® Postepy Hig Med Dosw (online), 2019; 73: 65-75
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 18.04.2018
Accepted: 27.11.2018
Published: 15.02.2019

Impact of obstructive sleep apnea on cerebral blood flow

Wpływ obturacyjnego bezdechu sennego na krążenie mózgowe

Katarzyna Postrzech-Adamczyk[1,2], Artur Nahorecki[2], Paweł Łyszczak[1,2], Robert Skomro [2,3], Andrzej Szuba[1,2]

[1]Department of Internal Medicine, 4th Military Teaching Hospital, Wroclaw, Poland
[2]Department of Angiology, Faculty of Health Science, Wroclaw Medical University, Poland
[3]University of Saskatchewan, Saskatoon, SK, Canada

Summary

Aim: Obstructive sleep apnea (OSA) is a common disorder with growing incidence. Major risk factors for OSA are obesity, aging, gender and menopause. As life expectancy lengthens and the obesity epidemic is ongoing, we can assume that OSA will affect an increasing part of the population. Pathological consequences of this disease include an increased risk of arterial hypertension, coronary artery disease, arrhythmia, heart failure as well as cerebrovascular diseases, such as stroke, transient ischemic attack and cognitive dysfunction. The cerebrovascular system differs significantly from other vessels in the body. Brain oxygen demands constitute about 20% of the total oxygen consumed by the body.

Conclusions: OSA significantly affects the cerebral blood flow both during sleep and daily activities. This can have serious health consequences and makes the brain more vulnerable to ischemia. In this review we describe the impact of OSA on cerebral circulation during both sleep and wakefulness and we also outline the pathophysiology of these changes.

Results: In patients with other risk factors for cerebral ischemia, early screening and treatment for OSA should be introduced.

Keywords: **cerebral blood flow • sleep apnea and stroke • sleep disorders • cerebrovascular disease**

GICID 01.3001.0013.0323
DOI: 10.5604/01.3001.0013.0323
Word count: 3405
Tables: 1
Figures: 2
References: 100

Author's address: Katarzyna Postrzech-Adamczyk, MD, Department of Internal Medicine, 4th Military Teaching Hospital, Rudolfa Weigla 5, 50-981 Wroclaw, Poland; e-mail: kpostrzech.adamczyk@gmail.com

INTRODUCTION

The main characteristic of obstructive sleep apnea (OSA) is the obstruction of the upper airways during sleep, which leads to intermittent hypoxia, reoxygenation, hypercapnia, and sleep fragmentation. The prevalence of this disease differs widely in the available data, depending on the size and characteristics of the study group [11, 40, 44, 70, 75, 87]. An analysis by Peppard, Young et al. estimates the incidence of moderate to severe OSA (Apnea+Hypopnea Index - AHI ≥15) in 13% of men and 6% of women between 30-70 years of age. In this study, 14% of men and 5% of women have symptoms of daytime sleepiness and an AHI ≥5 [70]. Some groups of patients show an increased incidence of OSA. These subpopulations include overweight or obese and middle--aged, older, post-menopausal subjects. Epidemiological results do not show substantial differences between developed and developing countries [99]. OSA is associated with numerous vascular complications, increased risk of hypertension, coronary artery disease, arrhythmia, heart failure as well as cerebrovascular diseases, such as stroke and transient ischemic attack [24, 28, 52, 80, 85]. The pathogenesis of the negative impact on vascular system includes endothelial dysfunction, oxidative stress, increased sympathetic activation, and systemic and vascular inflammation, which are caused mainly by intermittent hypoxemia [23]. The use of devices producing positive airway pressure (continuous positive airway pressure, CPAP) is recognized as an effective treatment for OSA. Regular and proper use of CPAP normalizes sleep architecture, significantly reduces snoring, daytime sleepiness and improves the quality of life [20, 33, 62, 68, 90]. OSA is well known as one of the most common causes of secondary arterial hypertension. Most studies show the positive effect of CPAP therapy in lowering blood pressure, although in patients with minimally symptomatic sleep apnea, the effect on blood pressure is not pronounced [8, 12, 58]. Patients with resistant hypertension or those taking antihypertensive pharmacotherapy are shown to have more substantial BP reduction [37]. A decreased risk of stroke is another beneficial effect of CPAP. In Sleep Apnea Cardiovascular Endpoints (SAVE) trial, the risk of a cerebrovascular event was significantly lower in patients using CPAP for more than 4 hours [59, 61]. The cerebrovascular system differs significantly from other vessels in the body. Brain oxygen demands constitute about 20% of the total oxygen consumed by the body. To meet this requirement, constant blood flow and efficient mechanisms for regulation of flow pressure are indispensable. In this work we want to focus on the impact of OSA on cerebral circulation.

CEREBROVASCULAR CONSEQUENCES OF OSA

Studies performed in a large group of patients showed a significant association between OSA and cardio- and cerebrovascular diseases, including stroke, coronary artery disease, and heart failure [28, 34, 52, 76, 96]. Minoguchi et al. performed MRI imagining on subjects with OSA and a control group to determine the incidence of silent brain infarctions (SBI) with OSA. The results showed that SBIs are more common in patients with moderate to severe OSA, approaching 25% vs 6.7% in control subjects [60]. Data presenting high association between OSA and stroke should be analyzed carefully, as numerous confounding variables co-exist with OSA. However, even after adjusting for age, sex, race, smoking, alcohol, BMI, diabetes, hyperlipidemia, atrial fibrillation, and hypertension, OSA increases the risk for stroke [96]. The damage caused by brain infarction is more severe in patients with obstructive sleep apnea. There is also an increased risk of subsequent stroke in untreated OSA patients [2, 16, 27, 46, 63, 86]. Longer hospitalization, rehabilitation and worse neurologic recovery are described in literature in comparison to patients without OSA. Higher incidence of delirium, depressed mood, latency in reaction, difficulties in everyday living decrease in attention and problem-solving are also observed [1, 6, 13, 79, 97]. The evidence of beneficial effects of CPAP on reducing negative stroke outcome is not so obvious. Some data shows that early use of CPAP in OSA-stroke- patients has a beneficial effect, as it improves neurologic recovery, delays the appearance of cardiovascular events [6]. Martínez-García et al. suggest that CPAP reduces the excess of incidence of nonfatal cardiovascular events [57]. On the other hand, Hsu et al. report no benefit from CPAP treatment, which was assessed by changes in the Nottingham Extended Activities of Daily Living scale (EADL) after 6 months of CPAP therapy. One of the reasons for this finding may be poor adherence to CPAP therapy, which has been reported in stroke patients [36, 69].

IMPACT OF OSA ON FUNCTIONAL AND STRUCTURAL DYSFUNCTION OF BLOOD VESSELS

Vascular damaging agents include both physical (blood pressure) and the cellular and molecular mechanisms (vasoactive substances).

The link between hypertension and OSA is well established [22, 23, 24, 71, 99]. The absence of nocturnal blood pressure dipping, extreme dipping, or reversed dipping have been associated with an increased risk of silent cerebral infarctions and strokes in older hypertensive patients [21]. Fluctuations in blood pressure during apneas and hypopneas can negatively affect cerebral vessels. As the fluctuations can be rapid, autoregulation may not be able to adapt to these changes. That fact exposes especially small arteries and arterioles to damage. Balfors and Franklin measured intra-arterial radial blood pressure during sleep. A gradual increase in blood pressure during apneas and a rapid decline after they terminated was observed. This period immediately after the apnea, when a fall in BP was noticed, is a time of particular vulnerability of the brain to hypoxia [5]. Repetitive surges in blood pressure at the end of apneas and hypopneas result in increased shear stress [31].

