Big Endothelin-1 and Nitric Oxide in Hypertensive Elderly Patients with and without Obstructive Sleep Apnea-Hypopnea Syndrome

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Abstract

Background: The role of oxidative stress in hypertensive elderly patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) is unknown.

Objective: The purpose was to evaluate the levels of big endothelin-1 (Big ET-1) and nitric oxide (NO) in elderly hypertensive patients with and without moderate to severe OSAHS.

Methods: Volunteers were hospitalized for 24 h. We obtained the following data: body mass index (BMI); 24-ambulatory blood pressure monitoring; and current medication. Arterial blood was collected at 7pm and 7am for determining plasma NO and Big ET-1 levels. Pulse oximetry was performed during sleep. Pearson’s or Spearman’s correlation and univariate analysis of variance were used for statistical analysis.

Results: We studied 25 subjects with OSAHS (group 1) and 12 without OSAHS (group 2) aged 67.0 ± 6.5 years and 67.8 ± 6.8 years, respectively. No significant differences were observed between the groups in BMI; number of hours of sleep; 24-h systolic and diastolic BPs; awake BP, sleep BP and medications to control BP between groups. No differences were detected in plasma Big ET-1 and NO levels at 19:00 h, but plasma Big ET-1 levels at 7:00 h were higher in group 1 (p = 0.03). In group 1, a negative correlation was also observed between the mean arterial oxyhemoglobin saturation level, 24-h systolic BP (p = 0.03, r = −0.44), and Big ET-1 (p = 0.04, r = −0.41).

Conclusions: On comparing elderly hypertensive patients with and without OSAHS having similar BP and BMI, we observed higher Big ET-1 levels After sleep in the OSAHS group. NO levels did not differ between the hypertensive patients with or without OSAHS. (Arq Bras Cardiol. 2013;101(4):344-351)

Keywords: Hypertension; Aged; Big endothelin-1; Obstructive sleep apnea-hypopnea syndrome.

Introduction

The endothelium plays a fundamental role in the regulation of vascular tone and peripheral resistance through the synthesis of numerous vasoactive compounds, i.e., vasodilators such as nitric oxide (NO) and vasoconstrictors such as big endothelin-1 (Big ET-1), by endothelial cells. Under pathological conditions such as systemic arterial hypertension, there is a disequilibrium of endothelium-derived factors with an attenuation of vasodilators and a predominance of vasoconstrictors. The elimination rate of endothelin-1 (ET-1) is higher than that of its precursor Big ET-1. In addition, plasma Big ET-1 levels of humans, rabbits, and rats are higher than plasma ET-1 levels, with studies suggesting that the precursor is a more appropriate indicator for the quantification of release by endothelial cells.

NO has an important influence on the tone of peripheral blood vessels, and it is released in response to the shear stress produced by blood flow and by the activation of various of receptors. Because NO is released continuously, systemic inhibition of its synthesis causes an elevation of blood pressure (BP). On this basis, oxidative stress plays an important role in hypertension pathogenesis.

Oxidative stress is also considered to be involved in the pathogenesis of arterial hypertension in obstructive sleep apnea-hypopnea syndrome (OSAHS). OSAHS is defined as a group of disorders characterized by periodic cessation of breathing, with consequent hypoxia, frequent awakenings, and sleep fragmentation during the night, triggering excessive daytime somnolence. This syndrome is more prevalent among the elderly. According to the apnea-hypopnea index (AHI/h), OSAHS is classified as mild (AHI/h, 5–15 events/h); moderate (AHI/h, 15– 30 events/h); and severe (AHI/h, >30 events/h). Furthermore, mortality is significantly associated with high rates of respiratory changes [awakenings and microawakenings during sleep]; a body mass index (BMI) of >30 kg/m²; and male sex.

Few studies have assessed endothelial function in OSAHS, and the role of oxidative stress in elderly hypertensive patients with OSAHS is unknown.
The objective of the present study was to evaluate Big ET-1 and NO before and after sleep in elderly hypertensive patients with and without OSAHS.

