Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep

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Objective **To assess spontaneous baroreceptor–heart rate reflex sensitivity during sleep in patients with obstructive sleep apnea syndrome, a condition associated with increased cardiovascular morbidity and mortality and characterized by marked sympathetic activation, which is believed to originate from hypoxic chemoreceptor stimulation, although little is known of other possible mechanisms such as baroreflex impairment.**

Design and methods **In 11 patients with severe obstructive sleep apnea syndrome (mean ± SD age 46.8 ± 8.1 years, apnea/hypopnea index 67.9 ± 19.1 h), who were normotensive or borderline hypertensive during wakefulness by clinic blood pressure measurements, finger blood pressure was monitored beat-by-beat non-invasively (Finapres) at night during polysomnography. Periods of wakefulness and sleep were identified based on electroencephalographic recordings. Baroreflex sensitivity was assessed by the sequence technique, as the slope of the regression line between spontaneous increases or reductions in systolic blood pressure (SBP) and the related lengthening or shortening in the RR interval, occurring over spontaneous sequences of four or more consecutive beats. The number of these sequences was also computed, as an additional index of baroreflex engagement by the spontaneous blood pressure fluctuations. The controls were age-related normotensive or borderline hypertensive subjects without sleep apnea who had been investigated in previous studies; in these subjects blood pressure was recorded intra-arterially over 24 h in ambulatory conditions and spontaneous baroreflex sensitivity was assessed by the sequence technique.**

Results **In our patients the lowest nocturnal arterial oxygen saturation was 78.6 ± 12.1% (mean ± SD). During sleep, the number of pooled +RR/+SBP and −RR/−SBP sequences per hour was 20.3 ± 2.7 per h in patients with sleep apnea and 27.1 ± 2.1/h in controls (means ± SEM). The average baroreflex sensitivity during sleep periods was 7.04 ± 0.8 ms/mmHg in sleep apnea patients and 10.05 ± 2.1 ms/mmHg in controls. Both the pooled number of sequences and baroreflex sensitivity values of the sleep apnea patients were significantly ($P < 0.01$) less than the corresponding night values of control subjects. In the sleep apnea patients, at variance from controls, baroreflex sensitivity did not show any increase during sleep compared with its values during wakefulness (6.9 ± 1.0 ms/mmHg).**

Conclusions **Our data provide evidence that spontaneous baroceptor reflex sensitivity is depressed in severe obstructive sleep apnea syndrome. This suggests that in such patients baroreflex dysfunction and not only chemoreceptor stimulation by hypoxia may be involved in the sympathetic activation which occurs during sleep. Such dysfunction may contribute to the higher rate of cardiovascular morbidity and mortality reported in these patients.**

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Keywords: obstructive sleep apnea, baroreflex sensitivity, blood pressure, sequence technique, hypertension, sympathetic nervous system

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Introduction

Obstructive sleep apnea syndrome is attracting increasing attention by clinicians and investigators [1–4] because of the evidence provided in the last 10 years that patients with this syndrome have a higher risk of systemic diurnal and nocturnal hypertension [5–7], nocturnal cardiac arrhythmias [8–10], pulmonary hypertension [11,12], congestive heart failure, myocardial infarction and stroke [3]. In particular, the higher prevalence of arterial hypertension in patients with obstructive sleep apnea syndrome (about 50%) has stimulated a number of studies aimed at evaluating the mechanisms responsible for this phenom-

