HYPOTHESIS

On the origin of cardiovascular complications of sleep apnea syndrome by the means of molecular interactions

[1]Jurkovicova I, [2,3]Celec P, [4]Mucska I, [2,3]Hodosy J

1st Department of Internal Medicine, Faculty Hospital, Bratislava, Slovakia. **petercelec@hotmail.com**

Abstract

In this article we present a novel hypothesis of the pathogenesis of cardiovascular complications of sleep apnea syndrome (SAS). Chronic intermittent hypoxia occurring in association with SAS represents a variation of chronic ischaemia reperfusion injury of the heart. In the hypoxic cells hypoxia inducible factor induces adaptation processes, including production of vascular endothelial growth factor and suppression of antioxidative mechanisms. Resulting oxidative and carbonyl stress are responsible for endothelial dysfunction leading to the development of systemic hypertension. Metabolic and vascular changes stimulate the atherogenic process. Besides the pathogenetic pathway of cardiovascular complications of SAS, we also present the latest concluding results from experimental observations and epidemiological studies concerning sleep disordered breathing and diseases of heart and vessels. Our theoretical assumption should be further proved.

Key words: sleep apnea syndrome, cardiovascular complications, hypoxia inducible factor, oxidative stress, carbonyl stress, hypertension

Introduction

Sleep apnea syndrome (SAS) is defined as a sleep-related breathing disorder by the apnea-hypopnea index (AHI; average number of apnea or hypopnea periods per hour sleep) of more than 10. Although apnea periods during sleep are common in about a quarter of the adult population, the prevalence of SAS is assumed to be 4% in men and 2% in women. Other symptoms are snoring, daytime sleepiness and fatigue. The exact diagnosis can be made only with the use of polysomnography (Flemons 2002). Central SAS and obstructive SAS are distinguished by the comparison of muscular effort of the patient during the apnea periods. In obstructive SAS the obstruction of upper airways is responsible for the apnea. Increased activity of respiratory muscles tries to overcome the resistance. In the central form no muscular activity can be seen during apnea. SAS is accompanied with risk factors like obesity, smoking, excessive alcohol intake and menopause-related estrogen depletion in women (Young et al. 2002). As polysomnography is expensive and often not available and clinicians do not bear this possible diagnosis in mind, most patients suffering from this disorder are still undiagnosed and thus, untreated.

The mortality of SAS patients is higher than in age- and BMI-matched healthy population. Lifetime limiting are especially traffic accidents, heart and lung diseases and hypertension-related cardiovascular causes (Tomori et al. 1999). Other connected problems are depression, impaired cognitive abilities, libido loss and enuresis, particularly in children (Lavie et al. 1995). Most of these complications are, however, preventable by the use of the only contemporary therapeutical standard – nasal continuous positive airway pressure (Bennett et al. 1999).

Cardiovascular complications of SAS are of interest not only due to their high prevalence but also due to the unsolved pathogenesis. It is known that the risk for stroke, coronary artery disease and for heart failure increases with AHI. Statistical multivariate analysis revealed that SAS is an independent risk factor for cardiovascular diseases, thus, the bias coming from shared common risk factors was eliminated (Shahar et al. 2001). In the other direction, patients with coronary artery disease have a worse long-term prognosis when

[1]1st Department of Internal Medicine, University Hospital, Bratislava, [2]Faculty of Natural Sciences, Comenius University, Bratislava, [3]Faculty of Medicine, Comenius University, Bratislava, and [4]Department of Respiratory Diseases, University Hospital, Bratislava, Slovakia

Address for correspondence: P. Celec, Galbaveho 3, SK-841 01 Bratislava 4, Slovakia.

The authors contributed equally to the preparation of the manuscript. The authors are grateful to the anonymous reviewer for helpful comments.

