

Sleep-Disordered Breathing and Cardio- and Cerebrovascular Diseases: 2003 Update of Clinical Significance and Future Perspectives

Schlafbezogene Atmungsstörungen und kardio- und zerebrovaskuläre Erkrankungen:
Update 2003 der klinischen Bedeutung und zukünftiger Entwicklungen

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Summary

The purpose of this review is to summarize current knowledge about the link between sleep-disordered breathing (SDB) and cardiovascular and cerebrovascular diseases. Obstructive sleep apnoea (OSA) is a well-established risk factor for systemic arterial hypertension, and its treatment with continuous positive airway pressure leads to a decrease in daytime and night-time blood pressure profiles. Pulmonary arterial hypertension occurs in 20–30% of OSA patients and is usually mild. It is not yet clear if OSA *per se* leads to pulmonary hypertension or if the coexistence of chronic obstructive pulmonary disease with daytime and/or sleep-related hypoxaemia is required to provoke a persistent rise in pulmonary artery pressure. Furthermore, OSA is associated with nocturnal cardiac arrhythmias, especially cyclical fluctuations of the heart rate in response to recurrent apnoeas. Atrioventricular conduction blocks and ventricular premature beats are less often observed and seem to be confined to patients with severe OSA and those with accompanying ischaemic heart disease. The association between OSA and vaso-occlusive disease (i.e. atherosclerosis) is less clear. However, accumulating experimental and epidemiological data support such a link. Thus, OSA may lead to coronary artery disease (CAD) and stroke by promoting atherosclerosis. Correspondingly, patients with CAD or acute stroke show a high prevalence of SDB. Cheyne–Stokes respiration (CSR) is a specific pattern of central sleep apnoea occurring in

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patients with advanced congestive heart failure (CHF). If present, CSR clearly has a negative impact on the clinical course of CHF. Although the optimal treatment strategy for CSR is less well defined than that for OSA, the successful reversal of CSR might increase overall survival in affected patients.

Keywords Sleep-disordered breathing – obstructive sleep apnoea – central sleep apnoea – Cheyne – Stokes breathing – pulmonary disease – cardiovascular disease – hypertension – stroke.

Zusammenfassung

Ziel dieser Übersichtsarbeit ist die Darstellung aktueller Zusammenhänge zwischen schlafbezogenen Atmungsstörungen und kardio- bzw. zerebrovaskulären Erkrankungen: Das obstruktive Schlafapnoe-Syndrom (OSAS) ist als unabhängiger Risikofaktor für die Entstehung einer arteriellen Hypertonie anzusehen. Die nasale Überdruck-Therapie (CPAP) führt zu einer Senkung des Tages- und Nachtblutdruckes. Ca. 20–30% der Patienten mit OSAS weisen eine pulmonal-arterielle Hypertonie auf; unklar ist jedoch, ob eine zusätzliche Lungenerkrankung mit Tages- und/oder Nachthyoxämie eine notwendige Voraussetzung zur Entstehung der pulmonal-arteriellen Hypertonie bei diesen Patienten ist. Herzrhythmusstörungen, insbesondere apnoebedingte Schwankungen der Herzfrequenz, treten bei OSAS gehäuft auf. Atrioventrikuläre Blockbilder oder ventrikuläre Extrasystolen sind seltener anzutreffen und scheinen auf schwere Formen des OSAS und solche mit zusätzlicher koronarer Herzkrankheit beschränkt zu sein. Die Zusammenhänge zwischen OSAS und der Entwicklung einer Arteriosklerose sind nicht vollständig geklärt, jedoch belegen experimentelle und epidemiologische Studien diesbezüglich eine enge Verbindung. Durch Induktion einer Arteriosklerose kann das OSAS zur Entstehung einer koronaren Herzkrankheit oder eines beitragen. Patienten mit einer koronaren Herzkrankheit oder einem apoplektischen Insult weisen dementsprechend eine hohe Prävalenz schlafbezogener Atmungsstörungen auf. Eine spezielle Form zentraler Apnoen stellt die Cheyne–Stokes Atmung dar, die bei Patienten mit fortgeschrittener Herzinsuffizienz gehäuft vorliegt. Gesichert ist der negative Einfluß der Cheyne–Stokes Atmung auf den klinischen Verlauf der Herzinsuffizienz. Obwohl die Behandlungsstrategie der Cheyne–Stokes Atmung weniger etabliert ist als beim OSAS, führt deren erfolgreiche Behandlung zu einer Steigerung der Lebenserwartung bei den Betroffenen.