enon. Chemoreflex stimulation appears to be a key factor, induced by repeated hypoxia and by the frequent arousals associated with the apneic episodes, which may all contribute to the enhanced sympathetic activity shown in these patients both during wakefulness and during sleep [13–19]. Also, an impairment of the arterial baroreflex control of circulation may be involved in the genesis of the sympathetic activation typical of obstructive sleep apnea syndrome [16,17,20,21]. However, information on baroreflex cardiovascular control in these patients has been obtained only by means of laboratory stimulations delivered during wakefulness, while little is known about the actual effectiveness of the arterial baroreflex at night in patients with obstructive sleep apnea. This issue is of crucial importance for an understanding of the mechanisms responsible for the cardiovascular effects of this syndrome. In contrast to normal subjects, in whom night sleep is characterized by a reduction in blood pressure, heart rate and sympathetic activity and by an increase in baroreflex sensitivity [22–26], during night sleep in patients with obstructive sleep apnea syndrome an increase in sympathetic activity and a blunted reduction in night-time blood pressure and heart rate values often occur [14]. The reported association in normal subjects between an increase in baroreflex sensitivity during sleep and nocturnal hypotension together with the evidence provided by animal studies of a major influence exerted by arterial baroreflexes on night-time hemodynamics [27,28] suggest that an impaired baroreflex modulation at night might contribute to the autonomic and hemodynamic changes observed in patients with repeated apneic episodes. This possibility, however, has not been systematically investigated so far in humans. The main reason for this lack of knowledge is the inability of the available laboratory techniques to properly estimate baroreflex sensitivity during sleep. This is because these methods (1) require external interventions which disturb patients' sleep and interfere with the neural mechanisms under evaluation, and (2) do not allow dynamic tracking of the changes in baroreflex sensitivity which may occur during night sleep [29,30].

The aim of the present study was to fill this gap in knowledge, by assessing the features of baroreflex sensitivity at night in patients with obstructive sleep apnea syndrome, by using a method for spontaneous baroreflex estimate, based on the computer analysis of spontaneous fluctuations in blood pressure and heart rate in the time domain [29,30].

Methods

Subjects

We studied 11 male patients, recruited at the Istituto di Fisiopatologia Respiratoria in Palermo (mean ± SD age 46.8 ± 8.1 years, body mass index 34.7 ± 6.4 kg/m^2) with obstructive sleep apnea syndrome and normal or borderline elevated sphygmomanometric systolic/diastolic blood pressure (SBP/DBP) values (133.6 ± 3.8/86.4 ± 3.1 mmHg, means ± SEM) by repeated office measurements. Ten normotensive or borderline hypertensive subjects with no sleep disturbances were taken as controls (age 41.7 ± 7 years, eight males, two females, 124.6 ± 6.5/63.9 ± 2.4 mmHg).