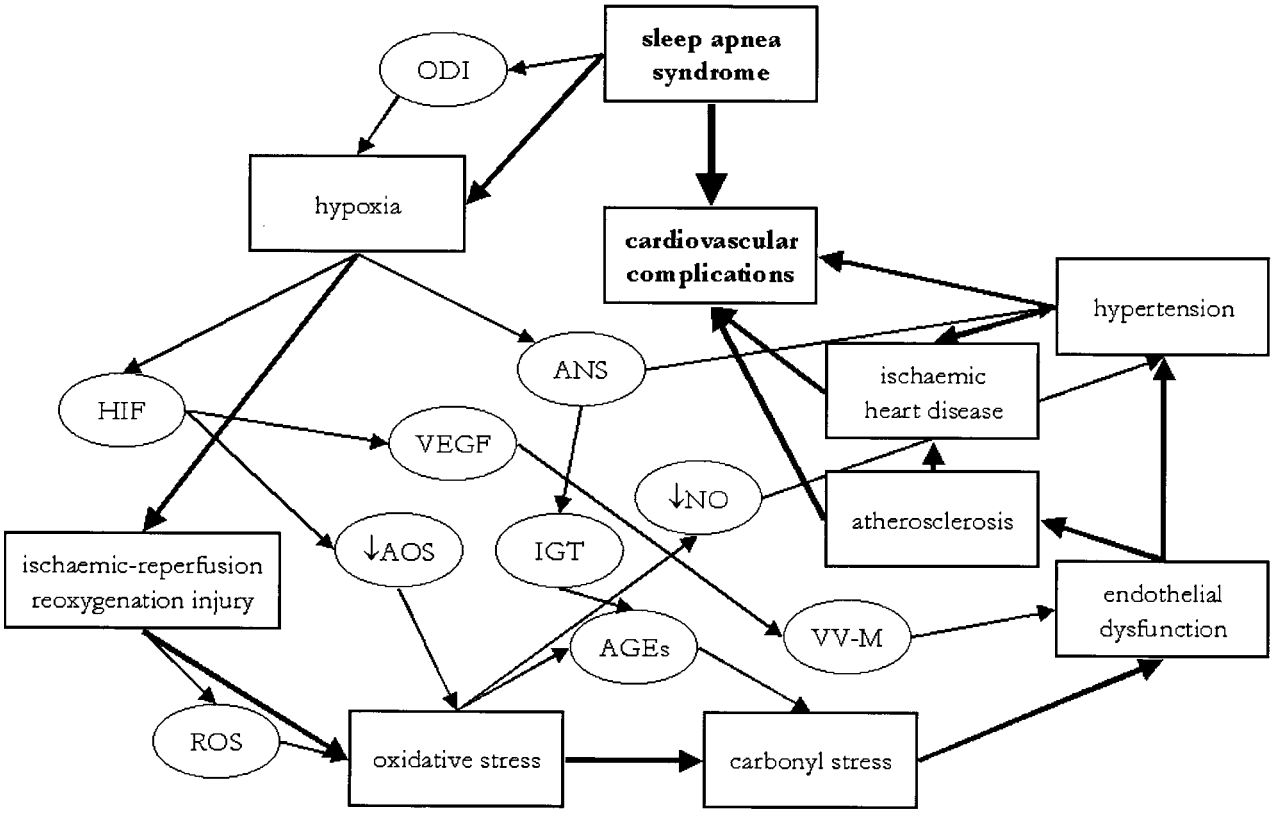

Fig. 1. The complex net of interactions resulting in cardiovascular complications of sleep apnea syndrome. See text for further details. ODI — oxygen desaturation index, HIF — hypoxia inducible factor, VEGF — vascular endothelial growth factor, AOS — antioxidative status, ROS — reactive oxygen species, AGEs — advanced glycation end products, ANS — adrenergic nervous system, IGT — impaired glucose tolerance, NO — nitric oxide, VV-M — vasa vasorum in the media.

concurrently suffering from SAS due to higher occurrence of cerebrovascular events (Mooe et al. 2001). Similarly, in patients with arterial hypertension a co-existing SAS increases the frequency and severity of nocturnal cardiac dysrhythmias explained by endothelial dysfunction (Szaboova 2003). However, the detailed pathophysiological pathway is still not clear.

We hypothesize, that chronic intermittent ischaemia occurring in SAS is responsible for endothelial dysfunction, development of hypertension consequently contributing to the increased occurrence of cardiovascular complications (Fig. 1). Moreover, we present herein the interactions that mediate this effect on the molecular level.

Activation cascade and the role of hypoxia inducible factor

Apnea periods are connected with oxygen desaturation phases reaching levels of less than 70%, depending on the severity of SAS in the patient. So-called oxygen desaturation index (ODI) is a quantitative marker of SAS that correlates with the occurrence of complications. Oxygen depletion in the heart or other tissues and a subsequent repletion in relation to apnea periods of SAS is a phenomenon that resembles to chronic intermittent ischaemia reperfusion injury (Mooe et al. 2000).

During the ischaemic phase the cells adapt to the new situation. Although the oxygen homeostasis is one of the most important and best-controlled metabolic mechanisms in the eucaryotic cell, the definite oxygen sensor is not known. Although a number of cytochromes, heme-binding proteins and other ferroproteins have been postulated to be the receptor for oxygen (Ryle & Hausinger 2002), no consensus exists yet, indicating, that either other not discovered proteins are responsible for the oxygen sensing or the process is dispersed between several molecular sensors that act as a receptor net (Semenza 2001a). Prolin hydroxylases that need oxygen as a substrate for the catalysed reaction belong to this net. An important protein that is related to oxygen sensing is hypoxia inducible factor (HIF) discovered in 1995. It consists of 2 subunits HIF-1α and HIF-1β. HIF-1β is continuously expressed, HIF-1α expression on the other hand is under multilevel regulation. Under normoxic conditions, prolin hydroxylases are active and they hydroxylate HIF-1α at several sites. This increases the affinity of HIF-1α to p53 and to the von Hippel-Lindau tumour suppressor protein (VHL). Interactions between p53 or VHL and HIF-1α in presence of the factor inhibiting HIF-1α (FIH) and histone deacetylase (HDAC) are required for the recognition of HIF-1á by ubiquitin ligase E3 complex containing elongin B and C and cullin 2 (Semenza 2002). Once ubiqiutinated, the protein is marked for degradation and cleavage. In hypoxia the detailed

