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Contribution of Autonomic Nervous System to the Hypertension Induced by Obstructive Sleep Apnea

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1. Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality in the adult population. The most common risk condition to almost all cardiovascular diseases is hypertension. The obstructive sleep apnea (OSA) syndrome, a growing worldwide sleep-breathing disorder is recognized as an independent risk factor for hypertension and is associated with other cardiovascular diseases, such as stroke, pulmonary hypertension, coronary artery disease and stroke. OSA is characterized by repeated episodes of airflow detention during sleep produced by the upper airway collapse. Among the disturbances produced by OSA, the chronic intermittent hypoxia is considered the main factor for the progression of the systemic hypertension. Although the link between OSA and systemic hypertension is well established, the pathogenic mechanisms responsible for the hypertension are not entirely understood. Autonomic dysfunction, oxidative stress and inflammation have been proposed as potential hypertensive mechanisms. However, conclusions from studies in OSA patients are controversial, because of concomitant comorbidities (i.e. obesity, metabolic disorders and cardiovascular diseases), which are confounding factors that increases the cardiovascular risk associated with OSA. Thus, experimental models of rodents exposed to chronic intermittent hypoxia, which reproduced several pathologic cardiovascular features of OSA, are the gold-standard to study the pathogenic mechanisms involved in the OSA-induced hypertension. In this chapter, we will review and discuss the evidence supporting an essential role of the carotid body chemoreceptor and the contribution of the autonomic nervous system to the progression of the hypertension in OSA patients and animals exposed to chronic intermittent hypoxia.

2. Pathogenic mechanisms of the hypertension induced by OSA

The OSA syndrome elicited by repeated airflow total or partial occlusions is diagnosed when patients has an apnea-hypopnea index (AHI) > 10 events/hour. OSA affects up to 9% of the adults men and 4% of women worldwide population [111]. However, according to a report of the American Heart Association in collaboration with the National Center on Sleep Disorders Research, “85% of patients with clinically significant and treatable OSA have never been diagnosed, and referral populations of OSA patients represent only the *tip of the iceberg* of OSA prevalence”. Therefore, the estimated adult population that present an AHI of 5 is ~20% [100]. The OSA syndrome is associated with clinical neurobehavioral dysfunction, such as daytime sleepiness, fatigue, depressed mood, attention and executive deficits, and verbal and visual-spatial memory impairments [5, 67]. Nevertheless, the OSA syndrome is also associated with diurnal systemic hypertension (~50% of the OSA patients developed systemic hypertension), and with stroke, pulmonary hypertension, coronary artery disease and atrial fibrillation [3, 8, 12, 19; 28, 30, 35, 52, 53, 64, 74, 79, 100].

Several epidemiological studies have shown that OSA is an independent risk factor for the progression of the hypertension. Indeed, OSA patients show a positive relationship between AHI and the hypertension, which is independent of other risks [23, 60, 61, 85, 96, 100, 111, 112]. Moreover, results obtained from the Wisconsin Sleep Cohort (an ongoing 21-years longitudinal study performed on 1500 Wisconsin state employees) have shown that untreated OSA patients have a high mortality risk associated with AHI [74, 112].

Although the link between OSA and hypertension is well established, the mechanisms underlying the hypertension are not entirely known. The most accepted explanation proposes that chronic intermittent hypoxia produces oxidative stress, inflammation, and sympathetic hyperactivity, which led to endothelial dysfunction and hypertension [19, 25, 28, 41, 43, 52, 53, 65, 99, 100], but it is likely that intrathoracic pressure changes causing excessive mechanical stress on large artery walls and the heart, and arousal-induced sympathetic hyperactivity may also contribute to the endothelial dysfunction [47]. OSA is characterized by repeated episodes of total or partial airflow detention during sleep produced by the pharyngeal collapse, eliciting intermittent hypoxia and hypercapnia, negative intrathoracic pressure, sleep fragmentation and arousal. During the airflow occlusion, the resulting hypoxia and hypercapnia stimulates the carotid body chemoreceptors producing reflex ventilatory, sympathetic and hypertensive responses. Among these disturbances, the chronic intermittent hypoxia is considered the main factor for the development of the hypertension [1, 19, 33, 41, 43, 51, 55, 56, 82, 83, 88, 93, 100]. However, conclusions from studies performed in OSA patients are partial and somehow controversial, because invasive procedures are precluded because of ethical reasons in humans, and OSA patients often present concomitant morbidities (i.e. obesity, metabolic alterations and other cardiovascular diseases), which are confounding factors that increase the cardiovascular risk. Therefore, experimental models of rodents exposed to intermittent hypoxia, which simulates the hypoxic-reoxygenation cycles and reproduce several of the cardiovascular pathologic features of OSA including hypertension, are the gold-standard to

study the pathogenic mechanisms involved in progression of the cardiovascular and respiratory alterations induced by OSA [15-18, 22, 27, 43, 83-84, 86, 88, 95].

3. Clinical aspects of OSA

There are a strong association between OSA and systemic hypertension in human patients. Indeed, several studies have shown that the prevalence of OSA is higher in hypertensive patients, while other studies have shown that OSA increases the predisposition for hypertension. In addition, there are observational studies that showed that patients with hypertension presented a high incidence of OSA, some of these studies are cross-sectional [27, 46, 51, 109]. It has been found in patients with resistant hypertension, that the main secondary cause was OSA [81]. On other hand, cross-sectional studies have shown that patients with sleep breathing disorders, including OSA and snoring, present a strong correlation with hypertension [8, 74, 112]. Prospective studies also showed a strong association between AHI and THE increased arterial blood pressure [85]. It is relevant to note that the OSA-hypertension link is independent from other comorbidities like obesity [33, 45, 51, 79, 100]. Other study performed in OSA patients without hypertension, which were follow-up during five years for the risk of hypertension, concluded that there is a trend of association between AHI > 30 and the occurrence of the hypertension [75]. OSA patients without treatment presented high risk of hypertension than those patients treated with continuous positive airway pressure (CPAP) therapy [61].

