Spectral analysis of heart rate variability before and during episodes of nocturnal ischaemia in patients with extensive coronary artery disease


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Spectral analysis of heart rate variability was used to assess autonomic nervous system activity associated with episodes of nocturnal myocardial ischaemia in 32 patients (20 men, age 58 ± 9 years) with extensive coronary artery disease. Twenty-four hour Holter tape recordings were analysed and spectral indexes of heart rate variability were computed by fast Fourier analysis on 2 min segments covering the period from 10 min before to 10 min after each nocturnal ischaemic episode, defined as ST segment depression ≥1 mm lasting at least 4 min. Spectral power was measured at low frequencies (LF: 0.06–0.10 Hz) and high frequencies (HF: 0.15–0.40 Hz) and the ratio LF/HF was calculated.

Results A total of 30 episodes of nocturnal ischaemia were analysed. High frequency spectral power showed a clear decrease during the 10 min before the onset of ischaemia, remained steady until the end of the episode, and returned to normal by 6 min after. Low frequency spectral power fluctuated throughout the ischaemic episodes with no clear pattern of variation. The low/high frequency ratio reflected mainly the changes in high frequency.

Conclusions Sympathetic predominance due to para-sympathetic withdrawal is the principal change in autonomic nervous system activity associated with episodes of nocturnal ischaemia.

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Key Words: Nocturnal ischaemia, autonomic nervous system, heart rate variability.

Introduction

In recent years analysis of heart rate variability has been shown to be a reliable non-invasive technique for the quantitative analysis of the activity of the two components of the autonomic nervous system. While this method has produced many valuable findings from the study of post-infarction patients, its application to the study of changes in the autonomic nervous system during episodes of myocardial ischaemia has been limited, particularly where nocturnal ischaemia is concerned.

In this study we used spectral analysis in order to study the changes in heart rate variability before, during and immediately after nocturnal ischaemic episodes in patients with extensive coronary artery disease but no history of myocardial infarction and good left ventricular function. The aim of the study was to contribute to a better understanding of the pathophysiology of nocturnal ischaemic episodes by means of a partial analysis of the activity and roles of the two components of the autonomic nervous system.

Patients and methods

Patient population

The study population consisted of 32 patients (20 men, mean age 58 ± 9 years). These were selected from a larger group of patients with symptomatic ischaemic heart disease who were treated in our Clinic during one calendar year. The inclusion criteria were as follows: (1) typical angina pectoris without appreciable change in symptoms during the previous 6 months; (2) positive exercise test result with ≥1 mm ST segment depression; (3) extensive coronary artery disease, defined as angiographically proven 3-vessel disease.

Exclusion criteria were: myocardial infarction within the previous 6 months, second, or third-degree atrioventricular conduction disturbances, atrial fibrillation, frequent (>10/min) ventricular extrasystoles, sinus node disease, arterial hypertension, permanent ST
changes on the ECG, permanent cardiac pacemaker, ejection fraction <45%.

All patients underwent an initial ECG recording during hyperventilation and in various postures (supine, sitting, standing) to check for the existence of artefactual ST segment deviation. Any such changes resulted in the patient’s exclusion from the study. All patients gave their informed, written consent to the study.

**Ambulatory electrocardiographic monitoring**

All patients underwent 3-lead ambulatory electrocardiographic monitoring for 24 h (8500 T, Marquette Electronics, Inc., U.S.A.). All antianginal medication was discontinued 72 h before the start of the monitoring. Patients were instructed to use only sublingual nitrates if they suffered symptoms of angina and to note in a log the time they got up in the morning, their daily activities and what time they went to bed. They were also told not to get up during the night unless absolutely necessary and to make a note of the exact time in any such case.

The recordings were analysed using a 8000 Laser Holter Analyser system (Marquette Electronics, Inc., U.S.A.), which is able to classify QRS complexes and to reject any technical errors or interference, as well as systoles which do not originate in the sinus node. A transient depression of the ST segment, horizontal or downsloping, ≥1 mm measured 80 ms after the J point, was considered as an ischaemic episode. For each 24-h recording we determined the following: the start and end of each ischaemic episode, the duration, the number of ischaemic episodes and the total duration of ischaemia. Also, the heart rate was measured 10 min and 5 min before and at the onset of ischaemia, at the moment of maximum ST depression, at the end of the ischaemic episode and 5 and 10 min later. For the purposes of this study, we selected the ischaemic episodes which satisfied the following criteria: (a) They occurred during the night, i.e. between going to bed and rising in the morning. (b) They were unrelated to any patient activity, i.e. rising during the night for any reason. (c) They lasted more than 4 min. (d) They were preceded and followed by 10 min without signs of ischaemia.

