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ORIGINAL ARTICLE

Non-dipping pattern of nocturnal blood pressure in obstructive sleep apnea syndrome: Possible role of oxidative stress and endothelin-1 precursor

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KEYWORDS

Obstructive sleep apnea syndrome;
Hypertension;
Non-dipping pattern;
Apnea hypopnea index;
Oxygen desaturation index;
Oxidative stress

Abstract *Background:* There is growing evidence suggesting that obstructive sleep apnea OSA is linked to the occurrence of cardiovascular disorders. Lack of normal nocturnal dipping of blood pressure has also been considered a risk factor for the occurrence of cardiovascular disorders. Non-dipping has been described in patients with OSA and is attributed to autonomic dysfunction. However, the search for a causal link between OSA and cardiovascular disease is still underway.
Objective: To evaluate the occurrence of non-dipping pattern of nocturnal blood pressure, and the possible role of oxidative stress and ET-1 precursor in patients with OSA.
Subjects and methods: Thirty eight patients with OSA and fourteen normal control subjects were enrolled in this study and were subjected to history taking, clinical examination, early morning blood samplings for the measurement of serum malondialdehyde (MDA) and endothelin 1 precursor (ET-1 precursor). All patients with OSA were subjected to full polysomnographic study and monitoring of nocturnal blood pressure changes.
Results: Nocturnal blood pressure measurement of all patients revealed that thirty six patients (94.7%) were non-dippers, 15 patients (39.5%) suffered from ischemic heart disease. Serum

Abbreviations: OSA, obstructive sleep apnea; BP, blood pressure; ET-1, endothelin-1; MDA, malondialdehyde; EEG, electroencephalogram; REM, rapid eye movement sleep

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endothelin-1 precursor and serum malondialdehyde levels were significantly higher in patients with OSA than in the control group. The systolic blood pressure measured before sleep was also significantly higher in patients than in the control group. The Epworth sleepiness scale and the clinical apnea score were significantly higher in patients than in the control group.

Conclusions: The high incidence of non-dipping pattern of nocturnal blood pressure in both normotensive and hypertensive patients with OSA may be considered a warning sign for the occurrence of cardiovascular complications in these patients. Both increased oxidative stress and ET-1 precursor may be among the causative factors responsible for the high prevalence of the non-dipping pattern through increasing sympathetic nervous system activity.

1. Introduction

Obstructive sleep apnea (OSA) syndrome is a sleep breathing disorder characterized by recurrent airflow obstruction caused by a total or partial collapse of the upper airway during sleep. It is associated with interruption of normal sleep by repetitive episodes of complete (apneas) and/or partial (hypopneas) cessations of breathing.[1] Such episodes are usually associated with a decrease in oxygen saturation (SaO2) that is normalized upon resumption of ventilation.[2] Several population-based studies have established an association between OSA and hypertension[3,4] and OSA is now considered as a new cause of secondary systemic hypertension.[4] There is also growing evidence suggesting that OSA is a risk factor for cardiovascular disorders[5] however, the search for a causal link between OSA and cardiovascular disease is still underway.

Several studies suggested that the repeated episodes of hypoxia-reoxygenation may predispose to the development of oxidative stress as well as endothelial dysfunction in OSA[6,7] which are critical pathways in the pathogenesis of cardiovascular disease in such patients.[8]

It has been proposed that vascular endothelial dysfunction and structural vascular changes have been implicated as early mechanisms in the pathophysiology of hypertension and cardiovascular disease in OSA.[7] Endothelins are 21-amino acid vasoconstricting peptides produced primarily in the endothelium and are used as markers of endothelial alterations. Endothelin-1 (ET-1) signals vasoconstriction and influences local cellular growth and survival.[9] For the biogenesis of ET-1, a larger precursor peptide (pre-proET-1) is cleaved at two sites to give rise to ET-1 precursor, which is subsequently cleaved to generate mature ET-1.[10] ET-1 has been implicated in the development and progression of vascular disorders such as atherosclerosis and hypertension. The role of ET-1 in the pathogenesis of hypertension and cardiovascular disease in OSA patients has been previously investigated. However, there were inconclusive results as to whether it has a role in development of hypertension in such patients. Plasma levels of ET-1 have been shown to be higher in patients with OSA than healthy controls in one report,[11] while another study showed that plasma ET-1 values of patients with OSA were not elevated compared to controls.[12] Such conflicting results have underscored the value of the relatively stable endothelin-1 precursor, (ET-1 precursor) as a more appropriate marker of endothelial alteration than ET-1 because of its longer half-life.[13]

