There were no significant differences in baseline characteristics between the 44 patients included (35 men, nine women) and the 11 excluded (eight men, three women).

All patients were in sinus rhythm throughout the recordings. Bruce protocol exercise tests were carried out in 39 of the 44 patients included in the study and were positive (> 2 mm ST depression) at a mean (SD) time of 291 (120) seconds. Exercise tests were not carried out in the remaining five patients due to the severity of their angina.

Thirty seven of the patients were treated with \( \beta \) blockers, 33 with calcium antagonists, and 20 with long acting nitrates.

**CARDIAC CATHETERISATION**

All patients had severe coronary artery disease with significant stenoses in at least one main coronary artery; 19 patients had three vessel

<table>
<thead>
<tr>
<th>Patient characteristics (mean (SD) or range)</th>
<th>1VD</th>
<th>2VD</th>
<th>3VD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>35/9</td>
<td>7/3</td>
<td>12/3</td>
</tr>
<tr>
<td>No</td>
<td>44</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56/8</td>
<td>56/8</td>
<td>56/6</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>67/7</td>
<td>66/6</td>
<td>68/7</td>
</tr>
<tr>
<td>End diastolic pressure (mm Hg)</td>
<td>13/4</td>
<td>13/4</td>
<td>14/4</td>
</tr>
<tr>
<td>Time to 2 mm ST depression (s)</td>
<td>291 (120)</td>
<td>339 (94)</td>
<td>272 (129)</td>
</tr>
<tr>
<td>Waking heart rate (beats/min)</td>
<td>64/7</td>
<td>67/7</td>
<td>62/9</td>
</tr>
<tr>
<td>Sleeping heart rate (beats/min)</td>
<td>55/8</td>
<td>56/9</td>
<td>53/7</td>
</tr>
<tr>
<td>Total RR count/24 h</td>
<td>3912 (151-14454)</td>
<td>6109 (275-14454)</td>
<td>3206 (812-7413)</td>
</tr>
<tr>
<td>Waking RR count/h</td>
<td>112 (6-501)</td>
<td>171 (14-475)</td>
<td>80 (20-275)</td>
</tr>
<tr>
<td>Sleeping RR count/h</td>
<td>198 (0-812)</td>
<td>271 (0-812)</td>
<td>178 (56-562)</td>
</tr>
</tbody>
</table>

VD, vessel disease.
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disease, 15 had two vessel disease, and 10 had single vessel disease. Left ventricular function was normal in all patients, with a mean (SD) ejection fraction of 67 (7). No patient had an area of segmental wall motion abnormality consistent with a previous myocardial infarction. Left ventricular end diastolic pressure was normal in all patients. There were no significant differences in patient characteristics between the groups with one, two or three vessel disease (table).

HEART RATE VARIABILITY ANALYSIS
Group mean total 24 hour RR counts (3912), mean hourly waking (112), and mean hourly sleeping (198) RR counts fell well within the 95% CIs for counts in normal people. Figure 1 shows the total 24 hour RR counts for the individual patients plotted against age; 39 of the study patients fell within the age related normal 95% CI. Only three patients (7% of the group) fell below the lower 95% CI. Figures 2 and 3 shows the mean hourly waking and sleeping RR counts plotted against age; a similar pattern is present with < 10% of patients falling below the lower 95% CIs.

Mean (SD) waking (64 (8) beats/min) and sleeping (55 (8) beats/min) heart rates were unremarkable. Figure 4 shows the effect of the different antianginal drug treatments on total 24 hour counts. There were no significant differences in group mean total 24 hour counts when patients treated with β blockers were compared with those not receiving such treatment (p = 0.17). Similarly, calcium antagonists and nitrates had no significant effect on heart rate variability (p = 0.60 for the difference in mean counts in patients treated or not treated with calcium antagonists, p = 0.15 for difference in mean counts in patients treated or not treated with nitrates).

Figure 5 shows the total 24 hour RR counts plotted according to the distribution of coronary artery disease. There were no significant differences in total 24 hour counts in patients with one, two or three vessel disease (F = 1.35, p = 0.271).

Figure 1 Total RR counts/24 h plotted against age in 44 patients with severe coronary artery disease. Solid lines represent 95% CI for counts in normal people. Only 3 (7%) of the patients with coronary artery disease fall below the lower 95% CI and thus have reduced heart rate variability.