Endothelium plays a key role in the regulation of cerebrovascular circulation. A physiologically proper balance between vasoconstrictors and vasodilators must be preserved. The most important substance produced by endothelium is nitric oxide (NO). It is a strong vasodilator of major arteries and arterioles in parenchyma [26]. OSA significantly affects vascular endothelium function, promotes pro-inflammatory and pro-oxidant activation, increased coagulability and disturbed balance between metalloproteases and their inhibitors [26]. Nitric oxide is synthesized by endothelial nitric oxide synthase (eNOS). The main site of action of NO is soluble guanylate cyclase (sGC). Activation of sGC leads to increased production of cyclic guanosine monophosphate (cGMP). Further effects result from cGMP-dependent protein kinase I and include reductions in intracellular calcium, decreases in vascular tone, and changes in gene expression, which results in vessel dilatation [29]. Numerous research reports reveal lower plasma nitrates concentration in subjects with OSA compared to healthy patients. This occurrence is inversely related to the severity of OSA [14, 48, 67, 84]. Successful CPAP treatment, the gold standard in treating OSA, improves plasma nitrates concentration [17, 66, 72]. Other gas mediators, such as hydrogen sulfide (H2S) and carbon monoxide (CO), are also involved in physiological and pathological processes in the vascular system. CO is produced from heme by heme oxygenase (HO). The mechanism of action is similar to NO and also includes the activation of cGMP and calcium-gated potassium channels. Studies in animal models showed the vasodilatory effect of CO [42, 77]. However, in certain situations vasoconstrictor and NO antagonizing effects of CO were also described [38, 41]. Endothelial nitric oxide and prostacyclin interact with CO system in circulatory regulation. In cerebral arterioles in contrast to dilation to acute CO increase, a prolonged exposure to elevated CO produces progressive constriction by inhibiting nitric oxide synthase [55]. Patients with OSA demonstrate higher levels of CO. Azuma et al. evaluated exhaled and blood CO concentrations at night and in the morning. Exhaled CO levels at night in the OSA patients were significantly higher than in the control group. No significant differences in blood CO were observed [4]. Kobayashi et al also measured serum CO concentration in OSA patients before and after sleep. In this study CO levels were significantly increased in the morning, but not in the evening. The change in CO level, which was defined as a gap between the presleep and postsleep CO levels correlated with apnea-hypopnea index and hypoxia duration as a percentage of total sleep time [51].

Endogenous hydrogen sulfide is synthesized from cysteine by beta-cystathionine synthase (CBS) or gamma-cystathionine lyase (CSE). CBS plays a major role in the brain. Recent research proves that the another source of H2S can also be 3-mercaptopyruvate sulfurtransferase (3MST) and cysteine aminotransferase (CAT) which are both localized to vascular endothelium [82]. Its vasodilatory effect is mainly dependent on acting on the KATP-channels, but a direct impact on angiotensin converting enzyme (ACE) cannot be excluded [10, 54, 100]. Jain et

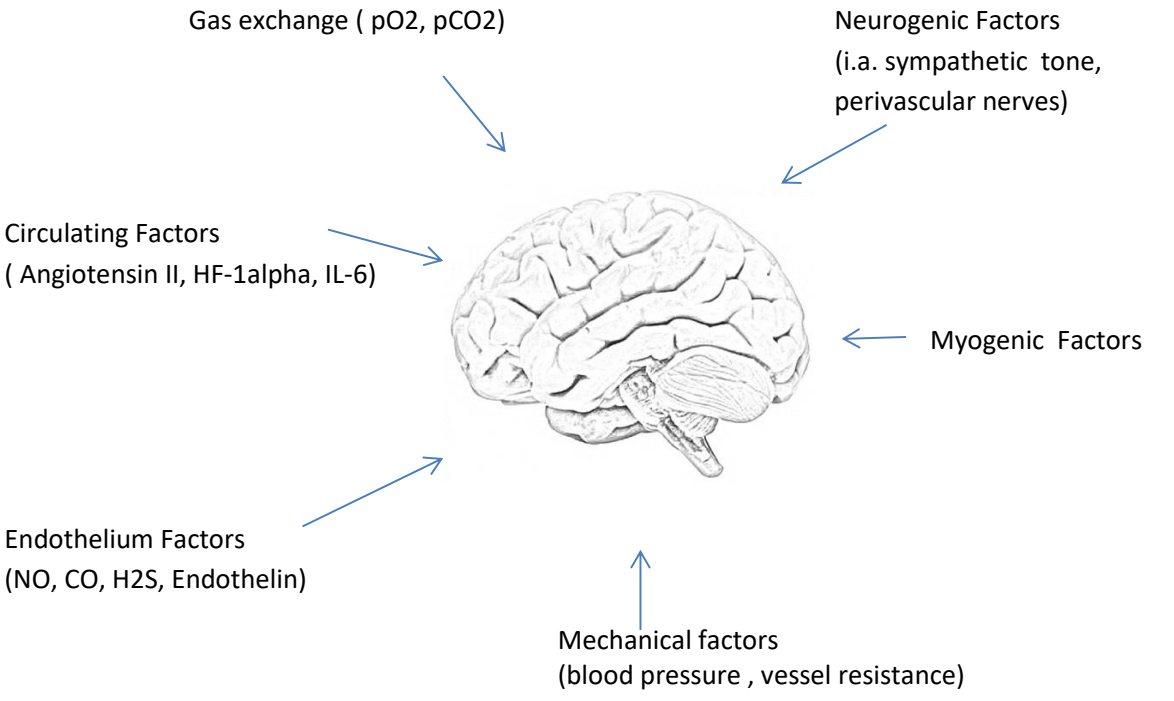

Fig. 1. Factors regulating cerebral blood flow

al. in their research observed a significant decrease in circulating H2S in diabetic patients with sleep apnea compared with diabetic patients without sleep disorders [43]. Reports on H2S in patients with OSA are still few and further studies are needed.

Intermittent hypoxia is one of the main features of OSA. The carotid bodies situated at the bifurcation of the common carotid arteries, as well as aortic bodies located in the aortic arch and at the thoraco-abdominal level, are the sensory organs which detect changes in oxygen levels in arterial blood and induce cardiovascular adaptation to provide sufficient oxygen supply. When these peripheral chemoreceptors are activated by hypoxia, a rise in the sympathetic nervous system occurs (leading to BP rise). Recurrent episodes of hypoxia activate pro-inflammatory molecules increase oxidative stress markers production, reactive oxygen species and reactive nitrogen species levels. These changes promote long-lasting stimulation of arterial chemoreflexes and elevated chronic sympathetic nerve activation [81]. The other factor contributing to sympathetic nerve activation is sleep fragmentation, a common feature of OSA. Additionally, recurrent episodes of hypoxia cause the activation of renin- angiotensin system, elevation of endothelin I, pro-inflammatory transcription factors such as hypoxia-inducible factor (HIF)-1α, and nuclear factor that determine an activation of some genetic factors and an induction of adhesion molecules, tumor necrosis factor-α, interleukin-6, chemokines, C-reactive protein, cyclooxygenase, and thromboxane synthase [29, 31].