Methods

The hypertensive patients were selected from the outpatient services of the following centers of the Ribeirão Preto School of Medicine, São Paulo University: the Hypertension Center of the Clinical Hospital; the Geriatric Clinic of the School Health Center; and the Center for Family Health –V. All hypertensive volunteers with moderate to severe OSAHS had previous diagnoses confirmed by polysomnography; control hypertensive subjects were also subjected to further examination to exclude OSAHS. The hypertensive patients diagnosed with moderate or severe OSAHS were diagnosed by the Laboratory of Clinical Neurophysiology (Clinical Hospital – Ribeirão Preto School of Medicine) and selected following the exclusion criteria described below.

Exclusion criteria were based on the following factors that could affect the evaluation of plasma Big ET-1 and NO levels: age < 60 years, diabetes mellitus, dyslipidemia, heart and lung diseases, smoking, past history of smoking, drinking, use of continuous positive pressure airway ventilation, cardiac arrhythmia, and use of medications that might interfere with sleep (anxiolytics, antidepressants, and neuroleptics). Patients who did not consent to participate were also excluded.

The volunteers were admitted to the Clinical Research Unit of HCFMRP-USP. Upon admission, weight and height were measured using a digital scale (Filizola), and the device for the ambulatory blood pressure monitoring (ABPM) was installed (SAPCELABS 90207, Redmond, USA). The ABPM device was left in place for 24 h, divided into a probable wakefulness period (7:00–23:00 h) and a probable sleep period (23:00–7:00 h). The device was programmed to take readings at 15 minute intervals during the probable wakefulness period and at 20 minute intervals during the probable sleep period. Before each blood collection for the determination of Big ET-1 and plasma NO, three BP measurements were made with the subject in the sitting position, using a mercury column device (auscultatory method) on the upper limb contralateral to that wearing the cuff for ABPM.

A 4.5-ml arterial blood sample was collected at 19:00 h on the day of admission and 7:00 h the following morning for the determination of plasma NO levels (µM). Each sample was divided into three aliquots, and 1.5 ml arterial blood was stored in an Eppendorf tube containing 0.08 ml heparin and centrifuged (Eppendorf AG, model 5418R) for 10 min at 5000 rpm and a standard temperature of 4°C. The supernatant (300 µl) of each Eppendorf tube was removed and transferred to a new tube, which was stored in a freezer at −70°C for later determination by chemiluminescence (specificity of 93.9%). Each arterial blood sample was also processed for the determination of plasma Big ET-1 levels (pg/ml). The collected sample was immediately divided into three aliquots in Eppendorf tubes. Each tube contained 0.1 ml EDTA/1.5 ml blood and 0.1 ml aprotinin/1.5 ml blood each. To reach this value, 0.39 mg EDTA was diluted in 350 ml 0.9% saline solution and 0.39 mg aprotinin was diluted in 350 ml 0.9% saline solution. The sample was then centrifuged in the same apparatus as that used for the sample used for quantifying NO levels for 15 min but at 1600 rpm and a temperature of 0°C. The supernatant (300 ml) of each Eppendorf tube was then removed, transferred to a new tube, and stored in a freezer at -70°C for later determination by ELISA (sensitivity of 0.30 pg/ml and specificity of 100%). The sensitivity for this kit was determined using the guidelines provided by the National Committee for Clinical Laboratory Standards (NCCLS) Evaluation Protocols. (National Committee for Clinical Laboratory Standards Evaluation Protocols, SC1, (1989) Villanova, PA, USA: NCCLS).

Pulse oximetry (DIXTAL, model DX 2022) was recorded from 7pm to 7am for all volunteers. A finger sensor placed on the index finger contralateral to the arm used for BP measurement by ABPM device was used in order to obtain the level of arterial oxyhemoglobin saturation (O2 Sat).

The polysomnography study was performed in the Clinical Neurophysiology Laboratory of HCFMRP-USP using the Biologic Sleepscan Vision PSG Polygraph (NatusBiologic Systems, San Carlos, CA, USA) to obtain the AH/h, as previously described, the total number of apnea and hypopnea (NAH) episodes during sleep, and the number of NAM.

The mean and standard deviation was calculated for data with a normal distribution (parametric), and the median was calculated for non-parametric data (those regarding Big ET-1 and NO). The SAS® 9.0 software was used for these analyses. Fisher’s exact test was used to describe the frequencies according to gender. To determine possible correlations between the variables, Pearson’s correlation coefficient was calculated for parametric data and Spearman’s correlation coefficient was calculated for non-parametric data using R software. For the study of Big ET-1 and NO, we corrected group comparison including BP, BMI and NAH in the analysis since these are factors that may influence the final result (univariate analysis of variance). The study was submitted to the Ribeirão Preto School of Medicine’s Ethics Committee and approved in accordance with protocol number 14103. All participants received detailed information about the goals and procedures of the study, and they signed an informed consent form in compliance with Resolution 196/96 of the National Health Council.