The pathophysiologic mechanisms by which intermittent hypoxia during sleep can lead to daytime hypertension may be more complex. Besides increase in oxidative stress and endothelial dysfunction there is evidence of increased sympathetic activity.[14] Blood pressure (BP) is under circadian diurnal control and normally declines during sleep, compared to daytime. Most people present a decline in arterial BP between 10% and 20% during nighttime intervals which is called dipper pattern.[14] A nocturnal BP decrease less than 10% of daytime BP is defined as "non-dipping."[15] It has been suggested that non-dippers show impairment in the autonomic nervous system and have an increased risk of hypertension and cardiovascular diseases.[14] Non-dipping has also been described in patients with OSA.[16] It could be possible that the increased sympathetic activity in OSA could result in non-dipping which could be one of the mechanisms by which OSA contributes to increased risk of hypertension and cardiovascular disease.

2. Aim of the work

To evaluate the occurrence of non-dipping pattern of nocturnal blood pressure, and the possible role of oxidative stress and ET-1 precursor in patients with OSA

3. Subjects and methods

3.1. Study Population and subjects

This study included 38 patients (22 males and 16 females) with obstructive sleep apnea hypopnea syndrome (OSA) having a median age of 53 years, and 14 normal normotensive subjects serving as the control (10 males and 4 females) with a median age of 54 years The study protocol was approved by the local ethics committee, and informed consents were obtained.

3.2. Study measurements

A- All subjects were subjected to the following:

(1) Full history taking including assessment of clinical apnea score[17] which comprises a questionnaire about: snoring, obesity (assessed by body mass index),[18] and daytime hypersomnolence (assessed by Epworth Sleepiness Scale),[19] witnessed apnea by bed partner and systemic hypertension. Also a history of diabetes mellitus (confirmed by fasting blood glucose measurement), ischemic heart diseases and arrhythmias were included.

(2) Systemic blood pressure measurements were obtained.[20] Daytime hypertension was defined as daytime BP values $\geqslant$140 mmHg systolic and $\geqslant$90 mmHg diastolic.[19]

(3) Measurement of serum ET-1 precursor (Big Endothelin-1). Blood samples were obtained early in the morning following full polysomnography. The ET-1 precursor levels in serum were measured by commercially available enzyme linked immunosorbent assay (ELISA) kits (Biomedica Group).[21]
(4) Serum malondialdehyde (MDA) as a marker for oxidative stress was measured in all subjects. To 0.5 ml serum, 2.5 ml of 20 mg/dl TCA was added, and the tube was left to stand for 10 min at room temperature. After centrifugation at 3500 rpm for 10 min, the supernatant was decanted and the precipitate was washed once with 0.05 M sulfuric acid. Then, 2.5 ml of 0.05 M sulfuric acid and 1 ml of 0.67% thiobarbituric acid (TBA) in 2 M sodium sulfate were added to this precipitate and the tube was heated in a boiling water bath for 30 min. After cooling, the resulting chromogen was extracted with 4 ml of *n*-butyl alcohol by vigorous shaking. Separation of the organic phase was facilitated by centrifugation at 3000 rpm for 10 min, and the optical density was measured at 530 nm. A standard curve was constructed using different concentrations of 1,1,3,3-tetramethoxy propane in ethanol. The concentration of MDA in the sample was determined in nmol/ml.[22]

B- All patients with OSA were subjected to full polysomnography (somnomedic™) Level II sleep study[23] to assess the following:

3.2.1. Sleep stages and arousals

Electroencephalogram (EEG) and electrooculogram (EOG) were used to detect different stages of sleep: 1 – Light sleep (stage 1 and 2), 2 – Deep sleep (stage 3 and 4), and rapid eye movement sleep (REM). Scoring of different stages of sleep was performed according to criteria established by the American Academy of Sleep Medicine[24] Total sleep time (TST) and sleep efficiency in addition to the period of each stage and its percentage in relation to total sleep time were calculated with assistance of the computer software. Also arousal was scored if there was abrupt shift of EEG to a lighter stage and/or full awakenings that lasted at least three seconds with at least 10 s of stable sleep preceding the change. An arousal index was calculated by dividing the total number of arousals by TST.[24]

3.2.2. Respiratory events

Monitoring of airflow using both thermistor and nasal cannula connected to the pressure transducer, respiratory effort using thoracic and abdominal belts, oxygen saturation using finger pulse oximeter and the evaluation of snoring using a microphone. Manual scoring was performed for all patients. Apneas and hypopneas were defined using criteria established by the American Academy of Sleep Medicine.[24] Apnea was considered when there is drop in the flow excursion by $\geqslant$90% of the baseline for at least 10 s and hypopnea was defined when there is drop by $\geqslant$30% of baseline and associated with $\geqslant$4% desaturation from pre-event baseline for at least 10 s. Another alternative definition for hypopnea is a drop in the flow excursion by $\geqslant$50% of baseline for at least ten seconds and associated with $\geqslant$3% desaturation from pre-event baseline and/or arousal. Utilizing these definitions, an apnea-hypopnea index (AHI) was calculated by dividing the total number of apneas and hypopneas by the TST.