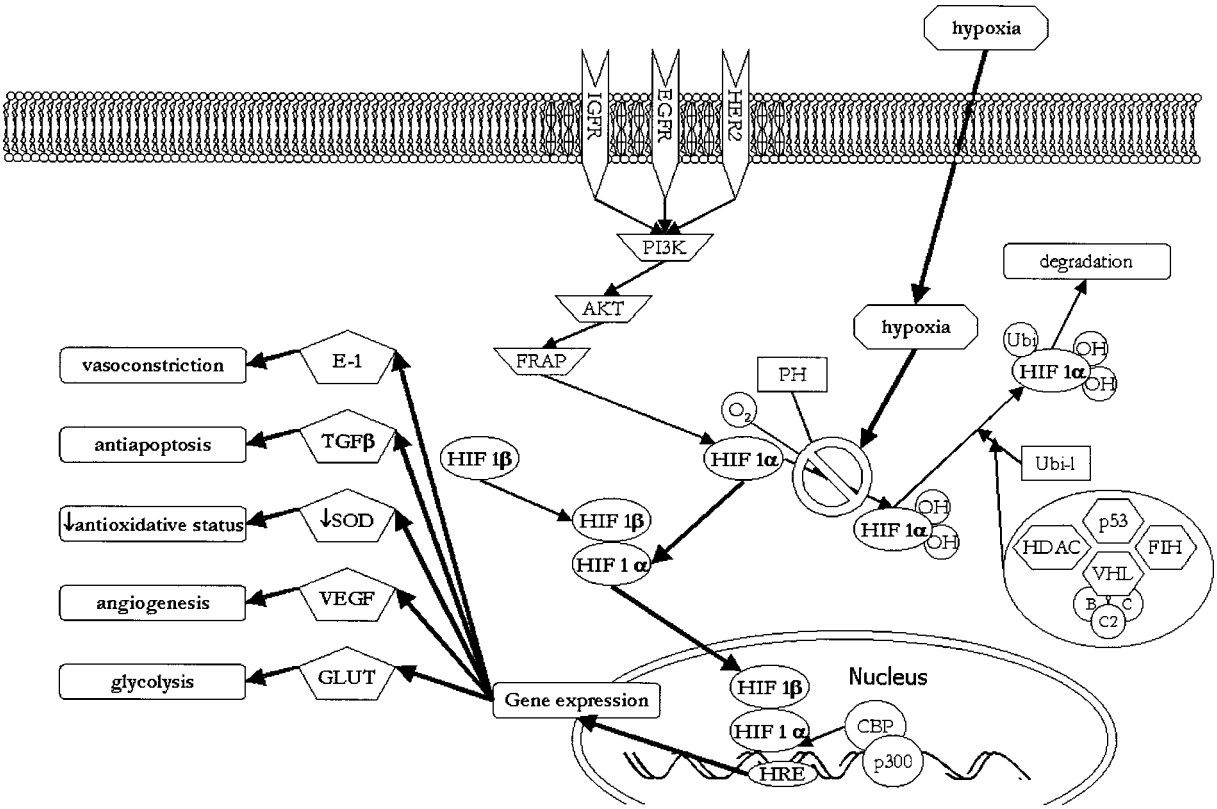

Fig. 2. Hypoxia inducible factor (HIF) degradation, activation by hypoxia and HIF-mediated gene regulation. IGFR — insulin like growth factor receptor, EGFR — epidermal growth factor receptor, HER2 — human epidermal growth factor receptor 2, PI3K — phosphatidylinositol-3-kinase, AKT — serine/threonine protein kinase B, FRAP — FKBP rapamycin associated protein, PH — prolin hydroxylases, Ubi-l — ubiquitin ligase, Ubi — ubiquitin, HDAC — histone deacetylase, VHL — von Hippel-Lindau tumour suppressor protein, FIH - factor inhibiting HIF-1α, B — elongin B, C — elongin C, C2 — cullin 2, CBP — CREB (3',5'-cyclic adenosine monophosphate response element binding protein) binding protein, HRE — hypoxia response element, GLUT — glucose transporter, VEGF — vascular endothelial growth factor, SOD — superoxiddismutase, TGFα — transforming growth factor ß, E-1 — endothelin 1.

role of mitochondria is not clear. However, primary two important things happen in the cytoplasm: the expression of HIF-1α increases and HIF-1α degradation is suppressed (Semenza 2001b). Activation of insulin like growth factor receptor (IGFR), epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) results in activation of the phosphatidylinositol-3-kinase cascade, serine//threonine protein kinase B – AKT and FKBP rapamycin associated protein (FRAP). FRAP enhances the expression of HIF-1α. Prolin hydroxylases cannot hydroxylate proteins when oxygen is depleted. HIF-1α is, thus, not hydroxylated either and cannot interact with tumour suppressor genes p53 and VHL. Ubiquitin ligase does not recognize HIF-1α as a substrate and the degradation of HIF-1α is stopped or at least decreased (Fig. 2).

Activated HIF-1α is a transcriptional factor that can interact with nuclear DNA. Enhancer sequences of target genes contain so-called hypoxia response elements (HRE; 5'-RCGTG-3'). Coactivators p300 and CBP are, however, needed for the activation of HIF-1α-mediated gene expression. A great number of genes contain HRE that have been reviewed recently in Trends Mol Med (Semenza 2001c). The HIF regulated proteins have three tasks – antiapoptotis (p21, TGFβ, IGF), metabolic shift from oxidative to glycolytic (hexokinases, aldolases, glucose transporters) and angiogenesis (vascular endothelial growth factor – VEGF, VEGF receptor). The changes in protein expression provide adaptation of the cells to the hypoxic environment.