All recordings were analysed by two investigators and only the episodes on which both agreed were included for analysis.

**Analysis of heart rate variability**

The same Laser Holter Analyser was used to calculate the spectral indexes of heart rate, using Fourier analysis, for each 2 min interval of the recording and a Hanning window to minimize spectral leakage. The spectral power was evaluated quantitatively and expressed in ln(ms²/Hz), where ln represents the natural logarithm of the quotient, for the following frequency bands: low frequency (LF), 0-06-0-10 Hz, an indicator of sympathetic tone[2,3] and high frequency, 0-15-0-40 Hz, reflecting parasympathetic activity[2,3,17]. The ratio LF/HF was calculated as a suitable index for the interaction of the sympathetic and parasympathetic systems[1,18].

**Statistical analysis**

The values of LF, HF and the LF/HF ratio were recorded for the following time intervals: five 2-min intervals immediately before the onset of ischaemia (P[—5] to P[—1]); five 2-min intervals immediately after the end of ischaemia (P[+1] to P[+5]); three 2-min intervals during the ischaemic episode, P[s] at the start, P[e] at the end and P[max] at the time of maximum ST depression. Seven values of heart rate were also recorded: two before (10 and 5 min), two after (5 and 10 min) and three during the ischaemic episode (start, max ST and end).

The fact that the same variables (heart rate, LF, HF) were measured during several time intervals for each subject produced a typical repeated measures design. The most appropriate method for analysing such data is the Repeated Measures Analysis of Variance (RM ANOVA) multivariate extension of the paired t-test[19,20]. Assuming certain regularity conditions hold[21], the multivariate approach is preferable to running a series of sequential paired t-tests because, first, the t-tests are not statistically independent and second, there is a much greater likelihood of committing a type-I error. Moreover, since our data were time-ordered, it was possible to determine whether there was evidence of a linear trend (a significant change in the mean values), or whether there was non-linearity and, if so, whether it was of quadratic or higher order. If there was an overall significant time effect, three separate subanalyses (for the measurements before, during and after ischaemia) were performed in order to determine the nature of the changes in the measured parameters (linear, quadratic, etc). A P value <0.05 was considered as significant throughout.

**Results**

**Incidence, duration and character of ischaemic episodes**

In 20 of the 32 patients who were initially enrolled in the study, we found a total of 136 episodes with transient ST segment depression during a total of 480 h ECG recording (6.8 ± 4.06 episodes/patient). The total duration of ischaemia was 1762 min (mean 88.1 ± 61.67 min/patient). Of the episodes recorded, 94 were diurnal and 42 nocturnal (2.10 ± 1.2 nocturnal episodes/patient). Of the latter, 30 (in 18 patients) fulfilled the criteria for
inclusion in this study. All the nocturnal episodes were silent but involved ST segment depression.

**Relationship of myocardial ischaemia to heart rate**

There were significant overall time effects with a strong quadratic tendency \((P<0.0001, \text{Table 1})\). More specifically, the mean heart rate remained steady at around 71 min \(^{-1}\) during the 10 min before the onset of ischaemia and then rose by 11 min \(^{-1}\) at the start of the episode \((P<0.0001)\). A very strong quadratic inverse U relationship appeared during the ischaemic episode, when the heart rate rose to 86 min \(^{-1}\) at ST max and then dropped to 78 min \(^{-1}\) at the end of the episode, after which it declined linearly \((P<0.0001)\) to its initial value.

Table 1 Heart rate before, during and after episodes of nocturnal ischaemia. Values are expressed as mean ± 1 standard deviation

<table>
<thead>
<tr>
<th>Time (min, relative to episode)</th>
<th>Heart rate (min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>-10</td>
<td>71 ± 16</td>
</tr>
<tr>
<td>-5</td>
<td>72 ± 16</td>
</tr>
<tr>
<td>Start of episode</td>
<td>83 ± 16</td>
</tr>
<tr>
<td>Max ST depression</td>
<td>86 ± 17</td>
</tr>
<tr>
<td>End of episode</td>
<td>78 ± 14</td>
</tr>
<tr>
<td>+1</td>
<td>73 ± 14</td>
</tr>
<tr>
<td>+10</td>
<td>71 ± 14</td>
</tr>
</tbody>
</table>