OSA and hypertensive patients frequently present a combination of comorbidities including obesity, diabetes and cardiovascular diseases ([1, 33, 45, 54, 56, 64, 100]. The mechanisms that could explain the association between OSA and hypertension are still in ongoing research. As was mentioned before, the pathogenesis of the association between OSA and hypertension is likely to be multifactorial, involving a varied range of pathogenic mechanisms comprising a group of systemic factors including inflammation, oxidative stress and metabolic dysregulation, which are beyond the scope of this review. Evidence supporting the role played by sympathetic dysfunction has been demonstrated by different invasive and noninvasive methods that quantify sympathetic activity in patients with OSA, the main methods reported are:

3.1. Muscle sympathetic nerve activity in OSA patients

This technique is based on the microneurographic recording with a tungsten electrode of the muscle sympathetic nerve activity in the peroneal nerve, which produce vasoconstriction in blood vessel of skeletal muscles. The muscle sympathetic nerve discharge plays a fundamental role in the homeostasis of the systemic arterial blood pressure. Studies comparing muscle sympathetic discharges between OSA patients and controls showed that patients had higher basal levels of muscle sympathetic nerve discharges [71-73, 99]. Also intermittent hypoxia in humans produced hypertension and elevated the muscle sympathetic nerve discharges [29]. Continuous positive air pressure therapy decrease muscle sympathetic nerve discharges overactivity in OSA patients [39, 72, 73, 99].

3.2. Heart rate variability in OSA patients

The spectral analysis of heart rate variability has two major components defined as the low frequency (LF) band related to sympathetic influences, and the high frequency (HF) band related mainly to vagal influences and respiratory sinus arrhythmia. The LF/HF ratio is believed to be an index of the sympathovagal balance on heart rate [105]. Normotensive patients with recently diagnosed OSA showed a shift of the HRV spectral indexes towards the low frequency band, which is associated with increased sympathetic discharges in the peroneal nerve [70, 97]. The spectral analysis of heart rate variability is performed using a Fast Fourier Transform or autoregressive methods. The spectrum of R-R intervals is assessed using the following frequency bands: very low frequency: DC-0.04 Hz, low frequency (LF): 0.04-0.15 Hz and high frequency (HF): 0.15-0.4 Hz in the frequency domain. HF power reflects the activity of parasympathetic nervous system activity, whereas LF power reflects a combination of sympathetic and parasympathetic activity [92, 105]. OSA patients showed increased sympathetic and reduced vagal modulation of HRV in comparison with controls [2, 4]. This sympatho-vagal imbalance is modified with CPAP therapy; in OSA patients with hypertension CPAP administration reduced the LF power [11, 114].

3.3. Catecholamine measurements in OSA patients

The measurement of blood or urinary catecholamines gives information about their release from neurons and from the adrenal medulla. Baseline values of the plasmatic concentration of norepinephrine (NE) characterize the balance between the amount of NE released and then re-uptake into the nerve terminals. The urinary NE is the amount of NE that is being eliminated by excretion and metabolism. Plasmatic concentration of epinephrine (E) represents a balance between adreno-medullary release, excretion and metabolism. In OSA patients, studies of catecholamines concentrations had shown the presence of elevated levels of catecholamines in plasma and urine [62, 24, 113], suggesting an elevated sympathetic activity. OSA patients with elevated NE levels in plasma and urine showed severe hypertension and excessive sweating, similar to what happened in pheochromocytoma, improved their condition with CPAP therapy ([36]. It has also been shown that CPAP reduces NE levels in patients with severe OSA [101, 113, 114]. In children with OSA an association between AHI and urinary NE and E has been also reported [76].

3.4. Noninvasive cardiovascular autonomic tests in OSA patients

These tests are grouping in two main categories: sympathetic and cardiovagal tests. The sympathetic tests include arterial blood pressure response to gravitational stress, isometric exercise and cold stimuli. Cardiovagal autonomic tests include heart rate changes on deep breathing, Valsalva maneuver ratio and heart rate changes on standing. These tests are performed during wakefulness and they have shown a diurnal sympathetic dysfunction [6, 14, 66, 103]. Also parasympathetic cardiac dysfunction has been found in OSA patients [14, 66, 107]. Overall, the results of these tests suggest an increased sympathetic tone and a decreased parasympathetic cardiac function in OSA patients.

4. Autonomic dysfunction in animals exposed to chronic intermittent hypoxia

Patients recently diagnosed with OSA, show enhanced vasopressor and ventilatory responses to acute hypoxia [69, 71], sympathetic hyperactivity, demonstrated by an increased muscle sympathetic neural activity [9, 68, 72-73, 99] and a higher accumulation of 24-h urinary norepinephrine [21]. Similarly, animals exposed to chronic intermittent hypoxia present enhanced sympathetic discharges and respiratory responses to acute hypoxia, and develop systemic hypertension [15, 20, 25, 26, 34, 37, 48, 59, 86, 87, 92, 115]. The autonomic alteration is characterized by an enhanced sympathetic outflow, reduction of the efficiency of the baroreflexes sensitivity and alterations of heart rate variability. Indeed, non-invasive spectral analysis of heart rate variability suggested a preponderance of the sympathetic drive in animals exposed to chronic intermittent hypoxia [15, 20, 57, 86, 88, 92], similarly to what was observed patients with OSA [68,72, 97,99]. Thus, it is likely that the enhanced sympathetic activity along with the reduction of the baroreflex sensitivity could impair heart rate variability and the regulation of vasomotor tone of blood vessels contributing to the hypertension. In addition, chronic intermittent hypoxia elicits vagal withdrawal, attributed in part to neuronal loss in ambiguous nucleus [57, 110].