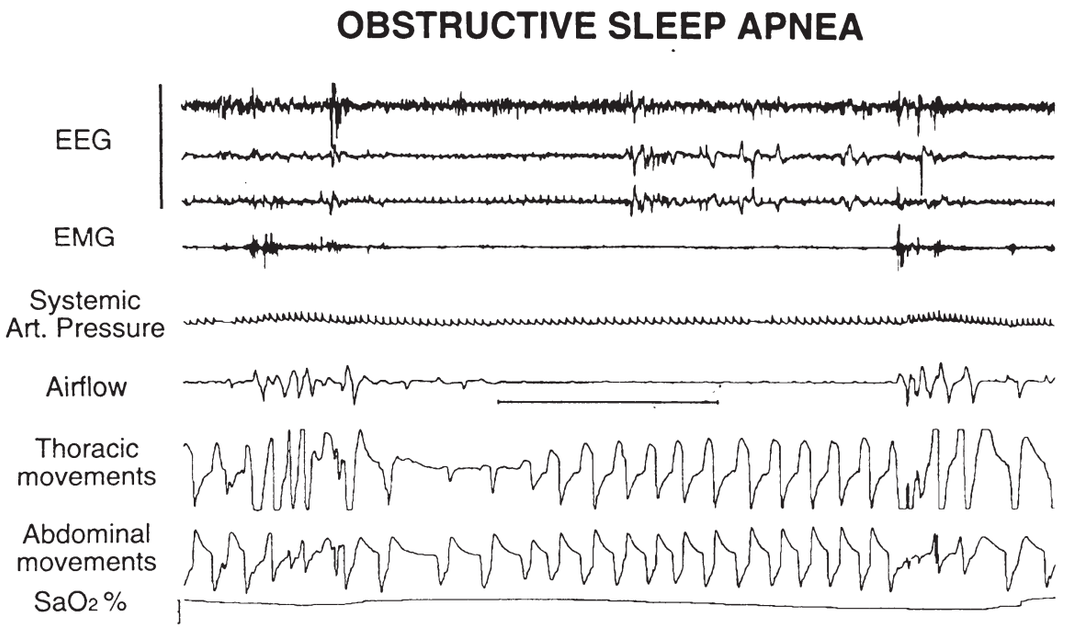
Measurements

After confirming that no subject was taking any cardiovascular drug, the sleep apnea patients were studied by nocturnal polysomnography (Somnostar, Sensormedics Corporation, Yorba Linda, California, USA), with electroencephalography, electromyography, airflow (nasal thermistor), thoracic and abdominal movements, arterial oxygen saturation and blood pressure recordings being taken throughout the night-time period (Fig. 1), including a baseline period of wakefulness. Arterial blood pressure was monitored non-invasively on a beat-to-beat basis through a Finapres device (Finapres 2300, Ohmeda, Englewood, Colorado, USA), the cuff of which was positioned on the middle or ring finger of the non-dominant hand. The Finapres device has been shown to reliably track changes in intra-arterial pressure under different behavioral and experimental conditions [31]. During the nocturnal recording, the Finapres autocalibration was left active, allowing the quality of the finger blood pressure recording to be automatically checked by the device. Every 30 min the Finapres was switched off for 5 min, in order to allow the finger wearing the cuff to resume its regular venous circulation and to prevent disturbance to patients' sleep. In the 10 control subjects, blood pressure was monitored intra-arterially for 24 h in ambulatory conditions (Oxford Medilog recorder, catheter percutaneously inserted into the radial artery of the non-dominant arm, [24,30]), after standardization of daily activities as well as of meal- and bed-times.

Data analysis

In the sleep apnea patients, finger blood pressure recordings were edited from artefacts through an interactive procedure. The edited signal was then sampled at 178 Hz, digitized on 12 bits and stored on a magnetic disk for further analysis. From each beat, SBP and pulse interval (PI) values were derived and stored on separate time series. The time series were further analyzed to estimate spontaneous baroreflex control of the heart rate in the time domain by the sequence method (described in detail previously [30,32]. Briefly, the computer was programmed to automatically identify spontaneously occurring sequences of four or more consecutive beats characterized by hypertension/bradycardia (+PI/+SBP) or by hypotension/tachycardia (–PI/–SBP). The number of sequences per hour which, at constant levels of blood pressure variability, reflected the number of times when sequential blood pressure changes were able to trigger reflex changes in the heart rate, was taken as a gross index of baroreflex activation, while baroreflex sensitivity was

Fig. 1



Original tracing of a polysomnographic recording in one of our patients with obstructive sleep apnea syndrome. EEG, electroencephalogram; EMG, electromyogram; Art, arterial; SaO_2: arterial oxygen saturation.

assessed by computing the slope of the +PI/+SBP and –PI/–SBP sequences. The frequency of baroreflex activation (the number of +PI/+SBP and –PI/–SBP sequences) and mean baroreflex sensitivity (the sequence slope) were determined during wakefulness and during sleep, respectively, in all subjects. Individual values were averaged separately for the group of controls and for the group of sleep apnea patients.