Schlüsselwörter Schlafbezogene Atmungsstörungen – obstruktives Schlafapnoe-Syndrom – zentrale Schlafapnoe – Cheyne – Stokes Atmung – COPD – kardiovaskuläre Erkrankungen – Bluthochdruck – apoplektischer Insult.

Introduction

In 2000, the working group ‘Kreislauf und Schlaf’ of the German Sleep Society (DGSM) was founded. In this group, scientists combine their efforts to promote research in the field of sleep medicine and cardio- and cerebrovascular disease (CVD). CVDs are the most common life-threatening and debilitating diseases in the industrialized world. Recent studies have elucidated the importance of sleep-disordered breathing (SDB) with new epidemiological data and modern pathophysiological concepts supporting the hypothesis of a complex association and pathophysiological interaction of SDB and CVD. Thus, a better understanding of both disease entities is gained, which may result in a reduction of morbidity and mortality. The interaction of SDB and CVD can be regarded from various points of view: for example, in obstructive sleep apnoea (OSA), SDB plays an important role as a risk factor leading to the development of CVD. On the other hand, CVD (especially chronic heart failure) can cause SDB (i.e. Cheyne–Stokes respiration). The first aim of the working group was to summarize current knowledge about the interaction between SDB and CVD. The results of this collaborative work are reported in the present review paper. To

avoid being too theoretical, the authors focussed on the interaction of SDB and relevant CVD, i.e. atherosclerosis, cardiac arrhythmias, systemic and pulmonary hypertension, coronary artery disease, heart failure, and cerebrovascular disease. All of these different subjects are similarly subdivided into introduction, epidemiology, physiology/pathophysiology, impact on clinical practice, therapeutic intervention, diagnostic and therapeutic recommendations, and conclusions and future perspectives in order to make life easier for the reader.

Atherosclerosis

H.-W. Duchna, R. Schulz

Introduction

Atherosclerosis forms the basis for many cardiovascular disorders, and patients with OSA present with a high comorbidity of CVD. However, it has been difficult to establish a cause–effect relationship between OSA and CVD because these patients typically present with traditional risk

factors for the development of CVD such as obesity and metabolic disease, i.e. hyperlipidaemia and insulin resistance. Keeping in mind these confounding factors, the interaction of OSA, vascular risk factors, and CVD has been called 'syndrome Z' [251].

Epidemiology

There is a low grade of evidence of epidemiological data dealing with systemic atherosclerosis in patients with OSA. As atherosclerosis is a causal factor in most CVDs, its prevalence in patients with OSA might be estimated from the prevalence rates of coronary artery disease, myocardial infarction, and stroke. Preliminary studies investigating the prevalence of carotid atheromas and stenoses indicate a significant correlation with the presence of OSA [1, 64], but the number of patients investigated is low.

Physiology/pathophysiology

Atherosclerosis is the end point of a vascular disease, which begins as a functional disorder of the complex interaction between blood with its cellular components, vascular endothelial cells, and vascular smooth muscle cells. The vascular endothelial cells are in control of vascular tone, immunomodulatory functions, growth, vascular permeability, cell adhesion, and vascular architecture via a multitude of enzymes and kinases [46, 131, 192]. Vascular endothelial cells, however, are integrated in systemic vascular reflex mechanisms, mainly influenced by sympathetic and parasympathetic tone, hormones such as catecholamines, atrial natriuretic peptide, angiotensin II, vasopressin, and others [85]. An endothelial dysfunction appears to play a key role in the development of atherosclerosis [91, 192, 193].

An endothelial dysfunction has been demonstrated in almost all known risk factors for CVD, as for example diabetes mellitus, smoking, hypercholesterolaemia, and arterial hypertension [27, 28, 35, 130, 180, 229]. Recent studies support the hypothesis that OSA also leads to vascular endothelial dysfunction. According to the results of three different studies, endothelium-dependent vascular relaxation is blunted in awake patients with OSA, in the absence of any other disease state or potential cause of endothelial dysfunction [26, 48, 107, 117]. These data from *in vivo* studies in humans are supported by the results of an investigation of vascular reactivity in rats, in which recurrent episodic hypoxia served as a model for OSA [232].