CEREBROVASCULAR CIRCULATION

As constant blood flow in the brain is necessary, multilevel regulation is needed. The most important mechanisms controlling the blood flow in the brain are vessel resistance, myogenic response in cerebral arteries and arterioles and neurogenic factors. The large and small arteries include perivascular nerves in their adventitial layer that originate from the peripheral nervous system but innervation of parenchymal arterioles and cortical microvessels comes directly from the brain tissue. In peripheral circulation, vessel resistance is mainly dependent on small vessels and arterioles. In the cerebrovascular system, the role of large arteries is more pronounced. When an increase of the blood flow is needed in some areas, vasodilation from distal to proximal arterial segments occurs. Upstream vessels must dilate in order to avoid reductions in downstream microvascular pressure. Myogenic response is the ability of smooth muscle of large and small vessels to constrict or dilate in response to changes in pressure. Increased blood pressure leads to constriction and decreased one to dilatation. Although response is myogenic, some factors released from the endothelium or perivascular nerves can affect this autoregulation [18]. Endothelium secretes a number of biologically active substances, which are involved in the regulation of vascular tone, pro-, anti- inflammatory and coagulation homeostasis. Substances regulating vascular tone can be divided in two groups with contradicting properties. Endothelial derived relaxing factors (ERDF), represented especially by nitric oxide (NO), are responsible for dilatation. On the other hand, endothelium-derived contracting factors (EDCF), represented among others by endothelin, cause the contraction of smooth muscles of blood vessels [98]. Some data suggests that cerebral arteries, as well as other cells of the cardiovascular system, have a functional circadian clock and show a diurnal rhythm in response to vasoactive substances. In animal models OSA affects these rhythms in cerebral arteries, which may contribute to adverse cerebrovascular outcomes [25].

IMPACT OF OSA ON CEREBRAL BLOOD FLOW (CBF) DURING APNEA

During an episode of apnea, oxygen partial pressure (PO2) decreases and carbon dioxide partial pressure (PCO2) increases. Such changes in gas pressures lead to vasodilatation. The elevation of PCO2, among other factors (such as the arousal and activation of the sympathetic nervous system) additionally raises systemic blood pressure. Although hypercapnia leads to a relatively uniform vasodilation effect in the whole cerebrovascular area, the role of sympathetic tone in the brain is not so pronounced as in the other vessels of the body. Sympathetic stimulation constricts large cerebral arteries, but at the same time this is compensated by the dilation of resistance arterioles [7, 18, 53, 78, 91, 93]. Kuznetsova and Kulikov measured the responses of middle cerebral arteries velocity (MCAv) and mean arterial blood pressure (MAP) to CO2 in humans. Hypercapnia in healthy volunteers was obtained by a rebreathing test. A breathing circuit with 1000 ml of dead space extra volume was connected to the face mask. This led to an increase in end-tidal partial pressure of CO2 (PETCO2) by 10-15 mmHg. During this maneuver, PETCO2 as well as middle cerebral arteries velocity (assessed by transcranial Doppler) started increasing during the first 10 s and continued to increase for 60 s, then remained at the level reached with minor alterations. No sharp growth in MAP at the beginning of rebreathing was observed. MAP started increasing after about 30 seconds of rebreathing and continued to 2 min, then remained at the level reached. SpO2 decreased gradually during 2-3 min and remained reduced until the end of rebreathing [53]. Similar results were reported by Battisti-Charbonney et al. In this research, the cerebrovascular response to increasing PCO2 at hyperoxic, hypoxic and isoxic pressures were measured using the Duffin rebreathing method. Dynamic rebreathing was implemented by programming the gas mixing device to supply a flow of gas with a pCO2 equal to the PETCO2 of the previous breath and O2 sufficient to maintain an isoxic PETCO2 at either 150 mmHg (hyperoxic test) or 50 mmHg (hypoxic test). An increase in MCAv and MAP was observed. Additional comparison of isoxic hyperoxic with isoxic hypoxic tests enabled the determination of the pO2 effect. Hypoxia significantly increased the maximum percentage rise in MCAv in the majority of subjects [7]. An important limi-

