Heart rate variability in patients with daytime sleepiness suspected of having sleep apnoea syndrome: a receiver-operating characteristic analysis

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INTRODUCTION

Sleep apnoea syndrome is associated with marked cardiovascular morbidity and mortality, and the diagnosis and treatment of sleep apnoea has, therefore, been discussed as a relevant public health problem [1]. However, the identification of patients who require further diagnosis and treatment is difficult, and a recent study found that up to 4% of middle-aged adults suffer from previously undiagnosed sleep-disorder breathing [1]. Since polysomnography is an expensive and only limitedly available diagnostic tool, numerous efforts have been undertaken to pre-select subjects who should undergo further clinical investigation [2-8].

Fluctuations in haemodynamic parameters, such as blood pressure and heart rate, during episodes of sleep apnoea are well-known phenomena. Guilleminault et al. [9] described long-wavelength oscillations in heart rate which occur during periodic breathing, and proposed that this phenomenon might serve as a screening method for the sleep apnoea syndrome. An appropriate method for the assessment and analysis of slow oscillations in heart rate may be spectral analysis of heart rate variability (HRV). HRV analysis of long-term ECG recordings is used for risk prediction of death [10, 11], and to investigate circadian fluctuations and the effects of different sleep stages on cardiac autonomic function in healthy subjects [12-15], and in patients with impaired autonomic nervous function [16-21]. Few studies have dealt with changes in HRV due to breathing abnormalities such as Cheyne-Stokes respiration [22] or sleep apnoea syndrome [23-27]. Some authors suggested that the power spectral analysis of heart rate variability may be a valuable additional diagnostic tool in patients undergoing Holter-ECG recording.

Key words: heart rate, sleep apnoea syndrome, spectral analysis.

Abbreviations: HF, high frequency; HRV, heart rate variability; LF, low frequency; RDI, respiratory disturbance index; ROC, receiver-operating characteristic; VLF, very low frequency.

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analysis of HRV could be helpful in the identification of patients suspected of having sleep-related breathing abnormalities [22, 26, 27]. In view of the frequency use of Holter-ECG diagnosis, the evaluation of this hypothesis should be of general interest, but the effectiveness of HRV analysis in discriminating between episodes with normal breathing and those with periodic breathing patterns due to sleep apnoea has, to our knowledge, not yet been investigated. We assessed the ability to discriminate between episodes with normal and periodic breathing by receiver-operating characteristic (ROC) analysis, this describes the entire spectrum of sensitivity and specificity of a test, thus indicating the accuracy of the test.

METHODS

Forty-eight subjects, aged 28–73 years, were consecutively enrolled in the study. The protocol of the prospective study design was approved by the Ethical Board of our institution, and all subjects gave their informed consent. The subjects were referred from the Outpatient Department of the Sleep Disorder Centre, and were suspected of having sleep-related breathing disorders, based on their subjective complaint of chronic daytime sleepiness, combined with self- or partner-reported heavy snoring or nocturnal breathing stops. The characteristics of the patients are reported in Table 1. The patients underwent nocturnal polysomnography, which included recording of the EEG (four leads, central and occipital, referenced to the mastoid of the opposite side), horizontal and vertical EOG, submental, and right and left anterior tibial EMG, oronasal airflow, chest wall and abdominal excursions, snoring sound, oxygen saturation, single-lead ECG and body position. Polysomnography was recorded by a Nihon Kohden polygraph (Neurofax 4317 or 4418) at 10 mm/s and by the Sleep Analyzing Computer (SAC) 847 T software (Oxford Instruments, Abingdon, Oxon., U.K.; software version 9.3). Additionally, patients underwent two-channel (leads CC5 and CS5) Holter monitoring using an analog Holter tape system with phase-locked time tracking (ELA-Medical, Munich, Federal Republic of Germany) and pulse oximetry (Pulse Oximeter 8500; Nonin, Plymouth, MN, U.S.A.). Arterial oxygen saturation was recorded every 6 s and stored on the Holter tape, thus allowing exact synchronization of the ECG and pulse oximeter recordings. The polysomnographic recording and the Holter monitoring were also synchronized and did not differ by more than a minute, thus excluding errors in the comparison of the two recordings.