Figure 2 Mean waking RR counts/h plotted against age in 44 patients with severe coronary artery disease. Solid lines represent 95% CI for counts in normal people. Only 4 (9%) of the patients with coronary artery disease fall below the 95% CI and thus have reduced heart rate variability.

Figure 3 Mean sleeping RR counts/h plotted against age in 44 patients with severe coronary artery disease. Solid lines represent 95% CI for counts in normal people. Only 3 (7%) of the patients with coronary artery disease fall below the 95% CI and thus have reduced heart rate variability.

Figure 4 Total 24 hour RR counts/h plotted according to drug treatment in 44 patients with severe coronary artery disease. There are no significant differences in count rates as a result of treatment.
Discussion

We have examined the hypothesis that coronary artery disease is associated with a specific reduction in cardiac parasympathetic activity. We made no attempt to study sympathetic activity, as previous investigators have reported that such patients have no evidence of any sympathetic abnormality. Our results indicate that heart rate variability as measured by our technique, and thus by inference cardiac parasympathetic activity, is normal in nearly all such patients. This finding is at variance with previous reports. There are several reasons for this discrepancy.

Acute myocardial infarction is associated with autonomic dysfunction and parasympathetic impairment that can persist for several months. Left ventricular dysfunction, hypertension, and diabetes mellitus are also associated with significant parasympathetic impairment. Up to 50% of the patients included in previous studies had one or more of the above associated conditions, and the reported impairment of parasympathetic activity in such patients may be principally related to these factors and not to the presence of coronary artery disease. We have excluded patients with previous myocardial infarction, impaired left ventricular function, hypertension, or diabetes from our study.

We used a 70% luminal narrowing as our criterion for defining a coronary artery stenosis as significant, unlike previous investigators who have included patients with only 50% luminal narrowing. Also, almost half of our patients had three vessel disease. Our study patients therefore have more severe and widespread coronary artery disease than those included in previous investigations.

Critical reanalysis of previous studies with the benefit of current knowledge lends support to our findings. Hayano et al reported that coronary artery disease is associated with a "vagal dominant" impairment of cardiac autonomic function. Their patients with abnormal heart rate variability had a significantly reduced left ventricular ejection fraction. Although these authors state that heart rate variability was unaffected by left ventricular function, this is at variance with our findings or those of others. If their patients with impaired left ventricular function are excluded, most of their remaining patients fall within their own age related 95% CIs. Although the same authors reported a correlation between severity of coronary artery disease and the size of the reduction in heart rate variability, this is not supported by our study or other published work. This association may be due to the known presence of left ventricular impairment in the patients with multivessel disease. Airaksinen et al also reported impaired parasympathetic function in patients with coronary artery disease. If the analysis of their results is confined to patients free of segmental dyskinesia or akinesia, a group analogous to our own, three quarters of their patients have no evidence of parasympathetic dysfunction.

In common with other investigators, we continued antianginal drug treatment during our study. Although it might have been preferable to study our patients in a drug free state, we considered this to be unethical. Rich et al and Airaksinen et al reported considerable abnormalities of parasympathetic activity in patients with coronary artery disease who were receiving antianginal drug treatment, and our study design is similar apart from the exclusion of patients with complications known to be independently associated with autonomic abnormalities.

We have previously shown that our technique is sensitive enough to detect small drug induced changes in heart rate variability. The comparison of patients receiving different drug regimes (fig 4) enables us to draw some conclusions relating to the effect of antianginal drugs on cardiac parasympathetic activity. Calcium antagonists decrease sympathetically mediated components of heart rate variability but have no effect on parasympathetic activity, consistent with our results. The effect of chronic oral nitrate treatment on cardiac parasympathetic activity has not previously been investigated. As there was no significant change in count rates in treated patients, chronic oral nitrate treatment does not seem to affect cardiac parasympathetic activity.