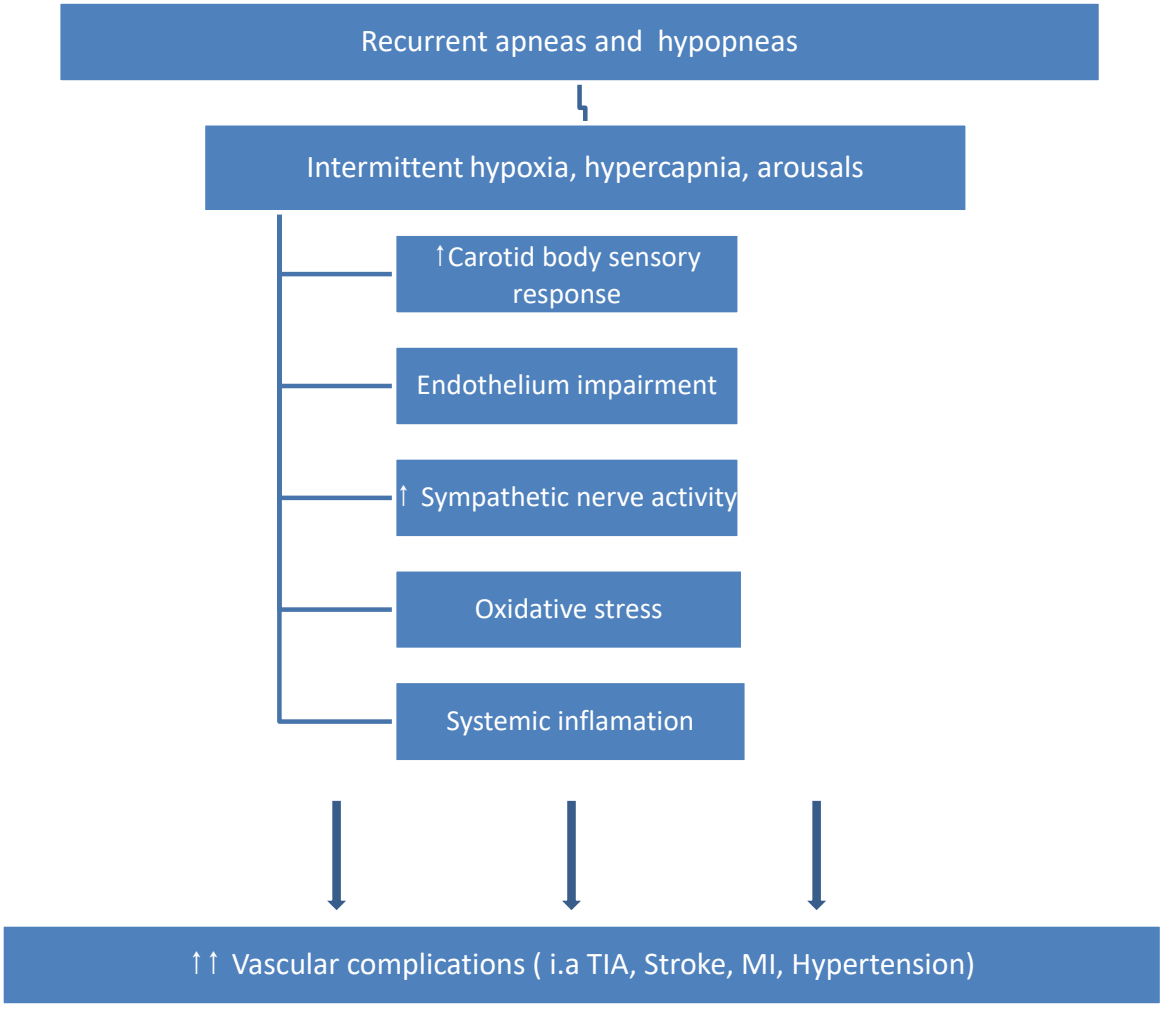

Fig. 2. Pathophysiology of vascular complications of OSA

tation of these studies is that responses to hypoxia have been assessed during wakefulness. OSA patients do not typically experience hypoxia during wakefulness, but during sleep. Research done by Staudacher et al. assessed CBF during sleep. TCD was performed continuously during the whole night and was co-registered with polysomnography. Blood flow was minimal before episodes of apneas or hypopneas and maximal closely after their termination [32]. Another mechanism that affects CBF (for example perivascular innervation as mentioned above) could also contribute to alterations in cerebral blood flow during episodes of apnea but none data evaluating that influence is now available [26].

IMPACT OF OSA ON RESTING CEREBRAL BLOOD FLOW (CBF)

Data in the literature indicates that CBF in patients with OSA is altered not only during sleep. One of effective and non-invasive methods assessing cerebral blood flow is a transcranial Doppler ultrasonography of cerebral blood flow velocity (CBFV) in the middle cerebral artery. Navarro et al. investigated 152 subjects; all participants underwent a daytime transcranial Doppler study of the right middle cerebral artery to record cerebral blood flow velocity. Results showed a significant reduction in mean cerebral blood flow velocity in OSA patients in comparison to non-OSA subjects [19]. The reasons why opposite changes in CBF occur during wakefulness and sleep are not fully understood. Some authors suggest a possible impact of an increase in peripheral resistance associated with small vessel disease or significant increase in middle cerebral artery diameter induced by nocturnal hypercapnia and hypoxia. [19, 39, 47, 95]. Arterial spin labeling (ASL) procedures are non-invasive MRI-based methods that quantify regional CBF values with greater sensitivity and specificity than Doppler techniques. Carrie and colleagues investigated cerebral perfusion in people with untreated obstructive

sleep apnea. Results showed no significant difference in regional perfusion between controls and people with mild OSA, but patients with moderate-severe OSA had decreased perfusion, while awake [17, 39]. These findings are in line with results from studies carried out by Yadav et al. In this research, which included 11 OSA patients (with mean AHI = 32.9/h), ASL MRI showed significantly reduced regional CBF values [95]. In addition in changes in CBF, Chen H.L. et al. examined leukocyte apoptosis as a marker of systemic inflammation. The patients with moderate-severe OSA showed decreased global and regional CBF and also significantly increased percentages of total leucocyte apoptosis and granulocyte late apoptosis, suggesting increased systemic inflammation [95]. Joo Y. et al. used the 99mTc-ethylcysteinate dimer (ECD) single photon emission computed tomography (SPECT) images to assess cerebral blood flow during wakefulness. This study showed reduced blood flow in the parahippocampal and lingual gyri and a negative correlation between AHI and the CBF during the daytime awake state [47]. Using the same technique, Kim at al. showed improvement in resting CBF after CPAP treatment in the brain regions with significant hypoperfusion in the pretreatment examination [50]. Regardless of the method chosen to assess cerebral blood flow numerous studies have shown that resting daytime CBF is significantly decreased in a subset of OSA patients with severe disease. This can contribute to the negative impact of OSA on attention, memory, learning and overall cognitive function [49].

IMPACT OF OSA ON AUTOREGULATION OF CBF

Autoregulation is indispensable to maintain stable blood flow in the brain, when blood pressure changes occur. Data suggests that this mechanism is also affected in subjects with OSA. Macey and colleagues assessed acute BOLD (blood oxygen level dependent signal, a magnetic resonance imaging procedure) responses in OSA subjects to pressor challenges that elicit cerebral blood flow changes – Valsava maneuver, hand grip and cold pressor. The results showed that the amplitude of the global BOLD signal indicative of brain blood volume and oxygenation is altered in OSA patients compared to healthy control subjects during hand grip and cold pressor autonomic challenges [56]. Nasr et al. measured mean cerebral blood flow velocity (CBFV) in the middle cerebral artery and mean arterial blood pressure (ABP) with transcranial Doppler. Autoregulation was assessed with the Mx autoregulatory index. Mx is a moving correlation coefficient between mean CBFV and mean ABP (the higher the Mx the worse autoregulation). Patients and controls were examined in the next day morning after an overnight complete polysomnography. Results showed that cerebral autoregulation was impaired in OSA patients compared to controls and the severity of autoregulation impairment was correlated to the severity of OSA [64]. Urbano and colleagues assessed cerebral artery blood flow velocity (CBFV) by using a transcranial Doppler ultrasound and arterial blood pressure during orthostatic hypotension and recovery as well as during 5% CO2 inhalation. Autoregulatory

Table 1. Summary studies of impact of hypoxemia on human and animal brain

Author	Model of achieving hypoxia	Population and Methods	Measurements	Outcome
Ainslie P., Shaw A. et al. [3]	Automated gas blender adjusted the composition and flow to a sequential gas delivery mask	Ten healthy adults. After a 15-min of breathing room air , PaO2 was sequentially decreased to 60, 44 and 35 mmHg for exactly 15 min each. These values were targeted to elicit SaO2 of 90, 80 and 70% respectively. Isocapnia was maintained during each trial.	Global CBF was estimated assuming a symmetrical blood flow of contralateral ICA and VA arteries and based on ultrasound messaurments	Global CBF was progressively increased. During progressive hypoxemia, elevations in CBF were correlated with the reductions in SaO2
Villien M., Bouzat P. et al. [89]	Exposure to high altitude	Eleven healthy volunteers. Measurements were taken prior to the 6 day stay at 4350m and within 6h after returning to sea level	Arterial spin labeling (ASL) MR and Transcranial Doppler to measure basal cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) to CO2	Significant increases in TCD MCAv compared to before altitude measurements. Decreased CO2 CVR after altitude exposure
Feddersen B., Neupane P. et al. [30]	Exposure to high altitude	26 mountaineers reaching 5,050 m altitude	Transcranial Doppler sonography at 100, 3,440 and 5,050 m above sea level	Cerebral blood flow velocity (CBFV) in the anterior and middle cerebral arteries (MCAs) increased in all mountaineers between 100 and 3,440 m altitude. During further ascent to 5,050 m altitude, mountaineers developed a further increase in CBFV in the MCA, whereas in posterior cerebral arteries CBFV decreased continuously with increasing altitude