The polysomnographic recordings were analysed using the sleep-stage scoring system of Rechtschaffen and Kales [28]; transient arousals were identified based on the guidelines of the American Sleep Disorder Association [29]. The results of the computerized scoring were reviewed by an experienced investigator. Apnoeas and hypopnoeas were analysed visually. They were defined as either a complete or incomplete cessation of airflow lasting 10 s or more, and were generally accompanied by an arterial oxygen desaturation of ≥4%. Periodic breathing was defined as ventilatory oscillations, generally accompanied by a fluctuation in arterial oxygen saturation of ≥4%. The respiratory disturbance index (RDI) was calculated as the number of episodes of apnoea and hypopnoea per hour of sleep.

The Holter-ECG recordings were primarily analysed using a computerized ECG analysis system (Elatec version 3.0; ELA-Medical), labelling QRS complexes as normal sinus beat, supraventricular or ventricular ectopic beat, or artefact, and measuring

| Table 1. Clinical characteristics of the patients. Age and body mass index (weight/height²) are reported as medians; ranges are in parentheses. Patients were considered to be hypertensive if they were taking antihypertensive medication or if their diastolic blood pressure exceeded 95 mmHg under resting conditions.
<table>
<thead>
<tr>
<th>Result of polysomnography</th>
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<tbody>
<tr>
<td>No pathological finding</td>
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<tr>
<td>RDI &lt; 20</td>
</tr>
<tr>
<td>No. of patients</td>
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<tr>
<td>(male/female)</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<tr>
<td>Coexisting diseases</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Medication</td>
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<tr>
<td>β1-Adrenoceptor agonist</td>
</tr>
<tr>
<td>β1-Adrenoceptor blocker</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
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<tr>
<td>Diuretic</td>
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</table>
Sleep apnoea and heart rate variability

the R–R interval length. All analyses were reviewed by two investigators.

HRV was analysed using a computer program based on commercially available software (LabVIEW; National Instruments, Austin, TX, U.S.A.), which meets the recently published criteria of HRV measurement [30]. To analyse HRV, the recordings of R–R intervals were divided into 20 min episodes, beginning approximately 1 h before preparing patients for polysomnography, and ending at 06.00 hours. Thus, the recording of each patient was divided into 20–24 segments. According to the results of polysomnography, the 20 min episodes were identified as recordings during normal breathing, during an episode of sleep apnoea with continuous periodic breathing, or during an episode with normal breathing as well as apnoeic and hypopnoeic events.

Stationarity of each 20 min episode of R–R intervals was evaluated by visual inspection of the data and by the reverse arrangement test, as proposed by Bendat and Piersol [31]. Each 20 min episode was divided into 10 equal segments and the reverse arrangement test was applied to the means and variances of these segments. Only those 20 min intervals which met the hypothesis of stationarity at the α = 0.05 level of significance were accepted for further analysis. The R–R intervals were re-sampled at 250 ms intervals using a moving 500 ms wide rectangular window [32]. Non-sinus beats were identified according to interval criteria and were replaced by means of preceding values. Only episodes with less than 5% ectopic beats or artefacts were accepted for spectral analysis. After direct current offset subtraction and application of a Hanning window, an autospectral density function was estimated by computing a discrete Fourier analysis for five 50% overlapping windows and subsequent averaging of the results [31]. The area under the curve and the amplitude and frequency of the maximum peak were calculated for standard frequency bands [30]: very low frequency (VLF; 0.0033 to <0.04 Hz), low frequency (LF; 0.04 to <0.15 Hz), high frequency (HF; 0.15 to <0.4 Hz) and total frequency (<0.4 Hz). An additional frequency band was defined from 0.01 to <0.07 Hz, according to an expected cycle length of periodic breathing from 15 s to 100 s. Spectral power was calculated for each frequency band as normalized units (power of a given component×100/total power). Additionally, the first 20 min episode, which was recorded while the subject was awake and awaiting for the preparation of polysomnography, was defined as a reference period, and the power spectral components, as well as the amplitude of the maximum peak between 0.01 and 0.07 Hz, were expressed as the ratio of the actual value to the reference value for each 20 min episode.