3.2.3. Nocturnal blood pressure monitoring

Electrocardiogram and oximeter were used to detect changes in blood pressure during sleep using pulse transit time (PTT). PTT-based method for indirect measurement of blood pressure was proved to be effective.[25] Measurement of blood pressure before sleep was obtained and blood pressure calibration was performed before starting manual scoring. The following parameters were measured during sleep: average systolic blood pressure, maximal blood pressure, time of maximal pressure, maximal increase in blood pressure and index of increase in blood pressure. Difference between systolic BP before sleep and average systolic BP during sleep was calculated to detect the level of dipping in systolic BP. Ten percent of the systolic blood pressure was calculated for each patient and considered as the minimal value for normal nocturnal dipping and compared with that actually obtained by the patient during sleep (Dipping = pre-sleep systolic BP – average systolic BP during sleep). Nocturnal hypertension was defined as average night-time BP values $\geqslant$ 125 mmHg systolic and $\geqslant$75 mmHg diastolic.[26]

4. Statistical analysis

After data entry into a specially designed sheet using Microsoft Excel, a print out of the data was thoroughly revised and data entry mistakes were corrected. Then the file was transferred into Statistical Package for Social Science (SPSS) version 17 format and data explore was carried out.

Testing normality using Kolmogorov–Smirnov test proved that some variables are abnormally distributed, so the median and inter-quartile range (IQR) was used for descriptive purposes. Non-parametric tests were used for comparison between the two groups (Mann–Whitney test). Box and Whisker graph was used to illustrate the minimum, maximum, median and IQR for the variables. Kendall's–Tau bivariate correlation was also performed. Alpha error was set to 5%.

5. Results

Out of 38 patients with OSA included in this study three patients (7.9%) had mild sleep apnea, six patients (15.8%) had moderate sleep apnea, and 29 patients (76.3%) had severe sleep apnea. History taking revealed that 15 patients (39.5%) suffered from ischemic heart disease and fasting blood glucose measurements revealed that 16 patients (42.1%) were diabetics. Diurnal blood pressure measurement in patients with OSA revealed that thirty two patients (84.2%) were hypertensive and 6 patients (15.8%) were normotensive, nocturnal blood pressure measurement of all patients revealed that thirty six patients (94.7%) were non-dippers and lacked the sleep-related, nocturnal systolic dipping in blood pressure, while only two patients of the 38 patients with OSA (5.3%) showed normal dipping. Thirteen patients of the non-dippers (36.1%) showed increase rather than decrease in average systolic BP during sleep than that before sleep. Thirty patients (83.3%) of the 36 patients with non-dipping pattern of nocturnal blood pressure also showed systemic hypertension, while the other 6 (16.6%) patients with non-dipping pattern were normotensive. Fig. 1 shows the comparison between normally expected dipping for the pre-sleep BP and the actual measured dipping in patients with OSA during sleep. All of the 15 patients with

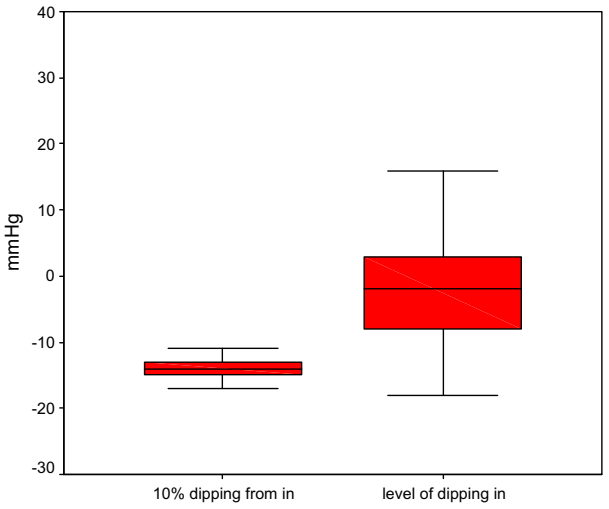

Figure 1 Boxplots comparing the normal 10% expected decrease in pre-sleep SBP and the actual degree of change in SBP during sleep in the 38 patients with OSA. It shows the absence of expected decrease and even increase rather than decrease in systolic BP during sleep.

ischemic heart disease were non-dippers and 7(46.6%) of them had an increase rather than a decrease of nocturnal blood pressure 14 of (93.3%) them were hypertensive.