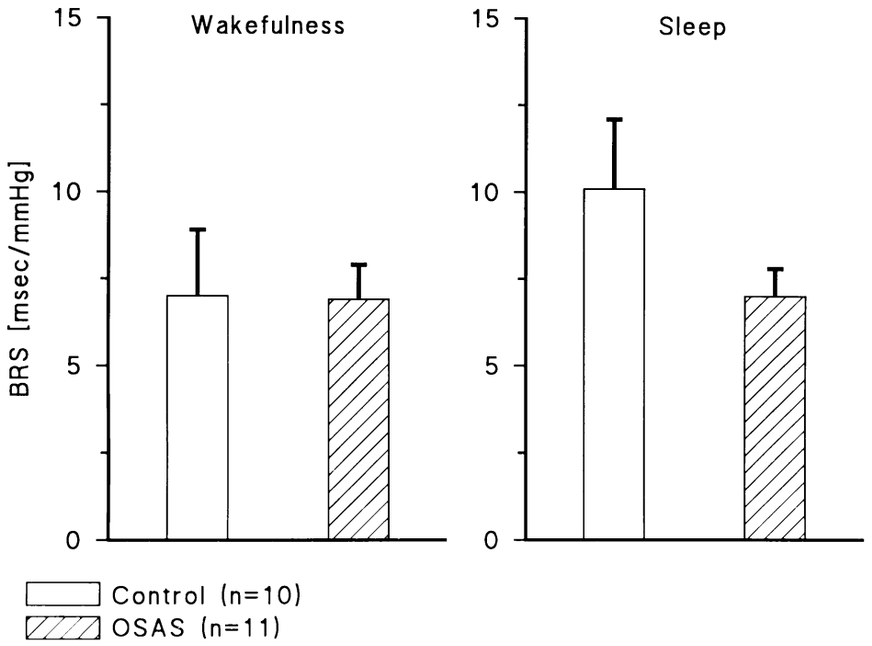
Results

The sleep apnea patients were characterized by a disease of remarkable severity, as shown by an apnea–hypopnea index of 67.9 ± 19.1, an arterial oxygen saturation during wakefulness of 95.4 ± 0.9%, but lowest values of arterial oxygen saturation of 78.6 ± 12.1% during non-rapid-eye-movement (NREM) sleep and 67.6 ± 17.8% during REM sleep, respectively. The data on average spontaneous baroreflex sensitivity during wakefulness and sleep in both the sleep apnea patients and the controls are shown in Fig. 2. Although no significant differences were found between the two groups while awake, possibly also because of the different recording conditions, the average spontaneous baroreflex sensitivity was significantly lower in the sleep apnea patients than in control subjects during sleep. As shown in Fig. 3, in the sleep apnea patients spontaneous baroreflex sensitivity was inversely related to the severity of the sleep apnea, as quantified by the apnea–hypopnea index, both during wakefulness and during non-REM sleep, while during REM sleep, which is known to be characterized by complex changes in cardiovascular autonomic regulation, no relationship between baroreflex sensitivity and the apnea–hypopnea index was observed. Figure 4 illustrates the number of hypertension/bradycardia and hypotension/tachycardia sequences observed in a subgroup of our sleep apnea patients during the apneic episodes and at the time of the interapneic ventilation, respectively. The initial phase of the apneic episodes was characterized by the predominant occurrence of hypotension/tachycardia sequences, while the resumption of ventilation, a condition in which the increase in blood pressure is usually most pronounced, was associated with a higher frequency of hypertension/bradycardia sequences.