Spectral analysis of oxygen saturation was performed in a similar manner to that of R–R intervals. The relationship between oscillations in oxygen saturation, as a sign of periodic breathing, and oscillations in heart rate was examined using the coherence function, which is a measure of the linear relationship between an input and an output record at each frequency, and ranges between 0 and 1 (a causal relationship between input and output is not necessarily indicated [31]). A coherence >0.5 was interpreted as a significant relationship between input (oxygen saturation) and output (R–R intervals).

The ability to distinguish between episodes with normal breathing and periodic breathing due to sleep apnoea was tested for each power spectrum component, expressed as normalized units, and expressed as the actual to reference value ratio. Additionally, test accuracy was assessed for the amplitude of the maximum peak in the frequency band 0.01 to <0.07 Hz in relation to the reference value.

The ability to discriminate between normal and continuous periodic breathing was analysed using ROC curves. The ROC curves were created by step-wise changes of the decision-threshold for the normal and pathological state for each investigated test parameter, and were based on the condition that the maximum peak of the total power spectrum, in the case of periodic breathing, was located between 0.0025 and 0.07 Hz. The area under the ROC curve (the minimal value of 0.5 indicates no discrimination; the maximum value of 1.0 indicates perfect discrimination) and its standard error were calculated using a non-parametric approach, as described by Hanley and McNeil [33]. The areas under two ROC curves were compared using an approximating procedure which took into account the correlation between ROC areas due to the paired statistical design [34].

RESULTS

Forty-one patients were suffering from sleep apnoea syndrome (Table 1). Six patients showed snoring (RDI <5) associated with transient EEG arousals, and one patient suffered from daytime hypersomnia without pathological polysomnographic findings. Five patients with RDI <20 suffered from periodic leg movements with transient EEG arousals during episodes with normal breathing.

Cardiac arrhythmias, mostly isolated supraventricular or ventricular ectopic beats, could be observed in 28 patients with sleep apnoea syndrome and in four snorers. Seven patients with sleep apnoea syndrome showed intermittent sinus bradycardias with frequencies of less than 40/min. One patient suffered from an intermittent third-degree atrioventricular block. Sinus arrests (pause >3 s) could be observed in three patients. Three patients with frequent supraventricular ectopic beats during the entire ECG recording (one patient with normal polysomnography; two patients with RDI <20) and
one patient with ventricular ectopic beats (Lown classification grade 2, RDI <20) were excluded from further analysis.

The recordings of the remaining patients were divided into 1044 20 min episodes (580 episodes with normal breathing, 163 episodes with both normal and abnormal breathing patterns, and 301 episodes with continuous periodic breathing). 387 episodes were excluded from spectral analysis because of non-stationarity of data. 54% of the episodes with normal breathing, 49% of the episodes with both normal and abnormal breathing, and 88% of the episodes with obstructive sleep apnoea met the criteria of stationarity and were chosen for power spectral analysis. A typical example of an episode with sleep apnoea is shown in Fig. 1, demonstrating a peak at about 0.03 Hz in the oxygen saturation spectrum as a sign of periodic breathing, as well as in the spectrum of R-R intervals. The relatively strong relationship between the spectra at that frequency is indicated by a coherence of 0.8.

ROC curves are shown in Fig. 2; the areas under the ROC curves are presented in Table 2. The area under a ROC curve represents the probability that a randomly selected interval, recorded during periodic breathing, has a test value larger than a randomly selected interval, recorded during normal breathing [35]. Power spectral components, expressed as normalized units, did not show sufficient accuracy to discriminate between episodes with normal breathing and episodes with sleep apnoea. However, the capability of power spectral components, calculated as an actual to reference value ratio, to discriminate between normal and pathological states was better, and ROC areas >0.9 could be obtained for three frequency components: 0 to <0.4 Hz, 0.01 to <0.07 Hz, and 0.0033 to <0.04 Hz. Additionally, the relative amplitude of the maximum peak between 0.01 and 0.07 Hz proved sufficient to distinguish between normal and periodic breathing. The best accuracy for discriminating between episodes with normal breathing and those with sleep apnoea was found in the spectral power frequency range between 0.01 and 0.07 Hz, expressed as the actual to reference value ratio. For this parameter, a given test sensitivity of 90% corresponded to a specificity of 77%.