Using a protocol of short hypoxic cycles (10% O₂, 10 times/hr for 8 hrs), we found that exposure of cats to chronic intermittent hypoxia for 4 days enhanced the ventilatory responses induced by acute hypoxia and reduced the sensitivity of the baroreflex control of heart rate, but did not evoke hypertension or enhanced the vasopressor responses to hypoxia [88, 90, 92]. However, normotensive animals exposed to chronic intermittent hypoxia like normotensive OSA patients, show a similar increased LF/HF ratio [88, 92]. Besides that, we found a positive linear correlation ($r=0.97$) between the LH/HF ratio and the baseline carotid body chemosensory discharges in the hypoxic-treated cats, suggesting that the potentiation of carotid body chemosensory discharges may be linked to early changes in the autonomic control of heart rate in cats exposed to short-term chronic intermittent hypoxia [92]. Thus, our results suggest that the hypertension induced by chronic intermittent hypoxia is preceded by early alterations in the autonomic balance of the heart rate, associated with an enhanced carotid body chemosensory response to hypoxia and a decreased baroreflex control [88, 92]. Lai et al., [See in 49] also found that chronic intermittent hypoxia increases the LF component and the LF/HF ratio of the blood pressure variability before the onset of the hypertension in conscious rats exposed to intermittent hypoxia.

5. Contribution of the carotid body to the cardiorespiratory alterations in OSA patients and animals exposed to chronic intermittent hypoxia

The enhanced cardiorespiratory responses to acute hypoxia observed in OSA patients has been attributed to a potentiated hypoxic peripheral chemoreflexes [12, 58, 69, 71], suggesting that carotid body chemoreceptors play a main role in the pathological alterations induced by OSA.

Moreover, Fletcher et al., [See in 26] found that the bilateral carotid body denervation prevented the hypertension in rats exposed to chronic intermittent hypoxia, suggesting that the carotid body contributes to the cardiovascular pathologies induced by OSA. In the last years, the proposal that the carotid body is involved in the progression of the intermittent hypoxia-induced hypertension received substantial attention [19, 22, 25, 28, 41, 43, 98, 100].

A growing body of new evidence supports the proposal that the carotid body is involved in the generation of the hypertension in OSA patients and animals exposed to intermittent hypoxia. OSA patients present enhanced ventilatory, pressor and sympathetic responses to acute hypoxia, attributed to a potentiation of the peripheral hypoxic chemoreflexes [58, 100]. Narkiewicz et al. [See in 69, 71] studied the reflex ventilatory, tachycardic and vasopressor responses to acute hypoxia in untreated normotensive patients with OSA, and found that the hypoxic stimulation produce larger increases in volume-minute ventilation, heart rate and arterial blood pressure in OSA patients than control subjects. Thus, the available data support the idea that the enhanced chemoreflex response observed in OSA patients is produced by the intermittent hypoxia. Similarly, animals exposed to chronic intermittent hypoxia show enhanced hypoxic ventilatory responses to acute hypoxia [15, 18, 43, 44, 87] and long-term facilitation of respiratory motor responses [63, 83, 88]. Recording of chemosensory nerve impulses from the carotid sinus nerve have confirmed the idea that chronic intermittent hypoxia produces long-term facilitation of the carotid body chemosensory responses to hypoxia. Indeed, exposure of rats and cats to intermittent hypoxia for few days increases the basal carotid body discharges measured in normoxia and enhances the chemosensory responses to acute hypoxia [15, 18, 43, 82-84, 88, 90].

The carotid body, located in the bifurcations of the carotid arteries is the main arterial oxygen chemoreceptor in terms of its contribution to the ventilatory reflex responses. In mammals, the hypoxic stimulation of the carotid body increases the sympathetic discharges to the arterial blood vessels and heart, producing hypertension. The primary oxygen sensors in the carotid body are the glomus cells, which are in synaptic contact with the nerve terminals of the chemosensory petrosal neurons [31, 40, 42]. The current model of chemoreception states that hypoxia induces the inhibition of voltage-independent tandem pore domain potassium channels (TASK K^+), leading to the depolarization of the glomus cells, the entry of Ca^{2+} through L-type Ca^{2+} channels, and the subsequent release of excitatory transmitters (Acetylcholine and adenosine triphosphate), which increases the discharges of the nerve endings of the petrosal chemosensory neurons [40, 42]. Recently, we found that chronic intermittent hypoxia potentiates the hypoxic inhibition of the TASK-like K^+ channel currents in glomus cells from intermittent hypoxia rats. This novel effect of intermittent hypoxia may contribute to explain its enhancing effect on carotid body hypoxic chemoreception [77]. The carotid body is a polymodal chemosensory receptor, which is activated by hypoxia, hypercapnia, acidosis, stop flow, temperature and respond to the levels of glucose [31]. The carotid body has been involved in several sympathetic-mediated diseases such as hypertension, heart failure, diabetes and renal failure [94]. Moreover, the denervation or ablation of the carotid body has been proposed for the treatment of severe and resistant hypertension [78].

6. Mediators of enhanced carotid body chemosensory responses to hypoxia in animal models of OSA

Reactive oxygen species (ROS) and reactive nitrogen species (RNS), and pro-inflammatory agents have been proposed as mediators of cardiovascular and cognitive alterations in OSA patients [7, 13, 33, 45, 52, 65, 102] and animal models [10, 15-18, 44, 48, 82, 84, 106]. Studies performed in OSA patients and animals exposed to intermittent hypoxia showed that the hypoxia-reoxygenation episodes produce systemic oxidative stress due to the accumulation of ROS and RNS, which are potential sources of cellular damage. Recently, we tested the hypothesis that oxidative stress contributes to the carotid body chemosensory potentiation and the progression of the hypertension in rats exposed to chronic intermittent hypoxia [15, 18, 44]. We found that intermittent hypoxia increased the plasma lipid peroxidation and the formation of the oxidative stress marker 3-nitrotyrosine in the carotid body. In addition, chronic intermittent hypoxia enhances carotid body chemosensory and reflex ventilatory responses to hypoxia, alters heart rate variability and elicits hypertension [15]. Ascorbic acid treatment reduced the increased systemic and local carotid body oxidative stress, the potentiation of the carotid body chemosensory and ventilatory responses to hypoxia, as well as the hypertension [15]. These results agree and extend previous observations that antioxidant pretreatment prevented the carotid body chemosensory potentiation [80, 82] and the hypertension [106] in rats exposed to intermittent hypoxia. Although, these results strongly suggest that the carotid body chemosensory potentiation is mediated by oxidative stress [15, 43, 44, 80], it is matter of debate if ROS *per se* increases the carotid body chemosensory discharges [32]. Thus, it is likely that other molecule downstream the ROS signals mediate the effects of ROS on carotid body chemoreception induced by intermittent hypoxia. The CB, the main contributor to the sympathetic activation and hypertension following intermittent hypoxia is extremely sensitive to peroxynitrites formation [15]. Thus, RNS formation is a common feature in both human and experimental OSA models, suggesting that may participate in the OSA pathophysiology. In conclusion, the available evidence supports and extends the idea that both oxidative and nitrosative stress plays a pivotal role in OSA pathophysiology.