Results

Table 1 shows the participant characteristics obtained at the initial clinical evaluation. No difference was observed between the groups regarding the distribution of antihypertensive medications used. Between group 1 and group 2, the respective use was as follows: diuretics, 68% and 66.6%; angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, 68% and 58.3%; calcium channel antagonists, 20% and 25%; and beta-blockers, 32% and 50%.
Table 1 - Anthropometric and clinical characteristics of group 1 (hypertensive patients with obstructive sleep apnea-hypopnea syndrome) and group 2 (hypertensive patients without obstructive sleep apnea-hypopnea syndrome)

| Characteristics                  | Group 1 (25) | Group 2 (12) |
|----------------------------------|--------------|--------------|
| Age                              | 67.0 ± 6.5   | 67.8 ± 6.8   |
| Weight (G)                       | 78.8 ± 15.1  | 75.8 ± 13.1  |
| Height (M)                       | 1.60 ± 0.11  | 1.60 ± 0.09  |
| BMI (kg/m²)                      | 30.3 ± 4.8   | 29.0 ± 5.0   |
| Number of antihypertensive medications | 1.9 ± 0.9  | 2.3 ± 0.9   |
| Hours of sleep                   | 5.3 ± 0.8    | 5.1 ± 1.6    |

Values are reported as mean ± standard deviation (unpaired Student t-test, p > 0.05); BMI: Body mass index

Discussion

Today, sleep changes are highly prevalent in the general population, in particular the elderly. Epidemiological studies have pointed out that BP elevation is associated with sleep disorders due to the high AHII, resulting in daytime hypersonmolence and cardiorespiratory changes. Furthermore, Mary et al. stated that BP elevation occurs at the end of each episode of obstructive apnea.

When evaluating BP by means of ABPM, we did not observe differences in systolic (S) BP or diastolic (D) BP between subjects with and without OSAHS during sleep, wakefulness and during a 24-hour period. This result differs from that reported by Martinez Garcia et al. who observed higher SBP and DBP in patients with OSAHS, but agrees with the report of Davies et al. who did not detect a difference in wakefulness or 24-hour SBP between groups with and without OSAHS, and also with an Oxford study cited by Davies et al. which, when comparing SBP and DBP between the same groups, did not detect a difference during sleep or wakefulness. In our study, the BP decrease during the sleep period was the same between the groups with and without OSAHS, and both groups showed an attenuation of the decline in BP, with values <10%. It is important to point out that the two groups studied were composed of controlled hypertensive subjects continuously taking antihypertensive medications, with no differences in the number of medications taken. However, the small number of volunteers may have limited the power for detecting differences in BP between the groups.

The result of conventional BP measurement performed at 19:00 h and 7:00 h by auscultatory method by a trained investigator correlated well with the 24-h BP obtained by ABPM. This suggests that where skills exist, auscultatory method can be used in clinical practice when ABPM is not readily available, or at times when periodic reevaluation is necessary. However, it is important to note that ABPM is the gold standard for BP evaluation, and that obtaining data in this manner allowed the study to take be conducted during sleep and wakefulness.

An important result of the present study was the difference in minimum and mean O₂ saturation levels observed during sleep, with the OSAHS group showing significant hypoxemia, as expected. Lima et al. observed the same hypoxic effect in patients with sleep apnea compared to healthy individuals, and similar data were obtained by Peled et al.
Table 2 - Systolic blood pressure (SBP) and diastolic blood pressure (DBP) during ambulatory blood pressure monitoring (ABPM) and blood pressure measurement by the auscultatory method in group 1 (hypertensive patients with sleep apnea-hypopnea syndrome) and group 2 (hypertensive patients without sleep apnea-hypopnea syndrome)

| BP       | Mean BP Group 1 (25) | Mean BP Group 2 (12) |
|----------|----------------------|----------------------|
| ABPM     |                      |                      |
| 24-Hours | SBP 122 ± 12         | 127 ± 13             |
|          | DBP 72 ± 11          | 74 ± 10              |
| Sleep    | SBP 116 ± 15         | 122 ± 13             |
|          | DBP 68 ± 12          | 70 ± 8               |
| Wakefulness | SBP 123 ± 13      | 127 ± 15             |
|          | DBP 75 ± 10          | 76 ± 11              |
| Auscultatory | SBP 130 ± 22      | 132 ± 12             |
|          | DBP 79 ± 13          | 78 ± 9               |
|          | At 19:00 Hours       |                      |
|          | SBP 129 ± 17         | 144 ± 22             |
|          | DBP 80 ± 11          | 85 ± 11              |