Comparison between the results obtained from patients and control groups showed that serum pro-endothelin-1 and serum malondialdehyde levels were significantly higher in patients with OSA than in the control group $Z = 2.971$, $P = 0.003$ and $Z = 5.468$, $P < 0.001$ respectively. The systolic pressure measured before sleep was also significantly higher in patients than in the control group $Z = 2.60$, and $P = 0.009$. The Epworth sleepiness scale and the clinical apnea score were significantly higher in patients than in the control group. $Z = 5.490$, $P < 0.001$, $Z = 5.736$, $P < 0.001$ respectively (Table 1, Figs. 2 and 3).

Table 2 shows the polysomnographic data of patients with OSA, and Fig. 4 demonstrates a 5-min fragment from a full night sleep study recording (polysomnography) of a 51 year old male patient complaining of excessive daytime sleepiness, snoring, sense of suffocation and chocking during sleep, unrefreshing sleep and morning headache. He is normotensive and non-diabetic. His Epworth sleepiness scale was 22/24 and his clinical apnea score was 4/5. His BP before sleep was 120/80 mmHg. (case no. 19). The recording shows repetitive obstructive apneas and hypopneas associated with repetitive hypoxia-reoxygenation, surges in BP (higher in systolic BP than diastolic BP), microarousals and increase in sympathovagal balance. Monitoring heart rate shows sinus bradytacharrhythmias. His polysomnographic study revealed very severe OSA (AHI = 110.8/h, ODI = 110.4/h). His average BP during sleep was 115/86 mmHg with absence of normal dipping in BP (non-dipper), his maximal systolic BP during sleep was 156/115 mmHg and index of increase in BP was 85.9/h. Fig. 5 shows the whole night graphics of the full polysomnography of the same patient showing the saw tooth pattern of the oxygen saturation curve characteristic for OSA.

6. Discussion

Blood pressure is under circadian control and normally declines during sleep, compared to daytime. Most people present a decline in arterial BP between 10% and 20% during nighttime intervals which is called dipper pattern.[14] A nocturnal BP decrease less than 10% of daytime BP is defined as "non-dipping."[15] In the present study the absence of normal dipping of systolic BP was one of the most prominent features of BP measurement in patients with OSA. Thirty six patients (94.7%) lacked the sleep-related, nocturnal decrease, or "dip" in blood pressure seen in normal individuals. Thirteen patients of the non-dippers (36.1%) showed increase rather than decrease in average systolic BP during sleep than before sleep. The incidence of systemic hypertension among non-dippers was 83.3% (30 patients) All normotensive patients with OSA (6 patients) included in the present study were non-dippers. Only two patients of the 38 patients with OSA (5.3%) showed normal dipping in their blood pressure during sleep. Similarly, Loredo et al.[27] reported that the incidence of non-dipping in 44 subjects with sleep apnea, was 84%. Pankow et al.[28] also demonstrated an increased prevalence of hypertension and non-dipping, in 93 patients with moderate and severe sleep-disturbed breathing. Hla et al.[16] reported a significant longitudinal association between baseline OSA status and the development of nocturnal BP systolic non-dipping among participants who initially had normal nocturnal BP dipping.

These findings together with our results suggest an association between OSA and nocturnal non-dipping which are interesting findings because previous studies have linked the non-dipping pattern of nocturnal BP to increased cardiovascular risk (stroke, myocardial infarction, etc.) and higher cardiovascular mortality in both hypertensive and normotensive non-

Table 1 Different studied parameters in patients with OSA and control subjects.

Variables	OSA ($n = 38$)		Control ($n = 10$)		Significance (P)
	Min–Max	Median (IQR)	Min–Max	Median (IQR)	
Age	33–87	53(19)	45–65	54(5)	$Z = 0.620$ $P = 0.536$
Epworth sleepiness scale (/24)	9–24	17(8)	5–7	5(1)	$Z = 5.490$ $P < 0.001^*$
Clinical apnea score (/5)	2–5	4(1)	0–2	0(1)	$Z = 5.736$ $P < 0.001^*$
Systolic BP before sleep (mmHg)	110–220	140(25)	110–140	130(10)	$Z = 2.60$ $P = 0.009^*$
Diastolic BP before sleep(mmHg)	70–140	90(10)	70–90	80(10)	$Z = 1.862$ $P = 0.063^*$
S. ET-1 precursor-1 (fmol/ml)	0.16–0.48	0.198(0.02)	0.17–0.19	0.18 (0.01)	$Z = 2.971$ $P = 0.003^*$
S. malondialdehyde (nmol/ml) Min–Max Mean ± SD	3.9–72.8	37.3(30.2)	2.2–3.9	3.3(1.1)	$Z = 5.468$ $P < 0.0001^*$