The analysis of the episodes classified as false-positive at this decision-threshold revealed that half of them were recorded during episodes of recurrent central nervous arousal reactions, due to periodic leg movements with an otherwise normal breathing pattern, or during episodes of obstructive snoring without apnoea or hypopnoeas. Figure 3 shows a recording obtained during an episode of periodic leg movements with a normal breathing pattern. The cycle frequency of the oscillations in heart rate corresponded with the frequency of arousal reactions; the coherence of less than 0.5 between the spectra of oxygen saturation and R-R intervals indicates that there is no significant relationship between these two parameters.

### DISCUSSION

Oscillations in heart rate and blood pressure during sleep apnoea are proposed to be caused by fluctuations in sympathetic and parasympathetic nervous activity. Multiple factors, such as upper airway occlusion, central nervous arousal reactions, hypercapnia and hypoxaemia, the effects of lung inflation and changes in intrathoracic pressure, and autonomic dysfunction, may contribute to these oscillations in the activity of the autonomic nervous system [9, 36–40].

**Fig. 1.** Recordings and power spectra of R-R intervals (A and B) and of arterial oxygen saturation (C and D) during an episode of obstructive sleep apnoea. The coherence >0.5 in the frequency region of 0.03 Hz (E) indicates that the relationship is sufficient between input (oxygen saturation) and output (R-R intervals).
In our patients, coherence analysis identified equal frequencies of oscillations in oxygen saturation, as a sign of periodic breathing, and oscillations in heart rate during sleep apnoea episodes. As breathing periodicities may vary over a wide range of cycle frequencies, different frequency components of the power spectrum of R–R intervals may, therefore, be influenced by sleep apnoea episodes: the

![Fig. 2. ROC curves which demonstrate the ability to discriminate between episodes of normal breathing and continuous periodic breathing for different parameters computed from power spectral analysis of R–R intervals. A, Power spectral components expressed as normalized units; B, power spectral components calculated as the ratio of actual value to reference value; C, amplitude of the maximum peak in the frequency range 0.01 to <0.07 Hz, calculated as the ratio of actual value to reference value. Reference values were obtained when subjects were awake and awaiting preparation of polysomnography.](image)

**Table 2. Areas under the ROC curves for different parameters, derived from power spectral analysis of R–R intervals, as a measure of the accuracy for discriminating between episodes of normal and periodic breathing.** Statistically significant differences are reported for areas >0.9: *P* <0.05, ††P <0.05 compared with other ROC areas.

<table>
<thead>
<tr>
<th>Calculated parameter</th>
<th>Frequency component (Hz)</th>
<th>Area under the ROC curve</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectral power (normalized units)</td>
<td>0.01 to &lt;0.07 Hz</td>
<td>0.889</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>0.0033 to &lt;0.04 Hz</td>
<td>0.663</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>0.04 to &lt;0.15 Hz</td>
<td>0.549</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>0.15 to &lt;0.4 Hz</td>
<td>0.516</td>
<td>0.024</td>
</tr>
<tr>
<td>Spectral power (ratio of actual value to reference value)</td>
<td>0.01 to &lt;0.07 Hz</td>
<td>0.929*</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>&lt;0.4</td>
<td>0.915†</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>0.0033 to &lt;0.04 Hz</td>
<td>0.903</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>0.04 to &lt;0.15 Hz</td>
<td>0.887</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>0.15 to &lt;0.4 Hz</td>
<td>0.880</td>
<td>0.014</td>
</tr>
<tr>
<td>Amplitude of maximum peak (ratio of actual value of reference value)</td>
<td>0.01 to &lt;0.07 Hz</td>
<td>0.915††</td>
<td>0.012</td>
</tr>
</tbody>
</table>
VLF component (located between 0.0033 and 0.04 Hz), as well as the LF component (located between 0.04 and 0.15 Hz). Furthermore, previous observations [41] revealed changes in the HF component of the power spectrum (located between 0.15 and 0.4 Hz) during periodic breathing in patients with sleep apnoea syndrome.