Another current pathophysiological concept is that the OSA-related stimuli of hypoxaemia and shear stress enhance vasoconstrictive and prothrombotic forces within the vascular milieu and thereby lead to accelerated atherosclerosis [39, 56, 67, 115, 121, 126, 138, 155, 191]. This is strongly suggested by abnormalities of biochemical markers of CVD, which have been described in patients with OSA. First of all, there is increased sympathetic tone as evidenced by elevated catecholamine levels in plasma and urine and by an increase of muscle sympathetic nerve activity [25]. Furthermore, endothelial nitric oxide (NO) generation is suppressed, thus giving an explanation for the above-mentioned reduction of endothelium-dependent vascular relaxation in OSA. In this context, decreased serum levels of NO-derived nitrite and nitrate have been found in OSA [100, 213]. In addition to its decreased release, NO is probably scavenged by excessively generated free oxygen radicals. This assumption is supported by the finding of an enhanced superoxide release from circulating neutrophils and monocytes in OSA patients [51,

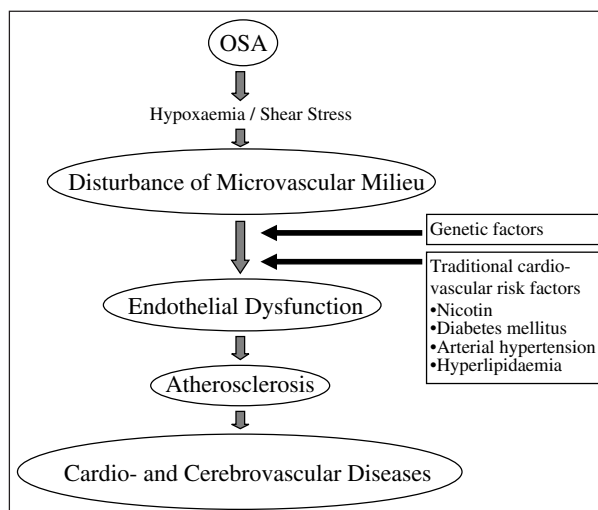


Figure 1. Hypothesis for the development of atherosclerosis and CVD in OSA.

211]. The role of the vasoconstrictor endothelin in the development of OSA-associated CVD is less well established. Some studies reported increased serum concentrations of endothelin in OSA [176, 195], whereas other investigations could not reproduce these findings [73]. Apart from these changes in vasoactive mediator systems, inflammatory markers of vascular injury are also upregulated in OSA. This concerns vascular adhesion molecules as evidenced by measurements of soluble VCAM, ICAM, and E-selectin [33, 166], levels of highly sensitive C-reactive protein [218] and cytokines such as IL-6 and TNF- α [242]. Finally, activation and aggregation of platelets and increased fibrinogen levels have been reported in OSA and are presumed to underlie the development of CVD in these patients [21, 34, 248]. The two major hypotheses regarding the development of CVD and atherosclerosis in OSA are summarized in figure 1.

The first direct evidence that OSA indeed leads to vascular remodelling and atherosclerosis is provided by ultrasonographic measurements of the intima media thickness of the common carotid artery (IMT-CCA). This parameter reflects the actual atherosclerotic burden of the organism and predicts the risk of future cardiovascular and cerebrovascular events in patients with or without pre-existing CVD. In this context, two independent studies have found an increase in IMT-CCA in untreated OSA patients as compared to matched control groups [210, 219].

Impact on clinical practice

Experimental data strongly suggest a negative effect of OSA-induced repetitive pressor surges and hypoxaemia on vascular endothelial function, although the level of clinical evidence is low. Endothelial dysfunction is a precursor of atherosclerosis. Abnormalities of microvessel function, structure and microvascular network are an important cause of hypertension, also likely to be central to many forms of atherosclerotic or hypertensive end-organ damage [125].

Therapeutic intervention

At present, there are no data available showing an improvement in atherosclerotic lesions by treatment of OSA *In vivo*

studies have shown that treatment of OSA with continuous positive airway pressure (CPAP) improves endothelial function [49, 99]. In a selected group of 11 patients with OSA, in the absence of any other disease state or potential cause for endothelial dysfunction, a 6-month therapeutic CPAP trial led to complete normalization of endothelium-dependent vascular relaxation, showing a restoration of endothelial cell function [49]. These data were confirmed by similar results in seven OSA patients treated with CPAP for 2 weeks, although a different technique investigating endothelial cell function had been used [99]. Furthermore, CPAP therapy is able to reverse the majority of the described biochemical alterations of the vascular system in OSA. Thus, there is good reason to speculate that by restoring normal vascular homeostasis, treatment of OSA may improve vascular function and thereby reduce cardiovascular morbidity and mortality in OSA.

Diagnostic recommendations

At present, a recommendation for screening patients with OSA for atherosclerotic lesions cannot be made. However, it is prudent to check for traditional risk factors (i.e. arterial hypertension, smoking, hyperlipidaemia, and diabetes). Investigation of endothelial function in order to estimate the 'atherosclerotic load' of a patient [57] would be of great value but is not practicable today.