Author	Model of achieving hypoxia	Population and Methods	Measurements	Outcome
Ter Minassian A., Beydon L. et al. [83]	Hypobaric chamber	8 healthy volunteers in a hypobaric chamber , progressive stepwise decompression to 8,848 m	transcranial Doppler was performed after at least 3 days at 5,000, 6,000, and 7,000 m and within 4 hours of reaching 8,000 m and returning to sea level	Middle cerebral artery blood flow velocity (MCAv) increased only during acute exposure to 8,000 m
Xie A. et al. [94]	Automated gas blender adjusted the composition and flow to a sequential gas delivery mask	Seven healthy humans during wakefulness. The intermittent asphyxia intervention consisted of 20-s asphyxic exposures alternating with 40-s periods of room-air breathing for a total of 20 min.	Postganglionic muscle sympathetic nerve activity in the right peroneal nerve was recorded directly by using the microneurography technique	Muscle sympathetic nerve activity increased progressively and remained elevated for at least 20 min after removal of the chemical stimuli
Wilson M.H. et al. [92]	Study 1.High altitude and Sea level hypoxic Study 2.Gas inhalation	1 study: Twenty-four trekked to 5,300 m, of whom 14 subsequently continued to 6,400 m and 5 to 7,950 m 2. study: Seven subjects were subjected to 3 hours of normobaric hypoxia using a tight fitting mask and hypoxicator	Transcranial Doppler in study 1 and transcranial Doppler and MRI in study 2	Study 1 : Calculated MCA Flow markedly increased at 6,400 m and above Study 2 Cerebral blood flow calculated with either methodology (TCD or MRI) increased
Prabhakar N., Peng Y. et al. [74]	Animal model	Adult rats exposed to chronic intermittent hypoxia (15 s of 5% O2 followed by 5 min of 21% O2, nine episodes per h, 8 h/day for 10 days)	Because IH-exposed animals had elevated blood pressure, experiments were performed on ex vivo carotid bodies wherein the influence of elevated blood pressure on chemosensory activity was effectively absent	Enhancement of carotid body sensory response to hypoxia
Polsek D. et al. [73]	Animal model	Mice were exposed to a three week period of intermittent hypoxia for 8 hours a day, with 90 s intervals of 5, 7% and 21% oxygen	Histology of hippocampal brain regions	Apoptotic neurons in the hippocampus were more numerous in the mice exposed to intermittent hypoxia than in the control group
Jensen M.L.F. et al. [45]	35 min of inhaling hypoxic air (10%–12% O2)	28 patients with moderate-to-severe OSA compared with 19 controls underwent brain MRI during 35 min of normoxia followed by 35 min inhaling hypoxic air (10%–12% O2). , 22 patients were also rescanned after 3 months of continuous positive airway pressure (CPAP) treatment	Global cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO2), and lactate concentration	During hypoxia, CBF significantly increased with decreasing arterial blood oxygen concentration in the control group, but was unchanged in the patient. The CBF response to hypoxia was significantly weaker in patients than in controls but normalized after 3 months of CPAP treatment . There was no difference in CMRO2 or cerebral lactate concentration between patients and controls

response was expressed by measuring the time to recovery of CBFV after a decrease in mean arterial pressure. Although there was no significant difference in response to CO2 inhalation, OSA patients had a lower rate of recovery of cerebrovascular conductance after orthostatic challenge [88]. In the study of Gregori-Pla et al., CBF measured at different head-of-bed positions showed a similar response after changing position from supine to 30° in OSA and healthy subjects. After being tilted back to the supine position, patients with severe OSA, contrary to control and the mild OSA group, did not recover to the initial baseline. After 2 years of CPAP treatment this altered cerebral vasoreactivity response was normalized [35]. The mechanisms for alterations in autoregulatory response can be partially explained by myogenic response of brain arteries or endothelium activity. Data in the literature indicate that the intermittent hypoxia leads to disruption of endothelial function, oxidative stress, inflammation, atherosclerosis and hypertension. All these factors contribute to the dysregulation of autoregulatory mechanisms related to cerebral blood flow. The impaired cerebral autoregulation significantly contributes to increased risk of stroke in OSA patients [39].

CONCLUSION

OSA significantly affects brain circulation. Cerebral blood flow both during sleep and daily activities is decreased and autoregulation is impaired. Endothelial dysfunction, oxidative stress, increased the carotid body response and sympathetic activity, systemic

inflammation have a major role in cerebrovascular complications. These changes can have serious health consequences and make the brain more vulnerable to ischemia. This suggests that in the group of patients with other risk factors for cerebral ischemia, early screening for OSA should be considered.

No funding was received for this research.

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

REFERENCES

[1] Aaronson J.A., van Bennekom C.A., Hofman W.F., van Bezeij T., van den Aardweg J.G., Groet E., Kylstra W.A. Schmand B.: Obstructive sleep apnea is related to impaired cognitive and functional status after stroke. Sleep, 2015; 38: 1431-1437

[2] Ahn S.H., Kim J.H., Kim D.U., Choo I.S., Lee H.J., Kim H.W.: Interaction between sleep-disordered breathing and acute ischemic stroke. J Clin Neurol. 2013; 9: 9-13

[3] Ainslie P.N., Shaw A.D., Smith K.J., Willie C.K., Ikeda K., Graham J., Macleod D.B.: Stability of cerebral metabolism and substrate availability in humans during hypoxia and hyperoxia. Clin. Sci., 2014; 126: 661-670

[4] Azuma M., Murase K., Tachikawa R., Hamada S., Matsumoto T., Minami T., Inouchi M., Tanizawa K., Handa T., Oga T., Mishima M., Chin K.: Relationship between obstructive sleep apnea and endogenous carbon monoxide. J. Appl. Physiol., 2017; 122: 104-111

[5] Bålfors E.M., Franklin K.A.: Impairment of cerebral perfusion during obstructive sleep apneas. Am. J. Respir. Crit. Care Med., 1994; 150: 1587-1591

[6] Bassetti C.L. Milanova M., Gugger M.: Relationship of sleep apnea to functional capacity and length of hospitalization following stroke. Stroke J. Cerebral Circ., 2002; 15: 1-14

[7] Battisti-Charbonney A., Fisher J., Duffin J.: The cerebrovascular response to carbon dioxide in humans. J. Physiol., 2011; 589: 3039-3048

[8] Bazzano L.A., Khan Z., Reynolds K., He J.: Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. Hypertension, 2007; 50: 417-423

[9] Beaudin A.E., Hartmann S.E., Pun M., Poulin M.J.: Human cerebral blood flow control during hypoxia: focus on chronic pulmonary obstructive disease and obstructive sleep apnea. J. Appl. Physiol., 2017; 123: 1350-1361

[10] Beer S., Khan F., Kesselring J.: Rehabilitation interventions in multiple sclerosis: An overview. J. Neurol., 2012; 259: 1994-2008

[11] Bixler E.O., Vgontzas A.N., Lin H.M., Ten Have T., Rein J., Vela-Bueno A., Kales A.: Prevalence of sleep-disordered breathing in women: effects of gender. Am. J. Respir. Crit. Care Med., 2001; 163: 608-613

[12] Bratton D.J., Stradling J.R., Barbé F., Kohler M.: Effect of CPAP on blood pressure in patients with minimally symptomatic obstructive sleep apnoea: a meta-analysis using individual patient data from four randomised controlled trials. Thorax, 2014; 69: 1128-1135

[13] Camilo M.R., Schnitman S.V., Sander H.H., Eckeli A.L., Fernandes R.M., Leite J.P., Bassetti C.L., Pontes-Neto O.M.: Sleep-disordered breathing among acute ischemic stroke patients in Brazil. Sleep Med., 2016; 19: 8-12

[14] Carlson J.T., Rångemark C., Hedner J.A.: Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. J. Hypertens., 1996; 14: 577-584

[15] Chen H.L., Lin H.C., Lu C.H., Chen P.C., Huang C.C., Chou K.H., Su M.C., Friedman M., Chen Y.W., Lin W.C.: Systemic inflammation and alterations to cerebral blood flow in obstructive sleep apnea. J. Sleep Res., 2017; 26: 789-798