We estimated the minimal cycle length of periodic breathing to be about 15 s (based on the standard definition of apnoea which comprises an absence of air flow for at least 10 s, plus intermittent breathing), and the maximal cycle length to be about 100 s (apnoeas with a duration of more than 100 s are well known, but are, in our clinical experience, mostly isolated events). Therefore, we defined an additional frequency range from 0.01 to <0.07 Hz and expected to find the oscillations in R–R intervals, which corresponds to breathing periodicities, in this frequency component of the power spectrum.

In 1984, Guilleminault et al. [9] suggested that changes in HRV may indicate episodes of sleep apnoea. In 1989, Ichimaru and Yanaga [22] investigated eight patients with congestive heart failure, constructed an algorithm for the detection of periodic breathing, and found a high sensitivity for the detection of Cheyne–Stokes respiration. However, no studies have been carried out using ROC analysis to describe the accuracy of parameters derived by spectral analysis in the detection of periodic breathing. Furthermore, problems related to the method of spectral analysis have rarely been discussed. Spectral analysis should be performed on data which have been shown to be at least weakly stationary. We only performed spectral analysis on data segments with constant means and variances, according to the suggestions of Bendat and Piersol [31]. Based on these criteria, 37% of the data segments, most of which were recorded during normal breathing or during both normal and abnormal breathing patterns, were excluded from spectral analysis. HRV during continuous sleep apnoea episodes proved most often to be stationary; only 12% of episodes, recorded during continuous periodic breathing, had to be excluded. Thus, short episodes of periodic breathing may have to be excluded due to unstationarity of data. A further methodological limitation can be caused by the Holter-ECG system. We used an analog tape recording system with phase-locked loop speed control (frequency 0.125 Hz). This system may cause significant errors in the determination of the LF and HF components in patients with a markedly reduced HRV, as in patients after heart transplantation. These errors were not found in control patients [42]. Since periodic breathing is related to oscillations in heart rate with frequencies <0.125 Hz, we regarded the Holter system as sufficient.

Arrhythmias may contribute to unstationarity of data, and previous studies showed a higher prevalence of cardiac arrhythmias in patients with sleep apnoea syndrome than in patients without the syndrome [43, 44]. On the other hand, another recent study could not find significant differences in the incidence of arrhythmias between patients with and without sleep apnoea who were not suffering from serious cardiopulmonary diseases [45]. The occurrence of arrhythmias might theoretically result in the exclusion of those ECG recordings from spectral analysis which may be of special interest. Four of our subjects were excluded from analysis due to arrhythmias, but these patients only had a mild form...
of sleep apnoea syndrome or were not suffering from any sleep-related disorder. In the remaining patients, unstationarity of data was mainly caused by changes in the baseline heart rate (time-varying mean value of R–R intervals), by a time-varying frequency structure of R–R intervals, or by artefacts. Several patients with severe sleep apnoea showed intermittent severe bradycardias or single supraventricular or ventricular ectopic beats which did not cause unstationarity of data. The effect of these single ectopic beats was excluded by replacing the preceding and following R–R intervals by mean values from neighbouring intervals.

In a recent study we observed a more than tenfold variation in total power and in power spectral components between patients during normal breathing and during periodic breathing [41]. Since changes in power spectral components during periodic breathing should be comparable between patients, we used power spectral components, expressed as normalized units, and power spectral components, related to a reference value, which was obtained when the patient was awake and awaiting the preparation of polysomnography.