Impact of chronic HIF activation

We assume a chronic sustained activation of HIF-1α in SAS patients as a result of chronic intermittent hypoxia not unlikely to the microenvironment of tumour cells in a progressive tumour (Maxwell et al. 2001) or in chronic inflammation (Hellwig-Burgel et al. 1999). A wide spectrum of effects is related to the chronic HIF activation. To the most important belong the down regulation of a number of antioxidative mechanisms, especially the activity of antioxidative enzymes like superoxiddismutase, catalase and gluthationperoxidase is suppressed during hypoxia. The cells do not need the protection against reactive oxygen species (ROS), as they cannot be produced due to the oxygen depletion and due to the glycolytic metabolic shift. Mitochondria providing the oxidative metabolism are "out of order". A unique problem arises due to the HIF-mediated overproduction of VEGF and its receptor (Tsuzuki et al. 2000; Hopfl et al. 2002).

Nitric oxide (NO) seems to be involved in the link between hypoxia and VEGF expression, but the detailed mechanism of NO action in this process is not clear by now (Sogawa et al. 1998; Kimura et al. 2000). Nevertheless, the enhanced VEGF production and sensitivity of the cells to this angiogenic factor induce neovascularisation of progressing tumours as well as the angiogenesis of vasa vasorum of arteries (Maxwell et al. 1997). In vivo, especially adventitial vasa vasorum formation was observed due to hypoxia in the arterial wall induced by experimental hypertension. However, the bias resulting from the short time period of hypertension in the experiments could not be excluded (Kuwahara et al. 2002). In patients with SAS, serum levels of VEGF were found to be higher than in control subjects (Imagawa et al. 2001). Moreover, the VEGF levels were higher in patients with severe SAS, the concentrations correlated well with ODI (Schulz et al. 2002). VEGF may be just a marker of the adaptation process to hypoxia (Kahler et al. 2003) or an artificial bias (Gunsilius et al. 2002). We hypothesize that increased circulating VEGF induce vasa vasorum formation in patients with SAS. This angiogenesis may be beneficial. VEGF response to hypoxia is age-dependent, children have much higher VEGF levels after the same hypoxic insult than adults (Gozal et al. 2002). Especially, the induction of vasa vasorum formation in the media of the vessels changes the mechanic characteristics of the arterial wall. The result is a higher susceptibility to atherosclerotic plaque development and to its rupture. Standard treatment of SAS reverses the VEGF levels to normal range (Lavie et al. 2002).

SAS patients were found to have an independent risk for insulin resistance and an impaired glucose tolerance as revealed by several studies (Punjabi et al. 2002; Ip et al. 2002). The metabolic shift towards anaerobic glycolysis instead of oxidative metabolism may be responsible for this effect. In addition, the glucocorticoid rise due to permanent nocturnal adrenergic stimulation may account for higher glycaemia. These processes could also explain higher cholesterol, particularly LDL found in SAS patients (Buchner et al. 1998).

Reperfusion injury and the consequences

What happens after repletion of oxygen during the reperfusion and reoxygenation? A high partial pressure of oxygen reaches the cells within seconds. The cells cannot compensate that quickly. A phenomenon similar to the calcium paradoxon, the oxygen paradoxon arises. In addition the neutrophils from patients with SAS showed enhanced respiratory burst, what might be a further source of ROS (Schulz et al. 2000). The dysbalance in ROS production and antioxidative mechanisms is called oxidative stress. Indeed, oxidative stress is often related to the reperfusion injury of the heart. One study dealing with the antioxidative status of SAS patients showed no difference to control subjects (Wali et al. 1998). Another one concentrating on melatonin circadian rhythm showed no differences in average melatonin levels, however, the study results were limited due to low number of participants and a problematic biochemical method. The slight changes in the pattern of melatonin levels must be further evaluated (Wikner et al. 1997). Other studies showed either directly increased ROS production, increased levels of peroxidation markers or enhanced expression of adhesion molecules, what is often accompanied with higher ROS generation (Ohga et al. 1999; Dyugovskaya et al. 2002; Carpagnano et al. 2002).

Posstranslational modification of protein in vivo with reducing aldehydes (eg. reducing sugars, malondialdehyde) initiates the formation of Amadori-type products, which in long-lived tissues rearrange to form irreversible end products, called also advanced glycation end products (AGEs). Congestion of AGEs in organism is termed carbonyl stress. Oxidative stress is directly linked to the carbonyl stress, as ROS facilitate the generation of AGEs and AGEs can induce ROS production. Higher levels of AGEs are a risk factor for the outcome of reperfusion injury during myocardial infarction. Moreover, oxidative stress results in increased homocysteine levels that are also found in SAS patients (Lavie et al. 2001).

Chronic oxidative and carbonyl stress incite the development of endothelial dysfunction. This effect is partly direct, partly mediated by the immune system. ROS react with NO to produce the highly toxic peroxynitrite radical, which deteriorate endothelocytes (Ip et al. 2000). The reaction also inhibits the vasodilatatory effect of NO (Tahawi et al. 2001). Structural changes during the AGEs production represent new antigens for the immune cells. Leukocytes are attracted to the endothelium and induce further local ROS generation as an immune reaction. Immune system activation can be observed by increased C-reactive protein levels (Shamsuzzaman et al. 2002). Evidence for the presence of endothelial dysfunction in SAS patients was already given. In SAS, vasodilatation (but only endothelium-dependent) is impaired (Kato et al. 2000; Duchna et al. 2001). Particularly, the response to hypoxia and not to ischaemia of the peripheral vasculature is abnormal (Remsburg et al. 1999). Endothelial defects lead to increased vascular resistance and to hypertension. In SAS, these effects are potentiated by the sustained activation of the adrenergic nervous system due to the arousals and CNS activation during nocturnal apnea episodes (Schafer et al. 1997; Zinkovska & Kirby 1997), increased peripheral muscular basal tonus (Narkiewicz et al. 1998b) and the following increased vasoconstrictor sensitivity (Kraiczi et al. 2000a). This is the rationale for the antihypertensive treatment of SAS patients with â-blockers on contrary to other possibilities (Kraiczi et al. 2000b). The contribution of the adrenergic system to SAS-associated hypertension was reviewed previously (Fletcher 2001).