Treatment with β adrenergic blocking drugs produced only a small non-significant change in total 24 hour counts in our study. Other investigators have reported variable effects of β blockers on parasympathetic activity. A limitation of the study of Hayano et al is that their patients had high dose β blockers (in a dose sufficient to produce total sympathetic blockade) given for short periods significantly increased 50 ms counts over 24 hours. In contrast, Counel et al found that low dose β blockers in the short-term decreased parasympathetically mediated components of heart rate variability in normal people and patients with heart failure and left ventricular hypertrophy. With a threshold of 6-25% to count beat to beat changes in RR intervals (a better index of parasympathetic activity when significant changes in heart rate occur between recordings) in a group of over 100 patients after infarction Molgaard et al were unable to
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show any significant effect of long-term (four weeks) \( \beta \) blockade on parasympathetic activity. This is consistent with the findings of Bennet et al and Pagani et al who found that both long-term oral (12 month) and intravenous \( \beta \) blockers had no effect on parasympathetic activity.\(^{24,25}\) Arousal level may also be important in modulating autonomic interactions. During most sleeping hours sympathetic activity is minimal.\(^{36}\) We have previously shown that parasympathetic activity during sleeping hours, measured by our technique, is unaffected by \( \beta \) blockade.\(^{7} \) The finding of normal sleeping counts provides additional supporting evidence that our results were unaffected by \( \beta \) blockers. The net effect of \( \beta \) blockers on parasympathetic activity depends on a complex interplay of many physiological factors. Our present finding that long-term treatment with \( \beta \) blockers has no effect on parasympathetic activity is consistent with previous work.

Autonomic function is normal before the onset of ischaemia.\(^{27,28}\) Acute ischaemic episodes are associated with short-term changes in heart rate variability\(^{39}\) that return to normal as the ischaemic episode resolves.\(^{38}\) This suggests that myocardial ischaemia, and not merely the presence of coronary artery disease, is associated with short-term reversible changes in autonomic function. Also, relief of critical coronary obstruction by coronary angioplasty does not affect cardiac autonomic function.\(^{31}\) The studies of Hayano et al\(^{29,30}\) were confined to the analysis of short-term series and their measurements could be considerably distorted by intermittent changes such as those due to episodic myocardial ischaemia. As our method of analysis of heart rate variability measures parasympathetic activity over prolonged periods, it is unlikely to be greatly influenced by short episodic fluctuations in activity such as those occurring during myocardial ischaemia. Methods of testing autonomic reflexes that rely on stressing the cardiovascular system, as used by Airaksinen et al,\(^{7}\) may themselves precipitate ischaemia. Abnormalities detected may thus be due to ischaemia alone, and cannot be confidently ascribed solely to the presence of coronary artery disease.

There are important clinical implications arising from our findings. Both Hayano et al\(^{30}\) and Airaksinen et al\(^{29,30}\) suggest that coronary artery disease is associated with a specific reduction of cardiac parasympathetic activity. Autonomic abnormalities increase the risk of ventricular arrhythmias\(^{52}\) and these authors postulate that reduced parasympathetic activity is an important mechanism of sudden death in such patients. Our study, as well as a critical reappraisal of the studies of Hayano et al\(^{30}\) and Airaksinen et al\(^{29,30}\) does not support this view. Hayano et al\(^{30}\) speculate that reduced cardiac parasympathetic activity predates the development of coronary artery disease, and is an independent risk factor contributing directly to the aetiology and progression of coronary atherosclerosis. The findings of our study render this hypothesis untenable.

Debate has recently centred around the relative contributions of coronary artery disease and left ventricular dysfunction to the reduced cardiac parasympathetic activity that occurs in patients with heart failure due to ischaemic heart disease.\(^{33}\) Our study shows that coronary artery disease is unlikely to contribute independently to autonomic dysfunction in heart failure. Where chronic heart failure accompanies coronary artery disease, any associated parasympathetic dysfunction is a result of left ventricular impairment alone.

In summary, we have used a time domain method of analysis of heart rate variability that is a sensitive and specific measure of cardiac parasympathetic activity to study ambulant outpatients with symptomatic and severe, but uncomplicated coronary artery disease. In contrast with previous studies most of our patients showed no evidence of reduced cardiac parasympathetic activity. Also, we found no evidence of a relation between the severity of coronary artery disease and cardiac parasympathetic activity. We have confirmed that calcium antagonists and chronic oral nitrate treatment do not affect parasympathetic activity.

In the absence of overt myocardial ischaemia or previous myocardial infarction, or left ventricular dysfunction, coronary artery disease is not an independent cause of reduced cardiac parasympathetic activity.
14 Ewing DJ, Neilson JMM, Shapiro CM, Stewart JA, Reid W. 24 Hour heart rate variability: effects of posture, sleep, and time of day in normal subjects and comparison with bedside autonomic function tests in diabetic patients. Br Heart J 1991;65:239-44.


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