Among the molecules upregulated in the carotid body by intermittent hypoxia, such as endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), and inducible nitric oxide synthase (iNOS) [15-18, 50, 89-91], pro-inflammatory cytokines have been proposed as mediators of the carotid body chemosensory potentiation induced by intermittent hypoxia [16, 18, 43, 44, 50] and cardiovascular pathologies in OSA patients [7, 65, 108, 104]. We found that chronic intermittent hypoxia induced a ROS-dependent increases of tumor necrosis factor (TNF) and Interleukin 1 β (IL-1 β) in the carotid body, suggesting that these pro-inflammatory cytokines may mediate the ROS-induced carotid body potentiation [16, 18]. To test this hypothesis, we studied the effects of ibuprofen on the increased TNF- α and IL-1 β levels in the rat carotid body, the potentiation of carotid body chemosensory and ventilatory hypoxic responses and the hypertension [18]. Ibuprofen prevented the carotid body cytokines overexpression, the enhanced hypoxic ventilatory response and the hypertension, but failed to block the enhanced carotid body chemosensory responses. Thus, our studies suggest that the

upregulation of $\text{TNF-}\alpha$ and $\text{IL-1}\beta$ in the carotid body induced by chronic intermittent hypoxia is linked to oxidative stress, as well as the enhanced carotid body chemosensory responsiveness to hypoxia, but the chemosensory potentiation does not depend on the increased $\text{TNF-}\alpha$ and $\text{IL-1}\beta$ levels in the carotid body [18]. However, pro-inflammatory cytokines contribute to enhance the hypoxic ventilatory response and the hypertension induced by chronic intermittent hypoxia, suggesting that multiple mechanisms may participate in the cardiorespiratory alterations induced by intermittent hypoxia [18]

Figure 1 shows a diagram of the proposed contribution of the intermittent hypoxic induced potentiation of CB chemosensory hypoxic responsiveness to the hypertension. It is likely that the hypoxic-reoxygenation cycles enhance the CB chemosensitivity to hypoxia, which in turn contributes to elicit a persistent augmented sympathetic neural output.

Figure 1. Diagram of the contribution of the carotid body (CB) to the hypertension induced by chronic intermittent hypoxia. ROS, reactive oxygen species. NTS, nucleus of the tractus solitarius. CG, chemoreceptor (glomus) cells.

7. Conclusion

OSA patients and animals exposed to chronic intermittent hypoxia show autonomic alterations and a potentiated carotid body chemosensory response to hypoxia. The autonomic alterations are characterized by an enhanced sympathetic outflow, a reduction of the efficiency

of the baroreflexes sensitivity and alterations of heart rate variability. Indeed, non-invasive spectral analysis of heart rate variability shows a predominance of the sympathetic drive in patients with OSA and animals exposed to intermittent hypoxia. Moreover, direct recordings of muscle nerve sympathetic discharges also showed an increased sympathetic tone and response to hypoxia. Thus, it is likely that the enhanced sympathetic activity along with the reduction of the baroreflex sensitivity could impair heart rate variability and the regulation of vasomotor tone of blood vessels eliciting sustained blood pressure elevation.

Studies performed in OSA patients and animals models exposed to chronic intermittent hypoxia have provide evidence that OSA is associated with enhanced sympathetic activation, mainly attributed to the chronic intermittent hypoxia. The link between the cardiovascular consequences of OSA, including hypertension is multifactorial, most likely related to enhanced sympathetic activity, but also with oxidative stress and systemic inflammation. Understanding how the autonomic dysfunction induced by intermittent hypoxia interacts with metabolic alterations, oxidative stress and inflammation will provide new insights into the pathogenesis of the hypertension associated with OSA. Further basic knowledge will allow proposing and developing new therapeutic strategies to moderate the severity of the cardiovascular alterations induced by OSA.

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References

- [1] Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI. Molecular signatures of obstructive sleep apnea in adults: A review and perspective. *Sleep* 2009; 32: 447-470.