Discussion

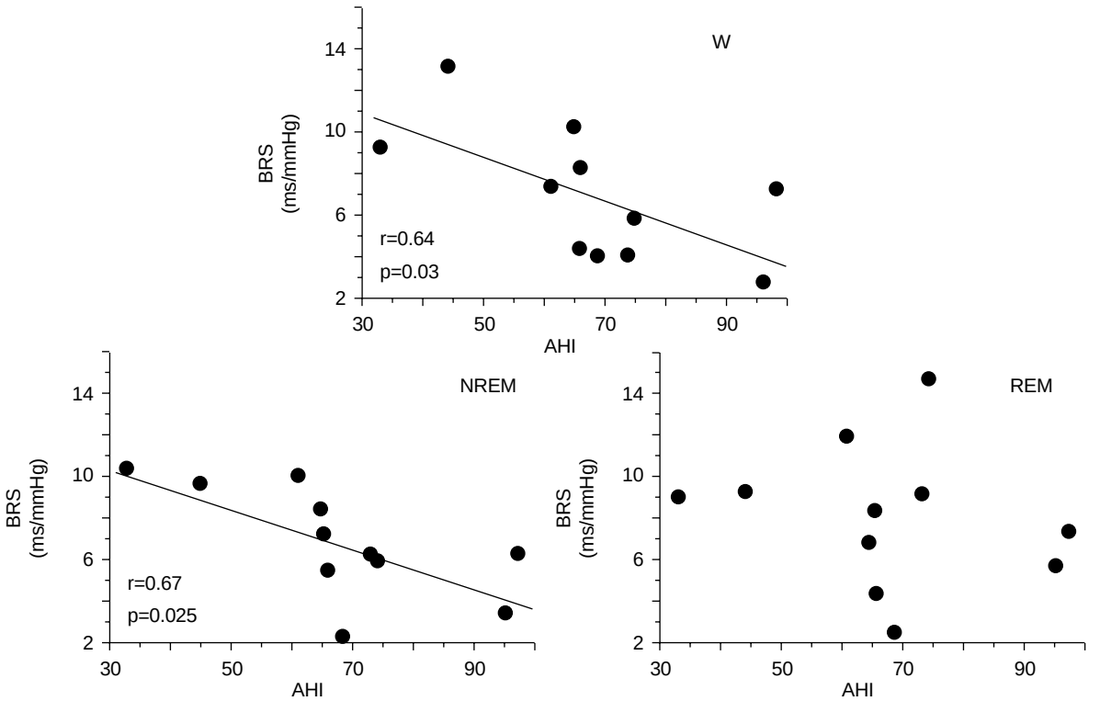
For the first time our study provides experimental evidence that in patients with obstructive sleep apnea syndrome the sensitivity of spontaneous baroreflex control of the heart rate is reduced at night. Our observations thus extend previous findings that baroreflex sensitivity is altered in awake subjects with obstructive sleep apnea syndrome [16–19] and offer a direct demonstration that an impaired baroreflex is involved in the nocturnal hemodynamic alterations of patients with frequent sleep apnea episodes. The data on spontaneous baroreflex modulation obtained by the sequence method have also allowed us to show that the derangement of this reflex function in sleep apnea patients is proportional to the severity of the

Fig. 2



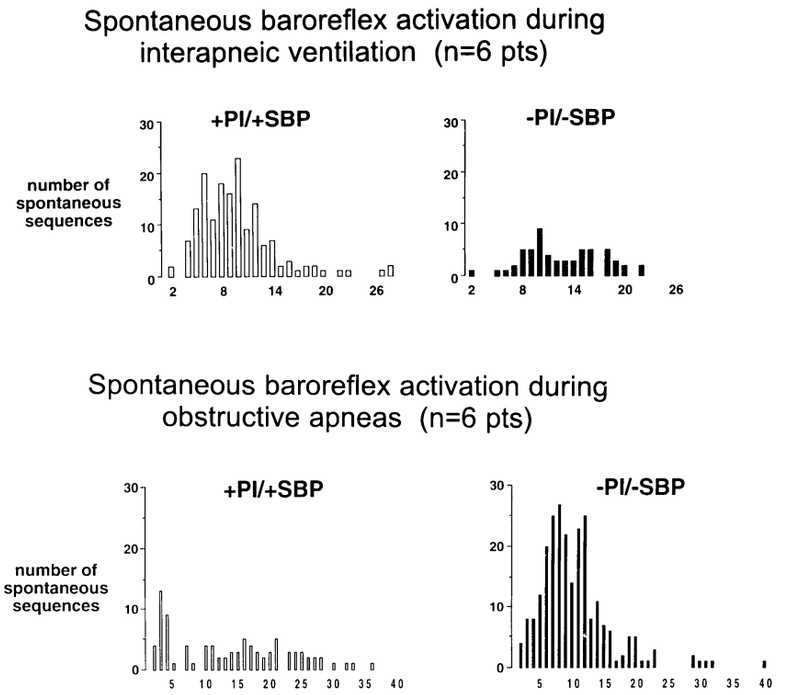
Spontaneous baroreflex sensitivity, quantified as the pooled slope of hypertension/bradycardia and hypotension/tachycardia sequences, in a group of 11 patients with severe obstructive sleep apnea syndrome (OSAS) and in 10 normal controls. Data are shown separately as average values for a period of wakefulness and night-time sleep. BRS, sensitivity of the baroreflex control of the heart rate.