Table 2 Heart rate variability before, during and after episodes of nocturnal ischaemia. Values are expressed as mean ± 1 standard deviation. Power is given in In (ms\(^2\)/Hz) where In is the natural logarithm of the quotient

<table>
<thead>
<tr>
<th>Interval</th>
<th>Variable</th>
<th>LF</th>
<th>HF</th>
<th>LF/HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P&lt;0)</td>
<td></td>
<td>4.12 ± 0.62</td>
<td>4.94 ± 1.05</td>
<td>0.83 ± 0.27</td>
</tr>
<tr>
<td>(P&lt;1)</td>
<td></td>
<td>4.20 ± 0.62</td>
<td>4.83 ± 1.03</td>
<td>0.86 ± 0.23</td>
</tr>
<tr>
<td>(P&lt;3)</td>
<td></td>
<td>4.35 ± 1.50</td>
<td>4.71 ± 1.04</td>
<td>0.92 ± 0.21</td>
</tr>
<tr>
<td>(P&lt;4)</td>
<td></td>
<td>4.43 ± 1.31</td>
<td>4.46 ± 0.97</td>
<td>0.99 ± 0.19</td>
</tr>
<tr>
<td>(P&lt;5)</td>
<td></td>
<td>4.60 ± 1.17</td>
<td>4.30 ± 1.05</td>
<td>1.08 ± 0.18</td>
</tr>
<tr>
<td>(P=0)</td>
<td></td>
<td>4.23 ± 1.28</td>
<td>4.28 ± 1.04</td>
<td>0.99 ± 0.15</td>
</tr>
<tr>
<td>(P=1)</td>
<td></td>
<td>4.52 ± 1.48</td>
<td>4.39 ± 1.02</td>
<td>1.01 ± 0.16</td>
</tr>
<tr>
<td>(P=2)</td>
<td></td>
<td>4.40 ± 1.49</td>
<td>4.42 ± 1.08</td>
<td>0.99 ± 0.1</td>
</tr>
<tr>
<td>(P=3)</td>
<td></td>
<td>4.56 ± 1.51</td>
<td>4.52 ± 1.04</td>
<td>1.01 ± 0.24</td>
</tr>
<tr>
<td>(P=4)</td>
<td></td>
<td>4.31 ± 1.53</td>
<td>4.74 ± 0.93</td>
<td>0.90 ± 0.26</td>
</tr>
<tr>
<td>(P=5)</td>
<td></td>
<td>4.23 ± 1.47</td>
<td>4.83 ± 0.97</td>
<td>0.87 ± 0.20</td>
</tr>
<tr>
<td>(P=6)</td>
<td></td>
<td>4.40 ± 1.51</td>
<td>4.81 ± 1.02</td>
<td>0.91 ± 0.21</td>
</tr>
<tr>
<td>(P=7)</td>
<td></td>
<td>4.45 ± 1.49</td>
<td>4.82 ± 0.98</td>
<td>0.92 ± 0.19</td>
</tr>
</tbody>
</table>

Even though the mean values did not appear to differ significantly after the end of ischaemia, there was the suggestion of a quadratic U-shape tendency, peaking 2 min after the ischaemic episode, dropping 3 min later and slowly rising at the end.

The ratio LF/HF (Fig. 1)

A very strong linear increase in LF/HF (from 0.83 to 1.08, \(P<0.0001\)) occurred during the 10 min before the ischaemic episode. The ratio then dropped markedly to 0.99 at the start of the episode \((P<0.0001)\), remained constant throughout the episode and then dropped to its final plateau at 0.92, 10 min later \((P<0.03)\).

**Discussion**

Previous studies have established that 8–10% of episodes of myocardial ischaemia in patients with severe coronary artery disease or Prinzmetal’s variant angina may occur
The mechanism which underlies these nocturnal episodes poses problems, perhaps because it differs from patient to patient, perhaps because more than one factor is involved. Some authors have reported an increase in heart rate before the onset of nocturnal ischaemic episodes, others a decrease in the myocardial ischaemic threshold during the night, probably as a result of a change in coronary artery tone. Others have reported that nocturnal ischaemia is significantly related to arousal from sleep, perhaps because of the increased platelet aggregability arising from the upright posture and the associated increase in sympathetic tone. These observations lead indirectly to the conclusion that the autonomic nervous system, and in particular sympathetic tone, plays a fundamental role in the pathogenetic mechanism of nocturnal ischaemia.