SAS and hypertension

It has been already shown in experimental chronic intermittent hypoxia that activated HIF-1á also enhances the expression of endothelin-1 (Kanagy et al. 2001). This may add to the development of hypertension during the hypoxic phase (Camenisch et al. 2001). On the other hand, inducible NO synthase, cyclooxygenase 2 and atrial natriuretic peptide expression is increased as a consequence of HIF-1á activation (Jung et al. 2000; Hierholzer et al. 2001; Chun et al. 2002). The patophysiological role of these relations should be further evaluated taking into account that not only blood pressure but also arterial stiffness is increased as the result of apnea (Jelic et al. 2002). Arterial stiffness changes

seem to play a major role in SAS of children having similar systolic but significantly increased diastolic pressure values in comparison to healthy control group (Marcus et al. 1998).

SAS was shown to be an independent risk factor for systemic hypertension and thus, should be considered by physicians in hypertensive patients (Collop 2002). Several pathomechanisms may be postulated in addition to the aforementioned. Increased renin activity found in experimental SAS may contribute to the increment of blood pressure (Fletcher et al. 1999), particularly through tissue specific upregulation of local angiotensin II (Fletcher et al. 2002). More answers may be found by comprehensive studying of the development of pulmonary hypertension that is observed in one third of SAS patients (Yamakawa et al. 2002). Although in opposite to systemic hypertension the pathophysiological link between hypoxia and increased pulmonary arterial pressure seems to be more straightforward (Schneider et al. 2000). Cor pulmonale resulting from the chronic pulmonary hypertension (Richter & Gottwik 2002) can be also prevented by nasal positive airway pressure treatment (Blankfield et al. 2003). This is true also for transient ischaemic attacks and strokes as the major complications of hypertension (Pressman et al. 1995). Truly, SAS patients have a clear higher risk for cerebrovascular events than healthy controls (Dyken et al. 1996). Moreover, sleep-disordered breathing is associated with worse prognosis of patients with stroke (Good et al. 1996), although the morphologic links are not clear yet (Bassetti et al. 1997).

Carotid artery wall thickness is an easy to obtain quantitative marker indicating the cardiovascular risk in SAS patients and should be considered more frequently in the clinical use (Silvestrini et al. 2002). Remarkably, when taking into account, that other sonographic parameters like left ventricular mass or left ventricular end diastolic volume do not correlate with AHI or ODI, if adjusted to BMI, age and blood pressure (Niroumand et al. 2001). Taking the results from the clinical studies together, the cardiovascular risk of SAS lies in hypertension and stroke on one side and in atherosclerosis and ischaemic heart disease with dysrhythmias on the other side (Peker et al. 2002, Szaboova 2003).

Conclusion

Acute haemodynamic and cardiovascular changes occurring during the apnea phases were discussed thoroughly. The long lasting effects of SAS on the cardiovascular system are known mostly from epidemiological studies. Therefore, the pathomechanism of SAS associated hypertension and atherosclerosis is generally unknown. It is unsatisfying to declare the pathogenesis as multifarious. Chronobiological distinctions are often made responsible especially for hypertension in SAS (Narkiewicz et al. 1998a; Harbison et al. 2000). It is likely that the altered circadian blood pressure, its variability and cardiac arrhythmias in SAS are not a cause but a serious and sometimes even lethal consequence of SAS-associated changes presented in this article.

There is a need to search for the origin of diseases in the cell. HIF-1α regulates the response to hypoxia of the cells and so is very likely to be directly involved in the pathogenesis of SAS-associated complications. Affecting the HIF-1α signalling pathway is a new and interesting approach in the anti tumour therapy (Comerford et al. 2002; Acker & Plate 2002). HIF inhibition may also be indicated in therapy of ischaemic heart disease and some retinal diseases (Rapisarda et al. 2002). However, the use of HIF-1α inhibitors is questionable in patients with SAS. HIF-1α may be responsible for the cardiovascular complications. In this paper we provide some new possible insights into their origin and the pathogenesis. Nevertheless, preventive therapy in form of nasal continuous positive airway pressure is relatively available and it should be preferred in comparison to any other therapy of the complications (Heitmann et al. 1998). Moreover, the nasal continuous positive airway pressure therapy can in a very short time reverse some cardiovascular SAS complications (Tkacova et al. 1998; Javaheri 2000), mainly in case of early indications where it can precede the development of hypertension, ischaemic heart disease with dysrhythmias etc., as it was repeatedly shown.