- [2] Aydin M, Altin R, Ozeren A, Kart L, Bilge M, Unalacak M. Cardiac autonomic activity in obstructive sleep apnea: time-dependent and spectral analysis of heart rate variability using 24-hour Holter electrocardiograms. *Tex Heart Inst J* 2004; 31: 132–136.
- [3] Baguet JP, Barone-Rochette G, Tamisier R, Levy P, Pépin JL. Mechanisms of cardiac dysfunction in obstructive sleep apnea. *Nat Rev Cardiol* 2012; 9: 679–688.
- [4] Balachandran JS, Bakker JP, Rahangdale S, Yim-Yeh S, Mietus JE, Goldberger AL, Malhotra A. Effect of mild, asymptomatic obstructive sleep apnea on daytime heart rate variability and impedance cardiography measurements. *Am J Cardiol* 2012; 109, 140–145.
- [5] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *J Sleep Res* 2002; 1: 1–16.
- [6] Belozeroff V, Berry RB, Khoo MC. Model-based assessment of autonomic control in obstructive sleep apnea syndrome. *Sleep* 2003; 26: 65–73.
- [7] Biltagi MA, Maguid MA, Ghafar MA, Farid E. Correlation of 8-isoprostane, interleukin-6 and cardiac functions with clinical score in childhood obstructive sleep apnoea. *Acta Paediatr* 2008; 97: 1397–1405.
- [8] Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, Kales, A. Association of hypertension and sleep-disordered breathing. *Arch Intern Med* 2000; 160, 2289–2295.
- [9] Carlson JT, Hedner J, Elam M, Ejnell, H; Sellgren, J Wallin, BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. *Chest* 1993; 103: 1763–1768.
- [10] Chen L, Einbinder, E, Zhang, Q, Hasday J, Balke, CW. Scharf SM. Oxidative stress and left ventricular function with chronic intermittent hypoxia in rats. *Am J Respir Crit Care Med* 2005; 172: 915–920.
- [11] Cheng JH, Hua CC, Chen NH, Liu YC, Yu CC. Autonomic activity difference during continuous positive airway pressure titration in patients with obstructive sleep apnea/hypopnea syndrome with or without hypertension. *Chang Gung Med J* 2011; 34: 410–417.
- [12] Cistulli PA, Sullivan CE. Pathology of sleep apnea. In: *Sleep and Breathing*. Saunders NA, Sullivan CE (eds) New York: Marcel Decker. 1994.
- [13] Christou IK, Moulas AN, Pastaka C, Gouroulisanis KI. Antioxidant capacity in obstructive sleep apnea patients. *Sleep Med* 2003; 4: 225–228.
- [14] Cortelli P, Parchi P, Sforza E, Contin M, Pierangeli G, Barletta G, Lugaresi E. Cardiovascular autonomic dysfunction in normotensive awake subjects with obstructive sleep apnoea syndrome. *Clin Auton Res* 1994; 4: 57–62.

- [15] Del Rio R, Moya EA, Iturriaga R. Carotid body and cardiorespiratory alterations in intermittent hypoxia: the oxidative link. *Eur Respir J* 2010; 36: 143-150.
- [16] Del Rio, R, Moya, EA, Iturriaga R. Differential expression of pro-inflammatory cytokines, endothelin-1 and nitric oxide synthases in the rat carotid body exposed to intermittent hypoxia. *Brain Res* 2011; 1395: 74-85.
- [17] Del Rio R, Moya EA, Muñoz C, Arias P, Court FA, Iturriaga R. Chronic intermittent hypoxia-induced vascular enlargement and VEGF upregulation in the rat carotid body is not prevented by antioxidant treatment. *Am J Physiol Lung Cell Mol Physiol*. 2011; 301: L702-L711.
- [18] Del Rio R, Moya EA, Parga MJ, Madrid C, Iturriaga R. Carotid body inflammation and cardiorespiratory alterations in intermittent hypoxia. *Eur Respir J* 2012; 39:1492-1500.
- [19] Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev*. 90:47-112, 2010.
- [20] Dick TE, Hsieh YH, Wang N. Prabhakar NR. Acute intermittent hypoxia increases both phrenic and sympathetic nerve activities in the rat. *Exp Physiol* 2007; 92: 87-97.
- [21] Dimsdale J.E, Coy T, Ziegler MG, Ancoli-Israel S, Clausen J. The effect of sleep apnea on plasma and urinary catecholamines. *Sleep* 1995; 18: 377-381.
- [22] Dumitrascu R, Heitmann J, Seeger W, Weissmann N, Schulz R. Obstructive sleep apnea, oxidative stress and cardiovascular disease: lessons from animal studies. *hindawi publishing corporation oxidative medicine and cellular longevity*, 7 pages <http://dx.doi.org/10.1155/2013/234631>, 2013.
- [23] Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008; 5: 144-153.
- [24] Elmasry A, Lindberg E, Hedner J, Janson C, Boman G. Obstructive sleep apnoea and urine catecholamines in hypertensive males: a population-based study. *Eur Respir J* 2002; 19: 511-517.
- [25] Feng J, Chen, BY. Cui LY. Carotid body-mediated changes of sympathetic nerve and their relationships with hypertension. *Chin Med J* 2008; 121: 1732-1735.
- [26] Fletcher EC, Lesske J, Behm R, Miller CC, Stauss H, Unger T. Carotid chemoreceptors, systemic blood pressure, and chronic episodic hypoxia mimicking sleep apnea. *J Appl Physiol* 1992; 72:1978-1984.
- [27] Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB. Undiagnosed sleep apnea in patients with resistant hypertension. *Ann Intern Med*. 1985;103:190-195.
- [28] Garvey JF, Taylor CT. McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. *Eur Respir J* 2009; 33: 1195-1205.