The ROC showed insufficient ability to discriminate between normal breathing and episodes of periodic breathing due to sleep apnoea for the HF components, as well as for the LF and VLF components, expressed as normalized units. The latter phenomenon may depend on different cycle frequencies of periodic breathing: breathing periodicities with cycle durations <25 s are expected to cause an increase in normalized units of LF power, and consequently a decrease in normalized units of VLF power and vice versa. The normalized power of the frequency component between 0.01 and 0.07 Hz showed a significant improvement in the ability to discriminate. A further improvement was obtained when spectral power was expressed in relationship to the individual reference values: all spectral power components were associated with ROC areas >0.8. The best test accuracy was obtained for the power spectral component in the 0.01 to <0.07 Hz range. For this parameter, a sensitivity of 0.9 was related to a specificity of 0.77. However, about half of the intervals classified as false-positive were recorded during rhythmic transient arousals without any breathing abnormalities, but associated with other sleep-related disorders. Besides the sleep apnoea syndrome, several other sleep-related disorders such as heavy snoring [46], the upper airway resistance syndrome [47] and periodic leg movements [48] are known to be related to transient arousal reactions and can cause periodic changes in the activity of the autonomic nervous system. Arousals have been shown to be associated with increased sympathetic nerve activity in healthy subjects [49], and transient arousals to be related to periodic fluctuations in heart rate and blood pressure under experimental conditions [50]. According to these findings, those of our patients who suffered from transient arousals due to heavy snoring or periodic leg movements showed LF oscillations in heart rate comparable with those during periodic breathing. With respect to our results, analysis of HRV cannot differentiate between sleep apnoea and other sleep-related disorders which cause periodic central nervous arousal reactions. However, the method might offer a possible means of detecting suspicious episodes of periodic leg movements which cannot be assessed by screening methods such as pulse oximetry, respiration movements or breathing sounds.

Analysis of HRV may be of limited value in patients with impaired cardiac autonomic control. Diabetic autonomic neuropathy is known to be associated with reduced HRV and altered circadian modulation of autonomic activity [51, 52]. Guilleminault et al. [9] found no changes in heart rate during periodic breathing in patients with autonomic neuropathy or a denervated heart. In our group there was one patient with diabetes mellitus who showed typical changes in HRV during sleep apnoea episodes. It is to be expected that this phenomenon is not present in severe autonomic neuropathy, but this question has not yet been evaluated.

Sleep apnoea syndrome is accompanied by significant cardiovascular co-morbidity, and cardiovascular diseases are known to be related to changes in autonomic nervous activity and reduced HRV. A recent study could not find differences in HRV during wakefulness between patients with and without cardiovascular diseases who suffered from sleep apnoea [24]. Other workers [53] did find signs of disturbed cardiac sympatho-vagal balance, a loss of circadian rhythm of HRV and disturbed autonomic regulation during different sleep stages in patients with cardiovascular diseases [18, 19, 54]. In a recent study we observed marked changes in HRV during periodic breathing in patients with coronary artery disease [55]. Furthermore, medications, such as β-adrenoceptor-blocking substances and calcium antagonists, influence cardiac sympatho-vagal balance [56–58]. However, the effect of these drugs on HRV during sleep apnoea has not yet been systematically analysed. In the present study, we investigated a heterogeneous group of patients and did not focus on analysing the influence of coexisting diseases and medication on HRV during sleep apnoea episodes.

In conclusion, we found that most episodes of R–R intervals, recorded during sleep apnoea, met the criteria for computation of spectral analysis. ROC analysis revealed that parameters derived from power spectrum of R–R intervals had a remarkable capability to distinguish between episodes with normal and those with periodic breathing. Further studies are needed to evaluate the usefulness of this method in the identification of patients with sleep-related breathing disorders. Yet, analysis of HRV cannot serve as a substitute for current screening methods and clinical assessment of sleep apnoea syndrome, but it may bring attention to the possi-
bility of sleep apnoea syndrome in patients undergoing Holter-ECG recording primarily to answer other clinical questions. Furthermore, power spectral analysis of HRV allows identification of episodes suspicious to sleep-related disorders, associated with transient central nervous arousal reactions, but without periodic breathing (such as periodic leg movements or heavy snoring), which may be difficult to assess by the known screening methods. These disorders can cause changes in HRV which are comparable with, and cannot be differentiated from, those during sleep apnoea. Since the analysis of HRV can be performed, at least in part, automatically by appropriate computer programs, it may be a valuable additional diagnostic tool in patients undergoing long-term ECG recording.

REFERENCES