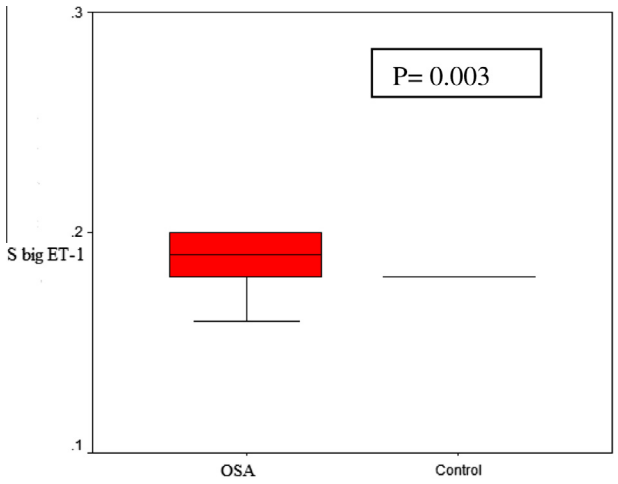

Figure 2 Boxplots showing Serum ET-1 precursor (endothelin-1 precursor) measured in fmol/ml, in patient with OSA and control group.

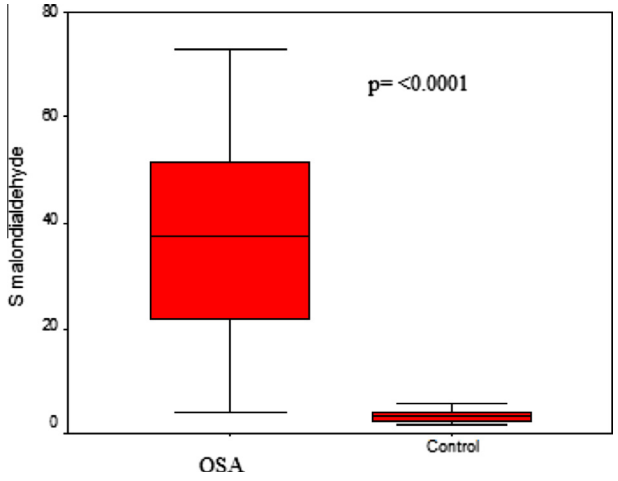

Figure 3 Boxplots for Serum MDA (Malondialdehyde), (nmol/ml) in patients with OSA and control group.

dippers.[29,30] Our results demonstrated that 15(39.5%) patients suffered from ischemic heart disease all of which were non-dippers and 14 of them were hypertensive. Patients with OSA were found to be at an increased risk for several cardiovascular diseases.[4,31,32] It can therefore be suggested that nocturnal non-dipping is an early sign in a process linking OSA to cardiovascular disease possibly via multiple pathways.[16,33,34]

The exact mechanisms responsible for the non-dipping pattern of nocturnal blood pressure are still not fully elaborated. Loredo et al.[27] investigated a possible association between nocturnal non-dipping pattern of BP and the quality of sleep, measured by the percent of slow wave sleep; percentage of time awake after sleep onset during the sleep period; sleep efficiency; and arousal index. They found the prevalence of non-dipping to be high in untreated patients with mild to severe OSA, nonetheless, there was no relation between the quality of sleep and nocturnal BP dipping. Sleep quality therefore did not appear to be related to nocturnal BP dipping in OSA.[27] Recently however, the occurrence of nocturnal non-

Table 2 Polysomnographic data for 38 patients with OSA.

Polysomnographic data	Min–Max	Median (IQR)
Polysomnographic respiratory data		
Apnea Hypopnea index (A + H/h)	12.5–127.5	51.5(41)
Oxygen desaturation index (OD/h)	2.3–113.1	35(44.2)
Average minimal desaturation (%)	69–94	87(8)
t90% (%)	0–99	23(57.5)
Polysomnographic dlood pressure data		
Average SBP during sleep (mmHg)	102–197	138(30)
Maximal SBP during sleep (mmHg)	134–256	184(48)
Maximal DBP during sleep (mmHg)	80–150	106.5(16)
Maximal increase in BP during sleep (mmHg)	15–91	34.5(22)
Index of increase in BP during sleep (/h)	0–111.5	29(39.2)
Level of dipping of BP during sleep (mmHg)	−18 to 27	-2(12)
PolysomnographicsSleep data		
Sleep efficiency (%)	52.2–99.8	79.5(23.7)
Arousal index (/h)	18.9–78.4	45(23.7)

dipping has been linked to the impaired function of the autonomic nervous system in the form of a decreased vagal tone and increased sympathetic tone.[35] In the present study, besides the characteristic non-dipping of BP, another feature of nocturnal BP in patients with OSA was repetitive increase in BP during sleep followed by fall in BP to the baseline or at higher level than the baseline pointing to the possible role of sympathetic activation. Arousals are immediate consequences of sleep apneas and hypopneas. With each arousal, there is transient reinstitution of the wakefulness, increased sympathetic and decreased parasympathetic activity consequently, heart rate and blood pressure increase.[36] It is possible that these repeated bouts of sympathetic activation prevent complete normalization of BP in the time between events, causing systolic BP to fail to fully experience the nocturnal dip typically seen in persons without OSA.[36]