- [29] Gilmartin GS, Lynch M, Tamisier R, Weiss JW. Chronic intermittent hypoxia in humans during 28 nights results in blood pressure elevation and increased muscle sympathetic nerve activity. *Am J Physiol Heart Circ Physiol* 2010; 299: H925–H931.
- [30] Godoy J, Mellado P, Tapia J, Santín J. Obstructive sleep apnea as an independent stroke risk factor: possible mechanisms. *Curr Mol Med* 2009; 9 :203-209.
- [31] Gonzalez C, Almaraz L, Obeso A, Rigual R. Carotid body chemoreceptors: from natural stimuli to sensory discharges. *Physiol Rev* 1994; 74 :829-898.
- [32] Gonzalez C, Agapito MT, Rocher A, Gonzalez-Martin MC, Vega-Agapito V, Gomez-Niño A, Rigual R, Castañeda J. Obeso, A. Chemoreception in the context of the general biology of ROS. *Respir Physiol Neurobiol* 2007; 157: 30-44.
- [33] Gozal D. Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea, oxidative stress, inflammation, and much more. *Am J Respir Crit Care Med* 2008; 177: 369–375.
- [34] Greenberg, HE, Sica, A, Batson, D. Scharf, SM. Chronic intermittent hypoxia increases sympathetic responsiveness to hypoxia and hypercapnia. *J Appl Physiol* 1999; 86: 298-305.
- [35] Hedner J, Grote L, Bonsignore M, McNicholas W, Lavie P, Parati G, Sliwinski P, Barbé F, De Backer W, Escourrou P, Fietze I, Kvamme JA, Lombardi C, Marrone O, Masa JF, Montserrat JM, Penzel T, Pretl M, Riha R, Rodenstein D, Saaresranta T, Schulz R, Tkacova R, Varoneckas G, Vitols A, Vrints H, Zielinski J. The European Sleep Apnoea Database (ESADA): Report from 22 European sleep laboratories. *Eur Respir J* 2011; 38 :635-642,
- [36] Hoy LJ, Emery M, Wedzicha JA, Davison AG, Chew SL, Monson JP, Metcalfe KA. Obstructive sleep apnea presenting as pseudopheochromocytoma: a case report. *J Clin Endocrinol Metab* 2004; 89: 2033-2038.
- [37] Huang J, Lusina S, Xie T, Ji E, Xiang S, Liu Y, Weiss JW. Sympathetic response to chemostimulation in conscious rats exposed to chronic intermittent hypoxia. *Respir Physiol Neurobiol*. 2009; 166:102-106.
- [38] Imadojemu VA, Mawji Z, Kunselman A, Gray KS, Hogeman CS, Euenberger UA. Sympathetic chemoreflex responses in obstructive sleep apnea and effects of continuous positive airway pressure therapy. *Chest* 2007; 131: 1406–1413.
- [39] Iturriaga R. Alcañaga, J. Neurotransmission in the carotid body: transmitters and modulators between glomus cells and petrosal ganglion nerve terminals. *Brain Res Rev* 2004; 47 :46-53.
- [40] Iturriaga R, Del Rio R, Rey S. Cardiovascular and ventilatory acclimatization induced by chronic intermittent hypoxia: A role for the carotid body in the pathophysiology of sleep apnea. *Biol Res* 2005; 38: 335-340.

- [41] Iturriaga, R, Varas, R, Alcayaga J. Electrical and pharmacological properties of petrosal ganglion neurons that innervate the carotid body. *Respir Physiol Neurobiol*, 2007; 57: 130-139.
- [42] Iturriaga R, Moya EA, Del Rio, R. Carotid body potentiation induced by intermittent hypoxia: implications for cardioventilatory changes induced by sleep apnoea. *Clin Exp Pharmacol Physiol*, 2009; 36: 1197-1204.
- [43] Iturriaga R, Del Rio R. Oxidative stress in the carotid body: implications for the cardioventilatory alterations induced by obstructive sleep apnea. In: *Oxidative Stress and Diseases*. Lushchak VI, Gospodaryov DV (eds.). INTECH. Open Access Publisher. www.intechweb.org. 71-86, 2012.
- [44] Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, Colombo PC, Basner, RC, Factor P, LeJemtel TH. Oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. *Circulation* 2008; 117: 2270-2278.
- [45] Kales A, Bixler EO, Cadieux RJ, Schneck DW, Shaw LC 3rd, Locke TW, Vela-Bueno A, Soldatos CR. Sleep apnoea in a hypertensive population. *Lancet* 1984; 2:1005-1008.
- [46] Kohler, M. Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol* 2010; 7: 677-685.
- [47] Kumar GK, Rai V, Sharma SD, Ramakrishnan DP, Peng YJ, Souvannakitti D, Prabhakar NR. Chronic intermittent hypoxia induces hypoxia-evoked catecholamine efflux in adult rat adrenal medulla via oxidative stress. *J Physiol* 2006; 575: 229-239.
- [48] Lai CJ, Yang CCH, Hsu YY, Lin YN, Kuo TBJ. Enhanced sympathetic outflow and decreased baroreflex sensitivity are associated with intermittent hypoxia-induced systemic hypertension in conscious rats. *J Appl Physiol* 2006; 100: 1974-1982.
- [49] Lam SY, Tipoe GL, Liong EC, Fung ML. Chronic hypoxia upregulates the expression and function of proinflammatory cytokines in the rat carotid body. *Histochem Cell Biol* 2008; 130: 549-659.
- [50] Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *BMJ* 2000; 320: 479-482.
- [51] Lavie L. Obstructive sleep apnoea syndrome: an oxidative stress disorder. *Sleep Med Rev* 2003; 7: 35-51.
- [52] Lavie L, Vishnevsky A, Lavie P. Evidence for lipid peroxidation in obstructive sleep apnea. *Sleep* 2004; 27: 123-128.
- [53] Lehnen AM, Leguisamo NM, Casali KR, Schaan BD. Progressive cardiovascular autonomic dysfunction in rats with evolving metabolic syndrome. *Auton Neurosci* 2013; 176: 64-69.