Therapeutic recommendations

The above-mentioned studies suggest an improvement in important vascular functions in OSA patients treated with CPAP therapy. This led to the discussion of whether even non-sleepy patients with OSA should be treated with CPAP [88, 222]. Thus, future studies will have to prove the beneficial effects of CPAP therapy on cardiovascular outcome parameters in OSA.

Conclusions and future perspectives

OSA patients without overt CVD present with subtle vascular abnormalities such as impaired endothelial function and alterations of biochemical vascular markers, which can be reversed by CPAP treatment. There is now ample evidence that these subtle disturbances are the beginning of a cascade that may lead to the development of atherosclerosis and end in overt CVD (figure 1). Among other aspects, future studies should investigate the time course of the emergence of CVD in OSA, the possible role of vasoprotective mechanisms, and the impact of effective therapy on cardiovascular morbidity and mortality in OSA.

Cardiac Arrhythmias and Sleep Disordered Breathing

H.F. Becker, H. Hein, U. Koehler

Introduction

Research in SDB began in patients suffering from the pickwickian syndrome. As these patients have a high mortality – hospital mortality was 70% in pickwickian syndrome patients admitted to hospital due to decompensated ventilatory failure – and often die from sudden cardiac death [141, 142], broad interest in the occurrence and significance of cardiac arrhythmias as a possible clue to the increased

mortality in these patients has evolved. It has become clear that not only pickwickian patients but also most patients with OSA exhibit characteristic arrhythmias. The current information concerning epidemiology, pathophysiology and clinical significance of cardiac arrhythmias in patients with OSA will be reviewed here.

Epidemiology

Concerning the epidemiology of cardiac arrhythmias, four different heart-rhythm disorders with different prevalence rates should be distinguished: (i) sinus arrhythmia/cyclical variation of heart rate, (ii) heart block (AV conduction block, sinoatrial block or sinus arrest), (iii) ventricular premature beats (VPBs) and (iv) atrial fibrillation.

Sinus arrhythmia/cyclical variation of heart rate (CVHR)

Sinus arrhythmia/CVHR is a typical finding in all patients with OSA except in cases with reduced heart rate variability due to diabetes or severe heart failure. CVHR is characterized by an abrupt increase in heart rate (HR) due to an arousal that terminates apnoeas, hypopnoeas, or obstructive snoring, followed by an HR decrease during respiratory events as a consequence of hypoxia and lack of thoracic expansion. This heart rate pattern is so typical that it may even be of diagnostic value: by the use of computerized analysis of Holter ECG alone, four algorithms of analysis correctly classified all patients with OSA out of a total of 35 patients. The best algorithm was able to detect 92% of 1-min epochs with or without breathing disorders correctly [173].

Heart block

In the early days of sleep research, heart block (second and third degree atrioventricular block [II° and III° AV block]), sinus arrest or sinoatrial block were thought to be highly prevalent in patients with OSA, and the reported incidence ranged between 18% and 50% [167, 235]. More recent data of unselected patients treated in a sleep laboratory revealed prevalence rates between 7% and 13% [15, 22, 142]. One publication has challenged previous results stating that the prevalence of bradyarrhythmias was not increased in patients with OSA compared to those without OSA [59].

Ventricular premature beats

Systematic evaluation of the incidence and severity of ventricular premature contractions (VPCs) in patients with OSA is still missing. Flemons et al. [59] compared the incidence of frequent or complex VPCs in 173 patients studied because of suspected OSA, 76 of whom were diagnosed with OSA defined by more than 10 apnoeas and hypopnoeas per hour of sleep. The prevalence of VPCs was higher in patients without OSA, but the differences were not statistically significant.

In 29 heart failure patients with more than 15 apnoeas per hour of sleep – predominantly central apnoeas in 21 and obstructive apnoeas in eight patients – the effect of CPAP on VPCs was studied prospectively [102]. SDB was almost completely prevented by CPAP in 16 patients. In these patients, the number of hourly episodes of nocturnal VPCs was significantly reduced from 66 ± 117 to 18 ± 20 and the

number of couplets decreased from 3.2 ± 6 to 0.2 ± 0.21 . In those 13 patients who did not respond to CPAP, VPCs remained unchanged. Based on the very limited data available, the influence of OSA on VPCs in patients without overt heart disease remains unclear, whereas SDB might worsen the occurrence of VPCs in heart failure patients.