Repeated apneic episodes are known to increase oxidative stress, however, the full consequences of the increased oxidative stress are not clearly elaborated. In the present study, serum malondialdehyde (MDA) was used as a marker of oxidative stress in OSA.[37] Our results demonstrated that MDA was significantly higher in patients with OSA than control subjects. Oxidative stress in OSA may be linked directly to intermittent hypoxia in resemblance to ischemia reperfusion injury. Several studies, particularly ones that involved larger numbers of patients, were able to demonstrate that OSA is indeed associated with increased markers of oxidative stress.[38–41] The increased oxidative stress may be one mechanism associating OSA to hypertension. Oxidative stress can induce the upregulation of numerous redox-sensitive transcription factors, and can also induce an increase in angiotensin II; and plasma endothelin which have been linked to hypertension by increasing vascular resistance.[38,42]

Chronic intermittent hypoxia and oxidative stress can also increase sympathetic activity in patients with OSA by increasing the sensitivity of peripheral chemoreflexes.[43] Peripheral

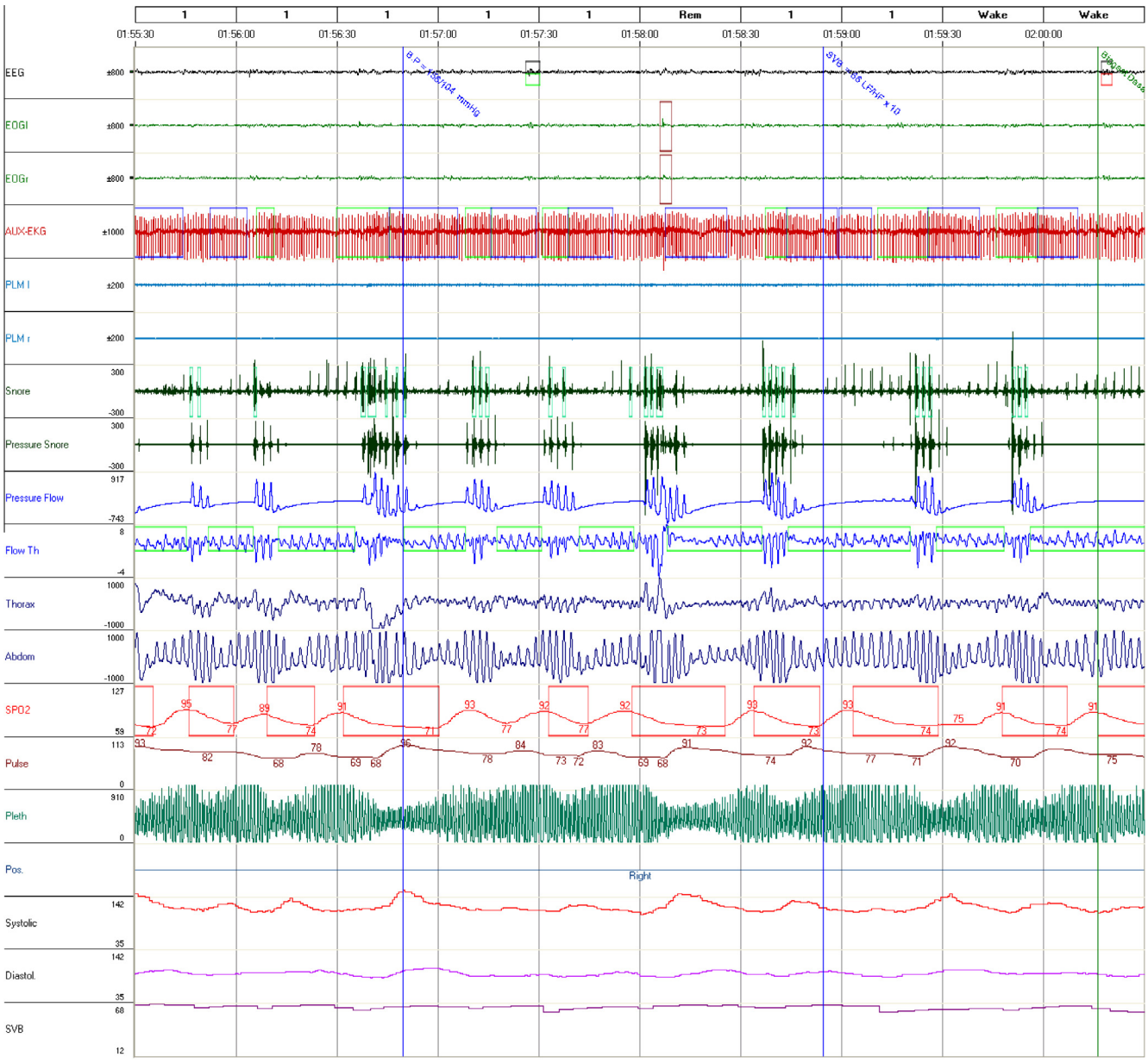

Figure 4 A fragment from a full night sleep study recording (polysomnography) of a patient with severe OSA (no. 19). Channels from top: EEG: electroencephalogram, LOC: left eye electrooculogram, ROC: right eye electrooculogram,; EKG: electrocardiogram, PLM l: left lower limb periodic limb movement, PLM r: right lower limb periodic limb movement, snoring assessed by microphone, Pressure flow: Air flow:measured by nasal pressure cannula; Flow Th: Air flow measured by thermistor, Thorax: chest effort