- [54] Lévy P, Pépin JL, Arnaud C, Tamisier R, Borel JC, Dematteis M, Godin-Ribuot D, Ribuot C. Intermittent hypoxia and sleep-disordered breathing: current concepts and perspectives. *Eur Respir J* 2008; 32:1082–1095.
- [55] Levy P, Bonsignore MR, Eckel J. Sleep, sleep-disordered breathing and metabolic consequences. *Eur Respir J* 2009; 34: 243–260.
- [56] Lin M, Liu R, Gozal D, Wead WB, Chapleau MW, Wurster R, Cheng ZJ. Chronic intermittent hypoxia impairs baroreflex control of heart rate but enhances heart rate responses to vagal efferent stimulation in anesthetized mice. *Am J Physiol Heart Circ Physiol* 2007; 293: 997–1006.
- [57] Loredó JS, Clausen JL, Nelesen RA, Ancoli-Israel S, Ziegler MG, Dimsdale JE. Obstructive sleep apnea and hypertension: are peripheral chemoreceptors involved? *Med Hypotheses* 2011; 56 :17-19.
- [58] Marcus NJ, Li YL, Bird CE, Schultz HD, Morgan BJ. Chronic intermittent hypoxia augments chemoreflex control of sympathetic activity: Role of the angiotensin II type 1 receptor. *Respir Physiol Neurobiol* 2010; 171: 36-45.
- [59] Marin JM, Carrizo SJ, Vicente E, Agustí AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *The Lancet* 2005; 65:1046–1053.
- [60] Marin JM, Agustí A, Villar I, Forner M, Nieto D, Carrizo SJ, Barbé F, Vicente E, Wei Y, Nieto FJ, Jelic S. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA* 2012; 23: 2169-2176.
- [61] Marrone O, Riccobono L, Salvaggio A, Mirabella A, Bonanno A, Bonsignore MR. Catecholamines and blood pressure in obstructive sleep apnea syndrome. *Chest* 1993; 103:722–727.
- [62] McGuire M, Zhang Y, White DP, Ling L. Chronic intermittent hypoxia enhances ventilatory long-term facilitation in awake rats. *J Appl Physiol* 2003; 95: 1499-1508.
- [63] McNicholas WT, Bonsignore MR, the Management Committee of ECAB. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J* 2007; 29: 156–178.
- [64] Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Tanaka A, Oda N, Okada S, Ohta S, Naito H, Adachi M. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005; 172: 625-630.
- [65] Montesano M, Miano S, Paolino MC, Massolo AC, Ianniello F, Forlani M, Villa MP. Autonomic cardiovascular tests in children with obstructive sleep apnea syndrome. *Sleep* 2010; 33:1349-1355.

- [66] Naëgelé B, Thouvard V, Pépin JL, Lévy P, Bonnet C, Perret JE, Pellat J, Feuerstein C. Deficits of cognitive executive functions in patients with sleep apnea syndrome. *J Sleep Res Sleep Med* 1995; 18: 43-52.
- [67] Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation* 1998; 98: 772-776.
- [68] Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. *Circulation* 1998; 97: 943-945.
- [69] Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998; 98: 1071-1077.
- [70] Narkiewicz K, van de Borne PJ, Pesek CA, Dyken ME, Montano N, Somers VK. Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea. *Circulation* 1999; 99: 1183-1189.
- [71] Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation* 1999; 100: 2332-2335.
- [72] Narkiewicz K, Somers VK. Sympathetic nerve activity in obstructive sleep apnoea. *Acta Physiol Scand* 2003; 177: 385-390.
- [73] Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *Sleep Heart Health Study. JAMA* 2000; 283: 1829-1836.
- [74] O'Connor GT, Caffo B, Newman AB, Quan SF, Rapoport DM, Redline S, Resnick HE, Samet J, Shahar E. Prospective study of sleep-disordered breathing and hypertension: the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2009; 79: 1159-1166.
- [75] O'Driscoll DM, Horne RS, Davey MJ, Hope SA, Anderson V, Trinder J, Walker AM, Nixon GM. Increased sympathetic activity in children with obstructive sleep apnea: cardiovascular implications. *Sleep Med* 2011; 12: 483-488.
- [76] Ortiz FA, Del Rio R, Ebensperger G, Reyes V, Alcayaga J, Varas R, Iturriaga R. Inhibition of rat carotid body glomus cells TASK-like channels by acute hypoxia is enhanced by chronic intermittent hypoxia. *Respir Physiol Neurobiol* 2013; 185: 600-607.
- [77] Paton JF, Sobotka PA, Fudim M, Engleman ZJ, Hart EC, McBryde FD, Abdala AP, Marina N, Gourine AV, Lobo M, Patel N, Burchell A, Ratcliffe L, Nightingale A. The carotid body as a therapeutic target for the treatment of sympathetically mediated diseases. *Hypertension* 2013; 61: 5-13.

- [78] Parati G, Lombardi C, Narkiewicz K. Sleep apnea: epidemiology, pathophysiology, and relation to cardiovascular risk. *Am J Physiol Regul Integr Comp Physiol* 2007; 293: 1671-1683.
- [79] Pawar A, Nanduri J, Yuan G, Khan SA, Wang N, Kumar GK, Prabhakar NR. Reactive oxygen species-dependent endothelin signaling is required for augmented hypoxic sensory response of the neonatal carotid body by intermittent hypoxia. *Am J Physiol Regul Integr Comp Physiol* 2009; 296: 735-742.
- [80] Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, De Paula LK, Amaro AC, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD, Lorenzi-Filho G. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension* 2011; 58: 811-817.
- [81] Peng YJ, Prabhakar NR. Reactive oxygen species in the plasticity of breathing elicited by chronic intermittent hypoxia. *J Appl Physiol* 2003, 94 :2342-2349.
- [82] Peng YJ, Overholt JL, Kline D, Kumar GK, Prabhakar, N.R. Induction of sensory long-term facilitation in the carotid body by intermittent hypoxia: implications for recurrent apneas. *Proc Natl Acad Sci USA* 2003; 100:10073-10078.
- [83] Peng YJ, Nanduri J, Yuan G, Wang N, Deneris E, Pendyala S, Natarajan V, Kumar GK, Prabhakar NR. NADPH oxidase is required for the sensory plasticity of the carotid body by chronic intermittent hypoxia. *J Neurosci* 2009; 29: 4903-4910.
- [84] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; 342:1378-1384.
- [85] Prabhakar NR, Peng YJ, Jacono FJ, Kumar GK, Dick TE. Cardiovascular alterations by chronic intermittent hypoxia: importance of carotid body chemoreflexes. *Clin Exp Pharmacol Physiol* 2005; 32 :447-449.
- [86] Reeves SR, Gozal E, Guo SZ, Sachleben LR, Brittan KR, Lipton AJ, Gozal D. Effect of long-term intermittent and sustained hypoxia on hypoxic ventilatory and metabolic responses in the adult rat. *J Appl Physiol* 2003; 95 :1767-1774.
- [87] Rey, S, Del Rio, R, Alcayaga, J, Iturriaga R. Chronic intermittent hypoxia enhances cat chemosensory and ventilatory responses to hypoxia. *J Physiol* 2004; 560 : 577-586.
- [88] Rey S, Iturriaga, R. Endothelins and nitric oxide: Vasoactive modulators of carotid body Chemoreception. *Curr Neurovasc Res* 2004; 1: 464-473.
- [89] Rey S, Del Rio R, Iturriaga R. Contribution of endothelin-1 to the enhanced carotid body chemoreception induced by intermittent hypoxia. *Brain Res* 2006; 1086: 152-159.
- [90] Rey S, Corthorn J, Chacón C, Iturriaga R. Expression and immunolocalization of endothelin peptides and its receptors, ETA and ETB, in the carotid body exposed to chronic intermittent hypoxia. *J Histochem Cytochem* 2007; 55: 167-174.