Fig. 3



Relationship between spontaneous baroreflex sensitivity (BRS) and the severity of obstructive sleep apnea syndrome, as quantified by the apnea–hypopnea index (AHI). Data are shown as individual values in 11 patients separately for a period of wakefulness (W), a period of non-rapid-eye-movement (REM) sleep (NREM) and a period of REM sleep (REM).

Fig. 1



Number of hypertension/bradycardia (+PI/+SBP) and hypotension/tachycardia (–PI/–SBP) sequences during apneic episodes and during the interapneic ventilation phase. Data are pooled from 6 patients (pts) and are expressed as number of sequences per minute, starting at the beginning of apnea or of the resumed ventilation, respectively. Numbers on the horizontal axis refer to minutes since the beginning of apnea or since the beginning of ventilation, respectively. PI, pulse interval; SBP, systolic blood pressure.

syndrome, baroreflex sensitivity being inversely related to the apnea–hypopnea index.

The above evidence may therefore support the hypothesis that the increases in blood pressure and in sympathetic activity which have been reported to occur in patients with obstructive sleep apnea syndrome at night, and which are likely to be triggered by the chemoreflex activation induced by hypoxia and by sleep fragmentation [1–3,13], are at least in part also due to a baroreflex impairment [16,17,20]. This is in line with previous evidence that an experimentally induced impairment of the arterial baroreflex in animals deeply affects the hemodynamic changes typical of the various sleep stages [23,24,33].

The reasons for the baroreflex impairment observed in sleep apnea patients cannot be clarified by our study. It is conceivable, however, given the well-known interactions between chemoreflexes and arterial baroreflexes [28,32,33], that the chemoreflex activation induced by hypoxia in these patients might have contributed to their blunted baroreflex sensitivity, a possibility which is in part supported by the evidence that treatment with nasal continuous positive air pressure (NCPAP) respiration may improve the autonomic alterations detected in patients with obstructive sleep apnea syndrome [13]. The negative effects of chemoreflex activation on baroreflex sensitivity may be exerted through a direct interaction at the brainstem level. They may also be indirectly mediated by the increase in sympathetic activity observed in this condition, however [32]. In turn, the resulting reduction in baroreflex sensitivity may contribute to a further increase in sympathetic firing, thus leading to a vicious cycle which may have adverse clinical implications. Notwithstanding the mechanisms responsible for a baroreflex impairment in this condition, our findings are also relevant to the increased risk of cardiovascular complications in patients with obstructive sleep apnea syndrome, given the recent evidence that reduced baroreflex sensitivity is associated with higher morbidity and mortality in several clinical conditions, such as myocardial infarction [34], congestive heart failure [35] and diabetes mellitus [36].

Another important result of our study is the difference in the distribution of hypertension/bradycardia and hypotension/tachycardia sequences observed during the apnea–ventilation cycles in our sleep apnea patients. The higher frequency of hypotension/tachycardia sequences at the beginning of the apneic episodes, when blood pressure displays a tendency to fall, and the corresponding higher frequency of hypertension/bradycardia sequences at resumption of ventilation, when blood pressure displays its maximal increase, seem to suggest that in spite of its impairment, the arterial baroreflex is engaged in coun-

teracting the blood pressure changes associated with the repeated apnea–ventilation cycles, although with a limited efficacy.

Finally, our findings further emphasize the importance of techniques for spontaneous baroreflex analysis in the understanding of the pathogenetic role of the arterial baroreflex in those conditions, such as obstructive sleep apnea syndrome, which are characterized by time-varying neural and hemodynamic alterations, where traditional laboratory tests cannot provide adequate information.

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