[16] Cherkassky T., Oksenberg A., Froom P., Ring H.: Sleep-related breathing disorders and rehabilitation outcome of stroke patients: a prospective study. Am. J. Phys. Med. Rehabil., 2003; 82: 452-455

[17] Ciftci T.U., Kokturk O., Demirtas S., Gulbahar O., Bukan N.: Consequences of hypoxia-reoxygenation phenomena in patients with obstructive sleep apnea syndrome. Ann. Saudi Med., 2011; 31: 14-18

[18] Cipolla M.J.: The cerebral circulation. In: Colloquium Series on Integrated Systems Physiology: From Molecule to Function Disease, Ed.: D.N. Granger and J.P. Granger,, Morgan & Claypool Life Sciences, 2009; 1-59

[19] Coloma Navarro R., Jiménez Caballero P.E., Vega G., Ayo-Martín O., Segura Martín T.: Cerebral hemodynamics is altered in patients with sleep apnea/hypopnea syndrome. Springerplus, 2016; 5: 51

[20] Cruz I.A., Drummond M., Winck J.C.: Obstructive sleep apnea symptoms beyond sleepiness and snoring: Effects of nasal APAP therapy. Sleep Breath., 2012; 16: 361-366

[21] Culebras A.: Sleep and stroke. Semin. Neurol., 2009; 29: 438-445

[22] Dempsey J.A., Veasey S.C., Morgan B.J., O'Donnell C.P.: Pathophysiology of sleep apnea. Physiol. Rev., 2010; 90: 47-112

[23] Devulapally K., Pongonis R., Khayat R.: OSA: the new cardiovascular disease: Part II: Overview of cardiovascular diseases associated with obstructive sleep apnea. Heart Failure Rev., 2009; 14: 155-164

[24] Dewan N.A., Nieto, F.J., Somers V.K.: Intermittent hypoxemia and OSA: Implications for comorbidities. Chest, 2015; 147: 266-274

[25] Durgan D.J., Crossland R.F., Bryan R.M. Jr.: The rat cerebral vasculature exhibits time-of-day-dependent oscillations in circadian clock genes and vascular function that are attenuated following obstructive sleep apnea. J. Cerebr. Blood Flow Metab., 2017; 37: 2806-2819

[26] Durgan D.J., Bryan R.M.Jr.: Cerebrovascular consequences of obstructive sleep apnea. J. Am. Heart Assoc., 2012; 1: e000091

[27] Dziewas R., Humpert M., Hopmann B., Kloska S.P., Lüdemann P., Ritter M., Dittrich R., Ringelstein E.B., Young P., Nabavi D.G.: Increased prevalence of sleep apnea in patients with recurring ischemic stroke compared with first stroke victims. J. Neurol., 2005; 252: 1394-1398

[28] Dziewas R., Ritter M., Usta N., Boentert M., Hor H., Dittrich R., Schäbitz W.R., Ringelstein E.B., Young P.: Atherosclerosis and obstructive sleep apnea in patients with ischemic stroke. Cerebrovasc. Dis., 2007; 24: 122-126

[29] Faraci F.M.: Protecting against vascular disease in brain. Am. J. Physiol. Heart Circ. Physiol., 2011; 300: H1566-H1582

[30] Feddersen B., Neupane P., Thanbichler F., Hadolt I., Sattelmeyer V., Pfefferkorn T., Waanders R., Noachtar S., Ausserer H.: Regional differences in the cerebral blood flow velocity response to hypobaric hypoxia at high altitudes. J. Cereb. Blood Flow Metab., 2015; 35: 1846-1851

[31] Fung M.L.: The role of local renin-angiotensin system in arte-

rial chemoreceptors in sleep-breathing disorders. Front. Physiol., 2014; 5: 336

[32] Furtner M., Staudacher M., Frauscher B., Brandauer E., Esnaola y Rojas M.M., Gschliesser V., Poewe W., Schmidauer C., Ritsch-Marte M., Högl B.: Cerebral vasoreactivity decreases overnight in severe obstructive sleep apnea syndrome: A study of cerebral hemodynamics. Sleep Med., 2009; 10: 875-881

[33] Giles T.L., Lasserson T.J., Smith B.J., White J., Wright J., Cates C.J.: Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst. Rev., 2006; 1: CD001106

[34] Gottlieb D.J., Yenokyan G., Newman A.B., O'Connor G.T., Punjabi N.M., Quan S.F., Redline S., Resnick H.E., Tong E.K., Diener-West M., Shahar E.: Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The sleep heart health study. Circulation, 2010; 122: 352-360

[35] Gregori-Pla C., Cotta G., Blanco I., Zirak P., Giovannella M., Mola A., Fortuna A., Durduran T., Mayos M.: Cerebral vasoreactivity in response to a head-of-bed position change is altered in patients with moderate and severe obstructive sleep apnea. PLoS One, 2018; 13: e0194204

[36] Hsu C.Y., Vennelle M., Li H.Y., Engleman H.M., Dennis M.S., Douglas N.J.: Sleep-disordered breathing after stroke: a randomised controlled trial of continuous positive airway pressure. J. Neurol. Neurosurg. Psych., 2006; 77: 1143-1149

[37] Hu X., Fan J., Chen S., Yin Y., Zrenner B.: The role of continuous positive airway pressure in blood pressure control for patients with obstructive sleep apnea and hypertension: A meta-analysis of randomized controlled trials. J. Clin. Hypertens., 2015; 17: 215-222

[38] Imai T., Morita T., Shindo T., Nagai R., Yazaki Y., Kurihara H., Suematsu M., Katayama S.: Vascular smooth muscle cell-directed overexpression of heme oxygenase-1 elevates blood pressure through attenuation of nitric oxide-induced vasodilation in mice. Circ. Res., 2001; 89: 55-62

[39] Innes C.R., Kelly P.T., Hlavac M., Melzer T.R., Jones R.D.: Decreased regional cerebral perfusion in moderate-severe obstructive sleep apnoea during wakefulness. Sleep, 2015; 38: 699-706

[40] Ip M.S., Lam B., Tang L.C., Lauder I.J., Ip T.Y., Lam W.K.: A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: Prevalence and gender differences. Chest, 2004; 125: 127-134

[41] Ishikawa M., Kajimura M., Adachi T., Maruyama K., Makino N., Goda N., Yamaguchi T., Sekizuka E., Suematsu M.: Carbon monoxide from heme oxygenase-2 is a tonic regulator against NO-dependent vasodilatation in the adult rat cerebral microcirculation. Circ. Res., 2005; 97: e104-e114

[42] Jafari B., Mohsenin V.: Endothelial dysfunction and hypertension in obstructive sleep apnea - Is it due to intermittent hypoxia? J. Cardiovasc. Dis. Res., 2013; 4: 87-91

[43] Jain S.K., Kahlon G., Morehead L., Lieblong B., Stapleton T., Hoeldtke R., Bass P.F. 3rd, Levine S.N.: The effect of sleep apnea and insomnia on blood levels of leptin, insulin resistance, IP-10, and hydrogen sulfide in type 2 diabetic patients. Metab. Syndr. Relat. Disord., 2012; 10: 331-336

[44] Jennum P., Riha R.L.: Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. Eur. Respir. J., 2009; 33: 907-914