measured thoracic belt, Abdom: Abdominal effort measured Abdominal belts, SaO2: oxygen saturation measured by pulse oximetry. Pulse: pulse rate measured by oximeter, Pleth: pulse wave of the oximeter, Pos: position of the patient, Systolic: systolic BP, Diasto: diastolic BP, SVB: sympathovagal Balance. Note the recurrent episodes of cessation (or decrease of the amplitude) of flow with persistent respiratory effort (obstructive apneas). Each episode is associated with hypoxia, and is terminated by an arousal and subsequent restoration of the patency of the airway and airflow. Apnea is associated with bradycardia and followed by tachycardia and increase in BP.

chemoreflex and baroreflex activity have a direct effect on efferent sympathetic outflow.[36,39,44,45]

Several studies measured circulating levels of ET-1 in patients with OSA as a possible link between OSA and hypertension, however results were contradictory and the exact role of ET-1 in OSA induced hypertension has not been confirmed.[12,46–48] One possible reason for the inconclusive results of endothelin measurement could be its short half life, only 4 ± 7 min. On the other hand ET-1 precursor has proven to be a more stable marker of endothelial alteration than ET-1 because of its longer half-life.[13] Pre-pro-ET and and ET-1 precursor are cleaved by ET converting enzymes into ET-1, -2, -3 and -4. These ET isoforms bind with different affinities to ET(A) and ET(B) receptors in the vascular smooth muscle, and in turn increase calcium ion, protein kinase C and mitogen-activated protein kinase and other signaling pathways of vascular smooth muscle contraction and cell proliferation.[49] In the present study, ET-1 precursor was found to be signifi-