Values are reported as mean ± standard deviation (unpaired Student t-test, p > 0.05 group 1 vs. group 2). BP: Blood pressure.

Table 3 - Number of awakenings and microawakenings (NAM), number of apnea-hypopnea (NAH) episodes and apnea-hypopnea index (AHI) obtained from polysomnography, and minimum oxygen saturation (min O₂ saturation) and mean oxygen saturation (mean O₂ saturation) in group 1 (hypertensive patients with sleep apnea-hypopnea syndrome) and group 2 (hypertensive patients without sleep apnea-hypopnea syndrome)

| Variables          | Group 1 (25) | Group 2 (12) |
|--------------------|--------------|--------------|
| NAM                | 259.7 ± 133.9| 140.2 ± 66.0*|
| NAH                | 140.2 ± 66.0 | 17.3 ± 11.0* |
| AHI                | 29.0 ± 13.7  | 3.1 ± 1.6*   |
| Minimum O₂ Saturation | 80.7 ± 7.1  | 92.3 ± 4.5*  |
| Mean O₂ Saturation | 91.1 ± 3.8   | 94.6 ± 2.4*  |

Values are reported as mean ± standard deviation (unpaired Student t-test, *p < 0.001 vs. group 1).

Figure 1 - Plasma levels of Nitric oxide (µM) in group 1 (OSAHS) and group 2 (no OSAHS).
Figure 2 - Plasma levels of Big-Endothelin-1 (pg/ml) in group 1 (OSAHS) and group 2 (no OSAHS).

Figure 3 - Correlation between body mass index (BMI) and number of awakenings and microawakenings (NAM) in hypertensive patients with and without OSAHS (Spearman, $r = 0.51, p = 0.002$).
When we evaluated the respiratory events by polysomnography we observed significant differences between groups regarding NAM, NAH and AHI, in agreement with published reports, since these are relevant data for the characterization of individuals. These data agree with those reported by Lima et al and Ventura et al.

The clinical importance of NO regarding BP has been well defined since this powerful vasodilator directly affects the tonus of peripheral blood vessels and its inhibition generates hypertension. Basal NO activity is known to be reduced in hypertensive patients. Ip et al. stated that endothelial NO can also play an important role in BP regulation in individuals with OSAHS. However, literature reports have shown that NO deficiency can be reversed in hypertensive individuals by the administration of antihypertensive medications. A study on hypertensive mice demonstrated that, after the use of captopril, no inhibition of NO synthesis was observed, with consequent BP regulation. Another antihypertensive agent that results in BP attenuation and improved NO-mediated vasodilation, is spironolactone. As already mentioned, basal NO levels in the present study did not differ between the hypertensive individuals with and without OSAHS. It should be pointed out that both groups consisted of hypertensive subjects controlled with antihypertensive medications with controlled BP. Based on these data, we can suggest that NO activity is equilibrated in cases of treated hypertension.

Studies conducted on elderly persons have demonstrated an increase in plasma ET-1 levels compared with young individuals. Zamarron-Sanz et al. confirmed a significant increase in ET-1 levels in individuals with OSAHS compared to healthy subjects. Jordan et al. detected increased plasma Big ET-1 levels in a group of patients with OSAHS not receiving clinical or surgical treatment. In the present study there was a higher Big ET-1 concentration in individuals with OSAHS at 7am, after the sleep period.

In general, plasma ET-1 levels tend to be low and there is no consensus on a definitive protocol that would facilitate the reproducible determination of ET-1 or Big ET-1 levels in different biological fluids. There are many variations in the extraction protocols above basal values, ranging from 0.5 to 50 pg/ml, with comparison of the results obtained often being difficult. In the present study, Big ET-1 determinations showed wide variability although identical processing and storage techniques were used.