- [91] Rey S, Tarvainen MP, Karjalainen PA, Iturriaga R. Dynamic time-varying analysis of heart rate and blood pressure variability in cats exposed to short-term chronic intermittent hypoxia. *Am J Physiol Regul Integr Comp Physiol* 2008; 295 :28-37.
- [92] Savransky V, Nanayakkara A, Li J, Bevans S, Smith PL, Rodriguez A, Polotsky VI. Chronic intermittent hypoxia induces atherosclerosis. *Am J Respir Crit Care Med*. 2007; 175: 1290–1297.
- [93] Schultz HD, Li YL, Ding Y. Arterial chemoreceptors and sympathetic nerve activity: implications for hypertension and heart failure. *Hypertension* 2007; 50: 6-13.
- [94] Schulz R, Eisele HJ, Murzabekova G, Weissmann N. Sleep apnea and cardiovascular disease--results from animal studies. *Pneumologie* 2008; 62:18-22.
- [95] Shahar E, Coralyn CW, Whitney W, Redline S, Lee ET, Newman AB, Nieto FJ, O'Connor GT, Boland LL, Schwartzet JE. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the sleep heart health study. *American Journal of Respiratory and Critical Care Medicine* 2001; 163: 19–25.
- [96] Shiomi T, Guilleminault C, Sasanabe R, Hirota I, Maekawa M, Kobayashi T. Augmented very low frequency component of heart rate variability during obstructive sleep apnea. *Sleep* 1996; 119: 370-377.
- [97] Smith ML, Pacchia CH F. Sleep apnoea and hypertension: Role of chemoreflexes in humans. *Exp Physiol* 2007; 92: 45-50.
- [98] Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995; 96, 1897–1904.
- [99] Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T. Sleep apnea and cardiovascular disease: An American Heart Association. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research NIH. *J Am Coll Cardiol* 2008; 52: 686-717.
- [100] Sukegawa M, Noda A, Sugiura T, Nakata S, Yoshizaki S, Soga T, Yasuda Y, Iwayama N, Nakai S, Koike Y. Assessment of continuous positive airway pressure treatment in obstructive sleep apnea syndrome using 24-hour urinary catecholamines. *Clin Cardiol* 2005; 28: 519–522
- [101] Suzuki YJ, Jain V, Park AM, Day RM. Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases. *Free Radic Biol Med* 2006; 40: 1683-1692.
- [102] Svanborg E, Carlsson-Nordlander B, Larsson H, Sachs C, Kaijser L. Autonomic nervous system function in patients with primary obstructive sleep apnoea syndrome. *Clin Auton Res* 1991; 1:125-130.

- [103] Tam CS, Wong M, Tam K, Aouad L, Waters KA. The effect of acute intermittent hypercapnic hypoxia treatment on IL-6, TNF-alpha, and CRP levels in piglets. *Sleep* 2007; 30: 723-727.
- [104] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996; 17: 354-381.
- [105] Troncoso-Brindeiro CM, Da Silva AQ, Allahdadi KJ, Youngblood V, Kanagy NL. Reactive oxygen species contribute to sleep apnea-induced hypertension in rats. *Am J Physiol Heart Circ Physiol* 2007; 293: H2971-2976.
- [106] Veale D, Pépin JL, Lévy PA. Autonomic stress tests in obstructive sleep apnea syndrome and snoring. *Sleep* 1992; 15: 505-513
- [107] Williams A, Scharf SM. Obstructive sleep apnea, cardiovascular disease, and inflammation: is NF-kappaB the key? *Sleep Breath* 2007; 11: 69-76.
- [108] Williams AJ, Houston D, Finberg S, Lam C, Kinney JL, Santiago S. Sleep apnea syndrome and essential hypertension. *Am J Cardiol* 1985; 55: 1019-1022.
- [109] Yan B, Soukhova-O'Hare GK, Li L, Lin Y, Gozal D, Wead WB, Wurster RD, Cheng ZJ, Attenuation of heart rate control and neural degeneration in nucleus ambiguus following chronic intermittent hypoxia in young adult Fischer 344 rats. *Neuroscience* 2008; 153: 709-720.
- [110] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230-1235.
- [111] Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, Stubbs R, Hla KM. Sleep disordered breathing and mortality: eighteen-year follow-up of the wisconsin sleep cohort. *Sleep* 2008; 31:1071-1078.
- [112] Ziegler MG, Nelesen R, Mills P, Ancoli-Israel S, Kennedy B, Dimsdale JE. Sleep apnea, norepinephrine-release rate, and daytime hypertension. *Sleep* 1997; 20: 224-231.
- [113] Ziegler MG, Mills PJ, Loreda JS, Ancoli-Israel S, Dimsdale JE. Effect of continuous positive airway pressure and placebo treatment on sympathetic nervous activity in patients with obstructive sleep apnea. *Chest* 2001; 120:887-893
- [114] Zoccal DB, Simms AE, Bonagamba LG, Braga VA, Pickering AE, Paton JF, Machado BH. Increased sympathetic outflow in juvenile rats submitted to chronic intermittent hypoxia correlates with enhanced expiratory activity. *J Physiol* 2008; 586: 3253-3265.