In summary, we present herein a novel hypothesis for the pathophysiological links between SAS and the impairment of heart and vessels, activation of HIF-1α playing the central role on molecular level. We also have shown how the HIF-1α-regulated gene expression may affect the vascular system and its metabolism and how oxidative and carbonyl stress may contribute to atherogenesis and endothelial dysfunction resulting in hypertension and ischaemic heart disease. Though the evidence that SAS induces hypertension is known for years (Brooks et al. 1997), we still lack an accepted detailed link between SAS and hypertension. Our hypothesis may contribute to the discussion of this problem of high clinical relevance. Molecular and cellular biology should offer more insights in the pathogenesis of cardiovascular diseases in SAS in the near future answering the majority of remaining questions partly mentioned here.

References

1. Acker T, Plate KH. A role for hypoxia and hypoxia-inducible transcription factors in tumor physiology. J Mol Med 2002; 80: 562—575.

2. Bassetti C, Aldrich MS, Quint D. Sleep-disordered breathing in patients with acute supra- and infratentorial strokes. A prospective study of 39 patients. Stroke 1997; 28: 1765—1772.

3. Bennett LS, Barbour C, Langford B, Stradling JR, Davies RJ. Health status in obstructive sleep apnea: relationship with sleep fragmentation and daytine sleepiness, and effects of continuous positive airway pressure treatment. Amer J Resp Crit Care Med 1999; 159: 1884—1890.

4. Blankfield RP, Sajkov D, McEvoy RD. Continuous positive airway pressure normalizes pulmonary artery pressures in subjects with obstructive sleep apnea and pulmonary hypertension. Amer J Resp Crit Care Med 2003; 167: 94.

5. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 1997; 99: 106—109.

6. Buchner N, Sanner B, Burmann-Urbanek M, Zidek W. (Obstructive sleep apnea and hypertension. Diagnostic procedure — exclusion of risk factors — nCPAP treatment). Fortschr Med 1998; 116: 24—27.

7. Camenisch G, Stroka DM, Gassmann M, Wenger RH. Attenuation of HIF-1 DNA-binding activity limits hypoxia-inducible endothelin-1 expression. Pflugers Arch 2001; 443: 240—249.

8. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ. Increased 8-isoprostane and interleukin-6 in

breath condensate of obstructive sleep apnea patients. Chest 2002; 122: 1162—1167.

9. Chun YS, Hyun JY, Kwak YG, Kim IS, Kim CH, Choi E, Kim MS, Park JW. Hypoxic activation of the atrial natriuretic peptide gene promoter through direct and indirect actions of hypoxia-inducible factor-1. Biochem J 2002; 370: 149—157.

10. Collop NA. Silent bedpartners: obstructive sleep apnea and hypertension, 6 years later. Chest 2002; 122: 1111—1112.

11. Comerford KM, Wallace TJ, Karhausen J, Louis NA, Montalto MC, Colgan SP. Hypoxia-inducible factor-1-dependent regulation of the multidrug resistance (MDR1) gene. Cancer Res 2002; 62: 3387—3394.

12. Duchna HW, Guilleminault C, Stoohs RA, Orth M, de Zeeuw J, Schultze-Werninghaus G, Rasche K. Obstructive sleep apnea syndrome: a cardiovascular risk factor? Z Kardiol 2001; 90: 568—575.

13. Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB. Investigating the relationship between stroke and obstructive sleep apnea. Stroke 1996; 27: 401—407.

14. Dyugovskaya L, Lavie P, Lavie L. Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. Amer J Resp Crit Care Med 2002; 165: 934—939.

15. Flemons WW. Clinical practice. Obstructive sleep apnea. New Engl J Med 2002; 347: 498—504.

16. Fletcher EC. Invited review: Physiological consequences of intermittent hypoxia: systemic blood pressure. J Appl Physiol 2001, 90: 1600—1605.

17. Fletcher EC, Bao G, Li R. Renin activity and blood pressure in response to chronic episodic hypoxia. Hypertension 1999; 34: 309—314.

18. Fletcher EC, Orolinova N, Bader M. Blood pressure response to chronic episodic hypoxia: the renin-angiotensin system. J Appl Physiol 2002; 92: 627—633.

19. Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S. Sleep-disordered breathing and poor functional outcome after stroke. Stroke 1996; 27: 252—259.

20. Gozal D, Lipton AJ, Jones KL. Circulating vascular endothelial growth factor levels in patients with obstructive sleep apnea. Sleep 2002; 25: 59—65.

21. Gunsilius E, Petzer AL, Gastl GA. Blood levels of vascular endothelial growth factor in obstructive sleep apnea-hypopnea syndrome. Blood 2002; 99: 393—394.

22. Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. Chest 2000; 118: 591—595.

23. Heitmann J, Grote L, Knaack L, Kohler U, Hinder M, Peter JH. Cardiovascular effects of mibefradil in hypertensive patients with obstructive sleep apnea. Europ J Clin Pharmacol 1998; 54: 691—696.

24. Hellwig-Burgel T, Rutkowski K, Metzen E, Fandrey J, Jelkmann W. Interleukin-1beta and tumor necrosis factor-alpha stimulate DNA binding of hypoxia-inducible factor-1. Blood 1999; 94: 1561—1567.

25. Hierholzer C, Harbrecht BG, Billiar TR, Tweardy DJ. Hypoxia-inducible factor-1 activation and cyclo-oxygenase-2 induction are early reperfusion-independent inflammatory events in hemorrhagic shock. Arch Orthop Trauma Surg 2001; 121: 219—222.