[45] Jensen M.L., Vestergaard M.B., Tønnesen P., Larsson H.B., Jennum P.J.: Cerebral blood flow, oxygen metabolism, and lactate during hypoxia in patients with obstructive sleep apnea. Sleep, 2018; 41: zsy001

[46] Johnson K.G., Johnson D.C.: Frequency of sleep apnea in stroke and TIA patients: A meta-analysis. J. Clin. Sleep Med., 2010; 6: 131-137

[47] Joo E.Y., Tae W.S., Han S.J., Cho J.W., Hong S.B.: Reduced cerebral blood flow during wakefulness in obstructive sleep apnea-hypopnea syndrome. Sleep, 2007; 30: 1515-1520

[48] Kato M., Roberts-Thomson P., Phillips B.G., Haynes W.G., Winnicki M., Accurso V., Somers V.K.: Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation, 2000; 102: 2607-2610

[49] Kerner N.A., Roose S.P.: Obstructive sleep apnea is linked to depression and cognitive impairment: Evidence and potential mechanisms. Am. J. Geriatr. Psychiatry, 2016; 24: 496-508

[50] Kim J.S., Seo J.H., Kang M.R., Seong M.J., Lee W.G., Joo E.Y., Hong S.B.: Effect of continuous positive airway pressure on regional cerebral blood flow in patients with severe obstructive sleep apnea syndrome. Sleep Med., 2017; 32: 122-128

[51] Kobayashi M., Miyazawa N., Takeno M., Murakami S., Kirino Y., Okouchi A., Kaneko T., Ishigatsubo Y.: Circulating carbon monoxide level is elevated after sleep in patients with obstructive sleep apnea. Chest, 2008; 134: 904-910

[52] Koo B.B., Bravata D.M., Tobias L.A., Mackey J.S., Miech E.J., Matthias M.S., Stahl S.M., Sico J.J., Vaz Fragoso C.A., Williams L.S., Lampert R., Qin L., Yaggi H.K.: Observational study of obstructive sleep apnea in wake-up stroke: The Sleep Tight Study. Cerebrovasc. Dis., 2016; 41: 233-241

[53] Kuznetsova D.V., Kulikov V.P.: Cerebrovascular and systemic hemodynamic response to carbon dioxide in humans. Blood Press Monit., 2014; 19: 81-89

[54] Laggner H., Hermann M., Esterbauer H., Muellner M.K., Exner M., Gmeiner B.M., Kapiotis S.: The novel gaseous vasorelaxant hydrogen sulfide inhibits angiotensin-converting enzyme activity of endothelial cells. J. Hypertens., 2007; 25: 2100-2104

[55] Leffler C.W., Parfenova H., Jaggar J.H.: Carbon monoxide as an endogenous vascular modulator. Am. J. Physiol. Heart Circ. Physiol., 2011; 301: H1-H11

[56] Macey P.M., Kumar R., Ogren J.A., Woo M.A., Harper R.M.: Global brain blood-oxygen level responses to autonomic challenges in obstructive sleep apnea. PLoS One, 2014; 9: e105261

[57] Martínez-García M.A., Campos-Rodríguez F., Soler-Cataluña J.J., Catalán-Serra P., Román-Sánchez P., Montserrat J.M.: Increased incidence of nonfatal cardiovascular events in stroke patients with sleep apnoea: Effect of CPAP treatment. Eur. Resp. J., 2012; 39: 906-912

[58] Martínez-García M.A., Capote F., Campos-Rodríguez F., Lloberes P., Díaz de Atauri M.J., Somoza M., Masa J.F., González M., Sacristán L., Barbé F., Durán-Cantolla J., Aizpuru F., Mañas E., Barreiro B., Mosteiro M., et al.: Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA, 2013; 310: 2407-2415

[59] McEvoy R.D., Antic N.A., Heeley E., Luo Y., Ou Q., Zhang X., Mediano O., Chen R., Drager L.F., Liu Z., Chen G., Du B., McArdle N., Mukherjee S., Tripathi M., et al.: CPAP for prevention of cardiovascular events in obstructive sleep apnea. N. Engl. J. Med., 2016; 375: 919-931

[60] Minoguchi K., Yokoe T., Tazaki T., Minoguchi H., Oda N., Tanaka A., Yamamoto M., Ohta S., O'Donnell C.P., Adachi M.: Silent brain infarction and platelet activation in obstructive sleep apnea. Am. J. Respir. Crit. Care Med., 2007; 175: 612-617

[61] Mokhlesi, B., Ayas N.T.: Cardiovascular events in obstructive sleep apnea - can CPAP therapy SAVE lives? N. Engl. J. Med., 2016; 375: 994-996

[62] Monasterio C., Vidal S., Duran J., Ferrer M., Carmona C., Barbé F., Mayos M., Gonzalez-Mangado N., Juncadella M., Navarro A., Barreira R., Capote F., Mayoralas L.R., Peces-Barba G., Alonso J., Montserrat J.M.: Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. Am. J. Respir. Crit. Care Med., 2001; 164: 939-943

[63] Munoz R., Duran-Cantolla J., Martínez-Vila E., Gallego J., Rubio R., Aizpuru F., De La Torre G.: Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke; J. Cerebral Circ., 2006; 37: 2317-2321

[64] Nasr N., Traon A.P., Czosnyka M., Tiberge M., Schmidt E., Larrue V.: Cerebral autoregulation in patients with obstructive sleep apnea syndrome during wakefulness. Eur. J. Neurol., 2009; 16: 386-391

[65] Nie S., Peng D.C., Gong H.H., Li H.J., Chen L.T., Ye C.L.: Resting cerebral blood flow alteration in severe obstructive sleep apnoea: an arterial spin labelling perfusion fMRI study. Sleep Breath., 2017; 21: 487-495

[66] Noda A., Nakata S., Koike Y., Miyata S., Kitaichi K., Nishizawa T., Nagata K., Yasuma F., Murohara T., Yokota M.: Continuous positive airway pressure improves daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe obstructive sleep apnea syndrome. Hypertens. Res., 2007; 30: 669-676

[67] Ohike Y., Kozaki K., Iijima K., Eto M., Kojima T., Ohga E., Santa T., Imai K., Hashimoto M., Yoshizumi M., Ouchi Y.: Amelioration of vascular endothelial dysfunction in obstructive sleep apnea syndrome by nasal continuous positive airway pressure--possible involvement of nitric oxide and asymmetric NG, NG-dimethylarginine. Circ. J.: 2005; 69: 221-226

[68] Orth M., Duchna H.W., Leidag M., Widdig W., Rasche K., Bauer T.T., Walther J.W., de Zeeuw J., Malin J.P., Schultze-Werninghaus G., Kotterba S.: Driving simulator and neuropsychological testing in OSAS before and under CPAP therapy. Eur. Respir. J., 2005; 26: 898-903

[69] Palombini L., Guilleminault C.: Stroke and treatment with nasal CPAP. Eur. J. Neurol., 2006; 13: 198-200

[70] Peppard P.E., Young T., Palta M., Skatrud J.: Increased prevalence of sleep-disordered breathing in adults. Am. J. Epidemiol., 2013; 177: 1006-1014

[71] Peppard P.E., Young T., Barnet J.H., Palta M., Hagen E.W., Hla K.M.: Prospective study of the association between sleep-disordered breathing and hypertension. N. Engl. J. Med. 2000, 342: 1378-1384