Up to now, information relating to the activity of the autonomic nervous system during sleep and its influence on coronary haemodynamic function has come primarily from experimental models. According to these, during rapid eye movement sleep there is an increase in the neuronal excitability and metabolic activity of the brain, which in turn results in increased sympathetic drive. The latter is believed to lead to a coronary blood flow decrement via stimulation of adrenergic receptors on the coronary vascular smooth muscle and/or a decrease in diastolic coronary perfusion time as a result of the bursts in heart rate.

In humans, evaluation of the sympathetic drive and the sympathetic–parasympathetic balance is usually performed indirectly, based on variations in heart rate and blood pressure. In this study, we used spectral analysis of heart rate variability, which is considered to be a reliable technique for the evaluation of the activity of the two branches of the autonomic nervous system, in order to measure the autonomic nervous system activity before, during and immediately after episodes of nocturnal myocardial ischaemia. Our findings confirm those of earlier studies that episodes of nocturnal ischaemia are preceded by an increase in heart rate, an indirect indication of sympathetic activation. The indirect predominance of the sympathetic system was also confirmed by the changes in the LF/HF ratio before and during the ischaemic episodes.

This ratio showed a very strong linear increase, which began about 10 min before the onset of each ischaemic episode, remained steady and high throughout the episode, and then declined to around normal after the end of the episode. Separate analysis of the high and low frequency components, however, showed that the linear increase in the LF/HF ratio was mainly the result of a significant reduction in the high frequency component, corresponding to a decrease in parasympathetic activity, and was less due to the increase in the low frequency component, which mainly reflects sympathetic activation. This gradual parasympathetic withdrawal was observed during the 10 min before the start of the ischaemic episode, which suggests that it is a causative factor for the appearance of myocardial ischaemia.

Another interesting finding was the fact that the nadir of the high frequency component was obtained at the start of the episode and was followed by a moderate, but not significant, increase throughout the episode. This observation is in accordance with animal studies that demonstrated an increase in the cardiac vagal efferent activity overriding the baroreceptor reflex in the first minute after coronary artery occlusion. These experimental results indirectly support the role of parasympathetic withdrawal as a causative factor and not a consequence of myocardial ischaemia.

Previous studies have noted parasympathetic withdrawal during episodes of silent ischaemia, but...
have not confirmed the predominance of sympathetic tone\textsuperscript{30-33}. However, one should note that in the study of Bigger \textit{et al}\textsuperscript{30} some of the patients were taking β-blockers, which could have influenced these researchers’ findings regarding an increase in sympathetic activity, while in the studies of Tada\textsuperscript{31}, Pellicia\textsuperscript{32} and Yoshio \textit{et al}\textsuperscript{33} the patients exhibited Prinzmetal angina, which probably has a different pathogenetic mechanism.

Our findings showing an increase in sympathetic tone could be attributed to the fact that the ischaemic episodes we studied were of relatively long duration (≥4 min). Such episodes might well cause activation of the sympathetic nervous system in addition to vagal withdrawal. Furthermore, we studied only nocturnal episodes, which might have a different mechanism to those occurring during the day. Similar findings to ours were reported by Bernardi \textit{et al}\textsuperscript{34} who, like us, studied only nocturnal episodes.

In conclusion, the findings of this study reinforce the view that the autonomic nervous system participates in the pathogenesis of nocturnal ischaemic episodes and suggest that the electrocardiographic changes are preceded by a gradual withdrawal of the parasympathetic and the predominance of the sympathetic tone. The process by which this occurs must involve complex interactions, which are manifested by an increase in heart rate and blood pressure, leading to an increase in myocardial oxygen demand, and/or by episodes of coronary artery spasm, resulting in a reduced oxygen supply to the myocardium.

\textbf{Limitations of the study}

(a) The onset of the ischaemic episode was defined as the occurrence of ST segment depression, although it is well known that this is not the earliest sign of ischaemia, but is preceded by a succession of other pathophysiological events. However, for the methodology of this study, it was convenient to record the electrocardiographic changes occurring during sleep and the value of the observations is not materially diminished.

(b) The 10-min period for measurements of autonomic nervous system activity before and after the ischaemic episodes was chosen arbitrarily. Of course, it is probable that changes in the activity of the autonomic nervous system occurred earlier than this; however, the fact that, by 10 min after the end of the ischaemic episode, the high frequency and LF/HF ratio had plateaued out at the same levels they had occupied 10 min before the episode provides strong evidence for a sequence of changes in the autonomic nervous system activity over time.

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