26. Hopfl G, Wenger RH, Ziegler U, Stallmach T, Gardelle O, Achermann R, Wergin M, Kaser-Hotz B, Saunders HM, Williams KJ, Stratford IJ, Gassmann M, Desbaillets I. Rescue of hypoxia-inducible factor-1alpha-deficient tumor growth by wild-type cells is independent of vascular endothelial growth factor. Cancer Res 2002; 62: 2962—2970.

27. Imagawa S, Yamaguchi Y, Higuchi M, Neichi T, Hasegawa Y, Mukai HY, Suzuki N, Yamamoto M, Nagasawa T. Levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea—hypopnea syndrome. Blood 2001; 98: 1255—1257.

28. Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC, Lam WK. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Amer J Resp Crit Care Med 2000; 162: 2166—2171.

29. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. Amer J Resp Crit Care Med 2002; 165: 670—676.

30. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation 2000; 101: 392—397.

31. Jelic S, Bartels MN, Mateika JH, Ngai P, DeMeersman RE, Basner RC. Arterial stiffness increases during obstructive sleep apneas. Sleep 2002; 25: 850—855.

32. Jung F, Palmer LA, Zhou N, Johns RA. Hypoxic regulation of inducible nitric oxide synthase via hypoxia inducible factor-1 in cardiac myocytes. Circulat Res 2000; 86: 319—325.

33. Kahler CM, Wechselberger J, Molnar C, Prior C, Schulz R, Seeger W, Grimminger F. Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe night time hypoxia. Amer J Resp Crit Care Med 2003; 167: 92—93.

34. Kanagy NL, Walker BR, Nelin LD. Role of endothelin in intermittent hypoxia-induced hypertension. Hypertension 2001; 37: 511—515.

35. Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, Somers VK. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation 2000; 102: 2607—2610.

36. Kimura H, Weisz A, Kurashima Y, Hashimoto K, Ogura T, D'Acquisto F, Addeo R, Makuuchi M, Esumi H. Hypoxia response element of the human vascular endothelial growth factor gene mediates transcriptional regulation by nitric oxide: control of hypoxia-inducible factor-1 activity by nitric oxide. Blood 2000; 95: 189—197.

37. Kraiczi H, Hedner J, Peker Y, Carlson J. Increased vasoconstrictor sensitivity in obstructive sleep apnea. J Appl Physiol 2000 a; 89: 493—498.

38. Kraiczi H, Hedner J, Peker Y, Grote L. Comparison of atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan for antihypertensive treatment in patients with obstructive sleep apnea. Amer J Resp Crit Care Med 2000 b; 161: 1423—1428.

39. Kuwahara F, Kai H, Tokuda K, Shibata R, Kusaba K, Tahara N, Niiyama H, Nagata T, Imaizumi T. Hypoxia-inducible factor-1alpha/vascular endothelial growth factor pathway for adventitial vasa vasorum formation in hypertensive rat aorta. Hypertension 2002; 39: 46—50.

40. Lavie L, Kraiczi H, Hefetz A, Ghandour H, Perelman A, Hedner J, Lavie P. Plasma vascular endothelial growth factor in sleep apnea syndrome: effects of nasal continuous positive air pressure treatment. Amer J Resp Crit Care Med 2002; 165: 1624—1628.

41. Lavie L, Perelman A, Lavie P. Plasma homocysteine levels in obstructive sleep apnea: association with cardiovascular morbidity. Chest 2001; 120: 900—908.

42. Lavie P, Herer P, Peled R, Berger I, Yoffe N, Zomer J, Rubin AH. Mortality in sleep apnea patients: a multivariate analysis of risk factors. Sleep 1995; 18: 149—157.

43. Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. Amer J Resp Crit Care Med 1998; 157: 1098—1103.

44. Maxwell PH, Dachs GU, Gleadle JM, Nicholls LG, Harris AL, Stratford IJ, Hankinson O, Pugh CW, Ratcliffe PJ. Hypoxia-inducible factor-1 modulates gene expression in solid tumors and influences both angioge-

nesis and tumor growth. Proc Natl Acad Sci USA 1997; 94: 8104—8109.

45. Maxwell PH, Pugh CW, Ratcliffe PJ. Activation of the HIF pathway in cancer. Curr Opin Genet Dev 2001; 11: 293—299.

46. Mooe T, Franklin KA, Holmstrom K, Rabben T, Wiklund U. Sleep-disordered breathing and coronary artery disease: long-term prognosis. Amer J Resp Crit Care Med 2001; 164: 1910—1913.

47. Mooe T, Franklin KA, Wiklund U, Rabben T, Holmstrom K. Sleep-disordered breathing and myocardial ischemia in patients with coronary artery disease. Chest 2000; 117: 1597—1602.

48. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. Circulation 1998 a; 98: 1071—1077.

49. 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 b; 97: 943—945.

50. Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. Amer J Resp Crit Care Med 2001; 163: 1632—1636.

51. Ohga E, Nagase T, Tomita T, Teramoto S, Matsuse T, Katayama H, Ouchi Y. Increased levels of circulating ICAM—1, VCAM-1, and L-selectin in obstructive sleep apnea syndrome. J Appl Physiol 1999; 87: 10—14.

52. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Amer J Resp Crit Care Med 2002; 166: 159—165.

53. Pressman MR, Schetman WR, Figueroa WG, Van Uitert B, Caplan HJ, Peterson DD. Transient ischemic attacks and minor stroke during sleep. Relationship to obstructive sleep apnea syndrome. Stroke 1995; 26: 2361—2365.

54. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Amer J Resp Crit Care Med 2002; 165: 677—682.

55. Rapisarda A, Uranchimeg B, Scudiero DA, Selby M, Sausville EA, Shoemaker RH, Melillo G. Identification of small molecule inhibitors of hypoxia-inducible factor 1 transcriptional activation pathway. Cancer Res 2002; 62: 4316—4324.

56. Remsburg S, Launois SH, Weiss JW. Patients with obstructive sleep apnea have an abnormal peripheral vascular response to hypoxia. J Appl Physiol 1999; 87: 1148—1153.

57. Richter P, Gottwik M. Cor pulmonale: interaction with pulmonary hypertension, sleep apnea and lung diseases. Internist (Berl) 2002; 43 (Suppl 1): S19—S32.

58. Ryle MJ, Hausinger RP. Non-heme iron oxygenases. Curr Opin Chem Biol 2002; 6: 193—201.

59. Schafer H, Koehler U, Ploch T, Peter JH. Sleep-related myocardial ischemia and sleep structure in patients with obstructive sleep apnea and coronary heart disease. Chest 1997; 111: 387—393.

60. Schneider H, Schaub CD, Chen CA, Andreoni KA, Schwartz AR, Smith PL, Robotham JL, O'Donnell CP. Neural and local effects of hypoxia on cardiovascular responses to obstructive apnea. J Appl Physiol 2000; 88: 1093—1102.

61. Schulz R, Hummel C, Heinemann S, Seeger W, Grimminger F. Serum levels of vascular endothelial growth factor are elevated in patients with obstructive sleep apnea and severe nighttime hypoxia. Amer J Resp Crit Care Med 2002; 165: 67—70.

62. Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, Seeger W, Grimminger F. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Impact of continuous positive airway pressure therapy. Amer J Resp Crit Care Med 2000; 162: 566—570.

63. Semenza GL. HIF-1 and mechanisms of hypoxia sensing. Curr Opin Cell Biol 2001 a; 13: 167—171.

64. Semenza GL. Hypoxia-inducible factor 1: control of oxygen homeostasis in health and disease. Pediat Res 2001 b; 49: 614—617.

65. Semenza GL. Hypoxia-inducible factor 1: oxygen homeostasis and disease pathophysiology. Trends Mol Med 2001 c; 7: 345—350.

66. Semenza GL. HIF-1 and tumor progression: pathophysiology and therapeutics. Trends Mol Med 2002; 8: S62—S67.

67. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier NF, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Amer J Resp Crit Care Med 2001; 163: 19—25.

68. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002; 105: 2462—2464.

69. Silvestrini M, Rizzato B, Placidi F, Baruffaldi R, Bianconi A, Diomedi M. Carotid artery wall thickness in patients with obstructive sleep apnea syndrome. Stroke 2002; 33: 1782—1785.

70. Sogawa K, Numayama-Tsuruta K, Ema M, Abe M, Abe H, Fujii-Kuriyama Y. Inhibition of hypoxia-inducible factor 1 activity by nitric oxide donors in hypoxia. Proc Natl Acad Sci USA 1998; 95: 7368—7373.

71. Szaboova E. Effect of sleep apnoea/hypopnoea on the development and severity of nocturnal cardiac dysrhythmias. PhD thesis. Medical Faculty, Safarik University, Kosice, 2003.

72. Tahawi Z, Orolinova N, Joshua IG, Bader M, Fletcher EC. Altered vascular reactivity in arterioles of chronic intermittent hypoxic rats. J Appl Physiol 2001; 90: 2007—2013.

73. Tkacova R, Rankin F, Fitzgerald FS, Floras JS, Bradley TD. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. Circulation 1998; 8: 2269—2275.

74. Tomori Z, Szaboova E, Donic V. Interaction of sleep apnoea syndrome with various diseases. Bratisl Lek Listy 1999; 100: 80—84.

75. Tsuzuki Y, Fukumura D, Oosthuyse B, Koike C, Carmeliet P, Jain RK. Vascular endothelial growth factor (VEGF) modulation by targeting hypoxia-inducible factor-1alpha—> hypoxia response element—> VEGF cascade differentially regulates vascular response and growth rate in tumors. Cancer Res 2000; 60: 6248—6252.

76. Wali SO, Bahammam AS, Massaeli H, Pierce GN, Iliskovic N, Singal PK, Kryger MH. Susceptibility of LDL to oxidative stress in obstructive sleep apnea. Sleep 1998; 21: 290—296.

77. Wikner J, Svanborg E, Wetterberg L, Rojdmark S. Melatonin secretion and excretion in patients with obstructive sleep apnea syndrome. Sleep 1997; 20: 1002—1007.

78. Yamakawa H, Shiomi T, Sasanabe R, Hasegawa R, Ootake K, Banno K, Wakayama H, Katada M, Kobayashi T. Pulmonary hypertension in patients with severe obstructive sleep apnea. Psychiatry Clin Neurosci 2002; 56: 311—312.

79. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Amer J Resp Crit Care Med 2002; 165: 1217—1239.

80. Zinkovska S, Kirby DA. Intracerebroventricular propranolol prevented vascular resistance increases on arousal from sleep apnea. J Appl Physiol 1997; 82: 1637—1643.

Received February 21, 2003.
Accepted April 18, 2003.