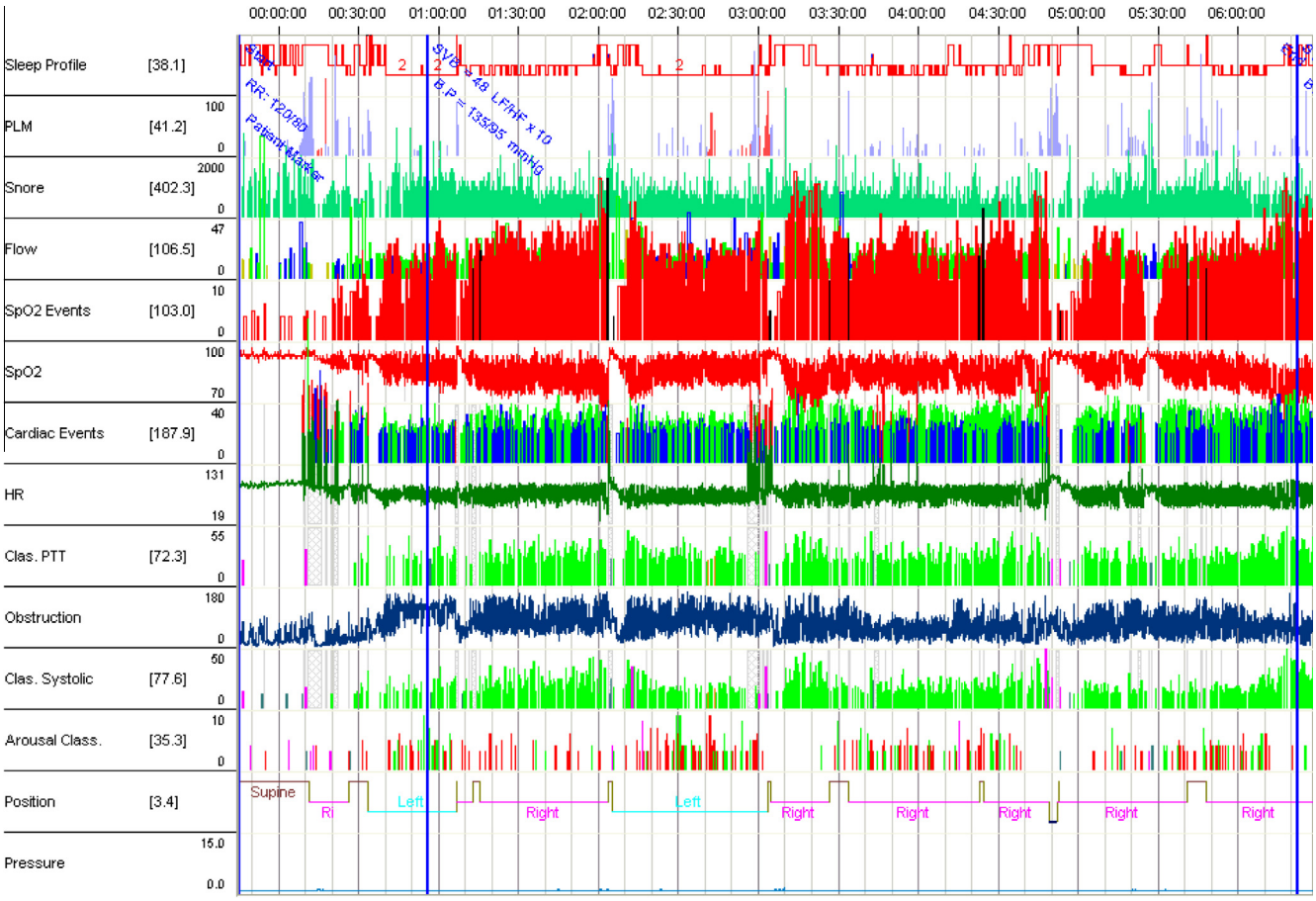

Figure 5 The whole night graphics of the full polysomnography of the patient no. 19 showing the saw tooth pattern of the oxygen saturation curve (representing the intermittent hypoxemia in the form of repetitive desaturation – reoxygenation) characteristic for OSAHS. Channels from top: sleep profile represented by the hypnogram, PLM: periodic limb movement events, snoring assessed by microphone, flow: Air flow, SpO2 events: marking events of decreased saturation, SpO2: oxygen saturation measured by pulse oximetry. Cardiac events: marking events of arrhythmias, deceleration and/or acceleration in pulse rate as detected by ECG, HR: pulse rate measured by oximeter, class. PTT: events of decrease in pulse transit time, obstruction; markings for obstructive respiratory events, class. Systolic: marking events of increasing systolic blood pressure, Arousal class.: marking arousal events, position of the patient, note that the recurrent episodes of desaturation associating to obstructed events of flow are associated with repetitive cardiac events, bradytachyarrhythmias, increase in systolic blood pressure and arousals.

cantly higher in patients with OSA than normal subjects. In agreement with our results, Jordan et al.[13] found that the ET-1 precursor, was considerably elevated in untreated patients with OSA and dropped to normal values after long-term continuous positive airway pressure depending on compliance. ET-1 besides being a potent vasoconstrictor has also been shown to increase sympathetic nervous system activity.[45]

It could therefore be postulated from the results of the present study that the intermittent hypoxia associated with OSA results in increased oxidative stress, ET-1 levels, measured by assessing the more stable precursor of endothelin ET-1 precursor. Both oxidative stress and the ET-1 precursor as well as repeated arousals have been demonstrated to increase sympathetic nervous system activity and may therefore contribute to the non-dipping pattern in patients with OSA which can be a risk factor for the occurrence of cardiovascular disease in such patients.

In conclusion, the high incidence of non-dipping pattern of nocturnal blood pressure both in normotensive and hypertensive patients with OSA may be considered a warning sign for the occurrence of cardiovascular complications in these patients. Both increased oxidative stress and the ET-1 precursor and repeated arousals may be among the causative factors responsible for the high prevalence of non-dipping pattern through increasing sympathetic nervous system activity. Screening for non-dipping pattern should be considered as part of the workup of patients with OSA even if they are normotensive, in addition to hypertensive patients especially those whose 24 h BP studies that yielded non-dipping should also be screened for occult OSA as a cause of secondary hypertension. Early treatment of such patients may cut down the cardiovascular risk factor.

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