[72] Pinto P., Bárbara C., Montserrat J.M., Patarrão R.S., Guarino M.P., Carmo M.M., Macedo M.P., Martinho C., Dias R., Gomes M.J.: Effects of CPAP on nitrate and norepinephrine levels in severe and mild-moderate sleep apnea. BMC Pulm. Med., 2013; 13: 13

[73] Polšek D., Bago M., Živaljić M., Rosenzweig I., Lacza Z., Gajović S.: A novel adjustable automated system for inducing chronic intermittent hypoxia in mice. PLoS One, 2017; 12: e0174896

[74] Prabhakar N.R., Peng Y.J., Jacono F.J., Kumar G.K., Dick T.E.: Cardiovascular alterations by chronic intermittent hypoxia: Importance of carotid body chemoreflexes. Clin. Exp. Pharmacol. Physiol., 2005; 32: 447-449

[75] Punjabi, N.M.: The epidemiology of adult obstructive sleep apnea. Proc. Am. Thorac. Soc., 2008; 5: 136-143

[76] Redline S., Yenokyan G., Gottlieb D.J., Shahar E., O'Connor G.T., Resnick H.E., Diener-West M., Sanders M.H., Wolf P.A., Geraghty E.M., Ali T., Lebowitz M., Punjabi N.M.: Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. Am. J. Respir. Crit. Care Med., 2010; 182: 269-277

[77] Robinson J.S., Fedinec A.L., Leffler C.W.: Role of carbon monoxide in glutamate receptor-induced dilation of newborn pig pial arterioles. Am. J. Physiol. Heart Circ. Physiol., 2002; 282: H2371-H2376

[78] Rudziński W., Swiat M., Tomaszewski M., Krejza J.: Cerebral hemodynamics and investigations of cerebral blood flow regulation. Nucl. Med. Rev. Cent. East. Eur., 2007; 10: 29-42

[79] Sandberg O., Franklin K.A., Bucht G., Gustafson Y.: Sleep apnea, delirium, depressed mood, cognition, and ADL ability after stroke. J. Am. Geriatr. Soc. 2001; 49: 391-397

[80] Schipper M.H., Jellema K., Rijsman R.M.: Occurrence of obstructive sleep apnea syndrome in patients with transient ischemic attack. J. Stroke Cerebrovasc. Dis., 2016; 25: 1249-1253

[81] Sforza E., Roche F.: Chronic intermittent hypoxia and obstructive sleep apnea: an experimental and clinical approach. Hypoxia, 2016; 4: 99-108

[82] Shibuya N., Tanaka M., Yoshida M., Ogasawara Y., Togawa T., Ishii K., Kimura H.: 3-Mercaptopyruvate sulfurtransferase produces hydrogen sulfide and bound sulfane sulfur in the brain. Antioxidants Redox Signal., 2009; 11: 703-714

[83] Ter Minassian A., Beydon L., Ursino M., Gardette B., Gortan C., Richalet J.P.: Doppler study of middle cerebral artery blood flow velocity and cerebral autoregulation during a simulated ascent of Mount Everest. Wilderness Env. Med., 2001; 12: 175-183

[84] Teramoto S., Kume H., Matsuse T., Ishii T., Miyashita A., Akishita M., Toba K., Ouchiet Y.: Oxygen administration improves the serum level of nitric oxide metabolites in patients with obstructive sleep apnea syndrome. Sleep Med., 2003; 4: 403-407

[85] Torres, G., Sánchez-De-La-Torre, M., Barbé, F.: Relationship between OSA and hypertension. Chest, 2015; 148: 824-832

[86] Turkington P.M., Allgar V., Bamford J., Wanklyn P., Elliott M.W.: Effect of upper airway obstruction in acute stroke on functional outcome at 6 months. Thorax, 2004; 59: 367-371

[87] Udwadia Z.F., Doshi A.V., Lonkar S.G., Singh C.I.: Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men. Am. J. Respir. Crit. Care Med., 2004; 169: 168-173

[88] Urbano F., Roux F., Schindler J., Mohsenin V.: Impaired cerebral autoregulation in obstructive sleep apnea. J. Appl. Physiol., 2008; 105: 1852-1857

[89] Villien M., Bouzat P., Rupp T., Robach P., Lamalle L., Troprès I., Estève F., Krainik A., Lévy P., Warnking J.M., Verges S.: Changes in cerebral blood flow and vasoreactivity to CO2 measured by arterial spin labeling after 6 days at 4350m. Neuroimage, 2013; 72: 272-279

[90] Weaver T.E., Mancini C., Maislin G., Cater J., Staley B., Landis J.R., Ferguson K.A., George C.F., Schulman D.A., Greenberg H., Rapoport D.M., Walsleben J.A., Lee-Chiong T., Gurubhagavatula I., Kuna S.T.: Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: Results of the CPAP apnea trial north american program (CATNAP) randomized clinical trial. Am. J. Respir. Crit. Care Med., 2012; 186: 677-683

[91] Willie C.K., Tzeng Y.C., Fisher J.A., Ainslie P.N.: Integrative regulation of human brain blood flow. J. Physiol., 2014; 592: 841-859

[92] Wilson M.H., Edsell M.E., Davagnanam I., Hirani S.P., Martin D.S., Levett D.Z., Thornton J.S., Golay X., Strycharczuk L., Newman S.P., Montgomery H.E., Grocott M.P., Imray C.H., Caudwell Xtreme Everest Research Group: Cerebral artery dilatation maintains cerebral oxygenation at extreme altitude and in acute hypoxia – an ultrasound and MRI study. J. Cereb. Blood Flow. Metab., 2011; 31: 2019-2029

[93] Winklewski P.J., Frydrychowski A.F.: Cerebral blood flow, sympathetic nerve activity and stroke risk in obstructive sleep apnoea. Is there a direct link? Blood Press, 2013; 22: 27-33

[94] Xie A., Skatrud J.B., Crabtree D.C., Puleo D.S., Goodman B.M., Morgan B.J.: Neurocirculatory consequences of intermittent asphyxia in humans. J. Appl. Physiol., 2000; 89: 1333-1339

[95] Yadav S.K., Kumar R., Macey P.M., Richardson H.L., Wang D.J., Woo M.A., Harper R.M.: Regional cerebral blood flow alterations in obstructive sleep apnea. Neurosci. Lett., 2013; 555: 159-164

[96] Yaggi H.K., Concato J., Kernan W.N., Lichtman J.H., Brass L.M., Mohsenin V.: Obstructive sleep apnea as a risk factor for stroke and death. N. Engl. J. Med., 2005; 353: 2034-2041

[97] Yan-fang S., Yu-ping W.: Sleep-disordered breathing: Impact on functional outcome of ischemic stroke patients. Sleep Med., 2009; 10: 717-719

[98] Zamarrón C., Valdés Cuadrado L., Álvarez-Sala R.: Pathophysiologic mechanisms of cardiovascular disease in obstructive sleep apnea syndrome. Pulm. Med., 2013; 2013: 1-16

[99] Zhang W., Si, L.: Obstructive sleep apnea syndrome (OSAS) and hypertension: pathogenic mechanisms and possible therapeutic approaches. Upsala J. Med. Sci., 2012; 117: 370-382

[100] Zhao W., Zhang J., Lu Y., Wang R.:The vasorelaxant effect of H2S as a novel endogenous gaseous KATP channel opener. EMBO J., 2001; 20: 6008-6016

The authors have no potential conflicts of interest to declare.