Evaluation of the variables in the OSAHS group revealed a negative correlation between SBP and O₂ saturation levels, i.e., SBP increased with decreasing arterial oxygenation. Moreover, increased Big ET-1 levels were correlated with higher O₂ saturation levels, and BP was positively correlated with Big ET-1 levels; thus, the greater the vasoconstriction caused by Big ET-1, the higher the SBP. Further, we observed a positive correlation between NAH, AHI, and plasma Big ET-1 levels, suggesting a possible increase in vasoconstriction associated with increasing NAH episodes. No matter how small the number of awakenings among individuals with the syndrome, an increase in sympathetic tonus will occur, with a marked elevation not only of BP, but also of heart rate. Depending on the intensity of sleep apnea, this process may occur hundreds of times during the night. Thus, NAM during sleep contributes to autonomic hyperactivity as one of the mechanisms that explains hypertension associated with OSAHS.

In the present study, a positive correlation was observed between NAM and DBP (during sleep, wakefulness, and on 24-h ABPM), with the increase in DBP being related to the greater sleep fragmentation during the total sleep time. We did not observe a significant correlation between NAM and SBP (p > 0.05).

Martinez-Garcia et al. found a more significant correlation between NAM and DBP (during sleep and wakefulness). In contrast, Logan et al. observed a greater correlation between sleep fragmentation and SBP.

On comparing BMI with NAM, we observed that a higher BMI was correlated with an increase in NAM, suggesting that BMI may interfere with the sleep of individuals with OSAHS. According to Ware, McBryar and Scott, apnea events are highly sensitive to changes in BMI, i.e., the greater the weight, the higher the probability of apneic events. As described earlier, obesity is an established, important pathogenic factor for OSAHS.

Approximately 70% of individuals diagnosed with sleep apnea are considered to be obese according to their BMI, with this being the only significant risk factor that is reversible. In the present group without OSAHS, an increased number of NAH and an increased AHI were correlated with SBP elevation. Grote et al. in studying the influence of AHI on BP observed that the probability of uncontrolled hypertension increases by 2% with each unit increase in AHI.

Antczak et al. reported that there is evidence that obesity, even in the absence of respiratory sleep disorders, negatively affects the quality of sleep, increasing daytime somnolence. Furthermore, studies have observed that obese patients without OSAHS had a higher frequency of awakenings during sleep compared with patients with normal weight. On this basis, we believe that, regardless of whether an individual has OSAHS or not, obesity is an extremely important factor regarding the quality of sleep. In the present study, groups did not differ in terms of the prevalence of obesity.

In addition, we observed that obesity negatively influences O₂ saturation levels, with an increased BMI causing greater desaturation. When correlating NAM with O₂ saturation levels, we observed a decline in saturation with increasing sleep fragmentation.

In conclusion, elderly hypertensive subjects with OSAHS presented a greater Big-ET-1 level after the sleep period regardless of BP, since their BP was controlled and similar to the SBP of hypertensive elderly subjects without OSAHS. In patients with OSAHS, a correlation was observed between Big ET-1 and SBP; Big ET-1 and NAH; and O₂ saturation and SBP. In both groups, a higher BMI was correlated with greater desaturation and NAM. NO levels did not differ between the hypertensive patients with or without OSAHS. It is noteworthy that both groups consisted of hypertensive patients controlled with antihypertensive medications.
Author contributions

Conception and design of the research: Anunciato IF, Lima NKC; Acquisition of data: Anunciato IF, Lobo RR, Verri Jr. WA, Eckeli AL, Évora PRB, Nobre F; Analysis and interpretation of the data: Anunciato IF, Lobo RR, Eckeli AL, Lima NKC; Statistical analysis: Coelho EB, Lima NKC; Obtaining funding: Lima NKC; Writing of the manuscript: Anunciato IF, Moriguti JC, Ferriolli E, Lima NKC; Critical revision of the manuscript for intellectual content: Anunciato IF, Coelho EB, Verri Jr. WA, Évora PRB, Nobre F, Moriguti JC, Ferriolli E, Lima NKC.;

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was funded by FAEPA.

Study Association

This article is part of the thesis of master submitted by Iara Felício Anunciato from Faculdade de Medicina de Ribeirão Preto - USP.
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