Atrial fibrillation

Systematic evaluations of the incidence of atrial fibrillation in patients with OSA are missing. There is one report demonstrating that OSA is an independent risk factor for the development of atrial fibrillation following coronary bypass surgery [147]. The odds ratio for postoperative atrial fibrillation was 2.8 in patients with an oxygen desaturation index of $\geq 5/h$ compared to patients without SDB. Atrial fibrillation has been identified as an important risk factor for Cheyne–Stokes respiration [221].

Physiology/pathophysiology

CVHR is caused by an alternation between increased sympathetic and parasympathetic tone. Hypoxaemia-induced peripheral chemoreceptor stimulation leads to an activation of the sympathetic nervous system. As a consequence, ventilation increases and the resulting lung inflation has a vagolytic influence via the Hering–Breuer reflex. Therefore, hypoxaemia causes tachycardia in the presence of lung inflation; however, in the absence of lung inflation it causes bradycardia. Arousal at the termination of breathing disorders causes sympathetic activation and thus tachycardia. The repetitive occurrence of both mechanisms leads to CVHR, which is markedly attenuated by oxygen. The physiological meaning of bradycardia during apnoea-induced hypoxia might be a reduction in oxygen consumption by the heart, as this can be regularly demonstrated in humans before or during birth if the foetus is hypoxic, and also in diving mammals.

Heart block mainly occurs during REM sleep, most likely because parasympathetic activation and hypoxaemia are most pronounced in this sleep stage [17, 93, 111]. Hypoxia, tachycardia, sympathetic activation and increased blood pressure are possible mechanisms that might lead to ventricular premature beats in patients with SDB; however, the importance of these mechanisms remains uncertain.

Impact on clinical practice

CVHR seems to be a symptom that does not cause cardiovascular sequelae *per se*. It has been suggested that VPBs might play a role in the increased mortality rate of patients with OSA. However, there is no proof for this hypothesis. Heart block may lead to asystole of up to 15 s or longer. If this occurs exclusively during sleep, patients are often asymptomatic. In fact, OSA is the main cause of asymptomatic heart block occurring mainly during the night [151]. In 29 OSA patients with heart block, bradyarrhythmias could be completely prevented with CPAP treatment. Furthermore, none of these patients experienced syncope or died after an average of 54 months of CPAP treatment without implantation of a cardiac pacemaker [72].

Diagnostic recommendations

All patients with predominant nocturnal arrhythmias should be investigated with polysomnography in order to identify or rule out SDB.

Therapeutic intervention – therapeutic recommendations

CVHR is prevented with effective treatment for OSA. In most patients, effective treatment for OSA using CPAP or tracheotomy prevents patients from getting heart block [15, 108, 112, 235]. In only two out of 45 OSA patients, relevant VPCs occurred, and in one of these patients VPCs were no longer present with CPAP therapy [84]. There are no data available concerning the effect of CPAP treatment on atrial fibrillation in patients with OSA. It has recently been shown that SDB can be improved by atrial overpacing at a heart rate of approximately 15 beats per minute above the patient's spontaneous heart rate [68], but further research is necessary to support the clinical value of these findings.

Conclusions and future perspectives

In patients presenting with asymptomatic intermittent bradyarrhythmias, OSA should be considered as a possible cause. Episodes of heart block can be expected in approximately 20% of patients with severe OSA (apnoea–hypopnoea index [AHI] $>60/h$) and in approximately 7.5% of an unselected group of OSA patients. There is no threshold of SDB degree above which bradyarrhythmia exclusively occurs, although the risk increases with the amount of oxygen desaturation. REM sleep is an independent factor leading to heart block, irrespective of apnoea duration and oxygen desaturation. Effective treatment with CPAP leads to complete prevention of heart block in 80–90% of OSA patients. Sinus arrhythmia/CVHR is a typical finding in most patients with OSA and is also removed with effective CPAP treatment. Data concerning VPCs are scarce. There does not seem to be a clear link between OSA and VPCs in patients without overt heart disease, but SDB may be a factor that worsens VPCs in heart failure patients.

Sleep Disordered Breathing and Systemic Hypertension

B. Sanner, L. Grote

Introduction

The link between systemic hypertension and cardiovascular disease is well documented in the medical literature. It has been hypothesized that systemic hypertension is a short-term complication of OSA that mediates the association between OSA and CVD and increases cardiovascular morbidity in the long term. In fact, there is increasing evidence that OSA may cause systemic hypertension and that effective treatment of sleep-disordered breathing lowers high blood pressure [75].

Epidemiology

Epidemiological studies in the general population and in large clinical cohorts have demonstrated an independent association between OSA and systemic hypertension after controlling for confounders such as age and body weight [76, 122, 257]. A recent prospective study showed that patients with SDB have an increased incidence of systemic hypertension as compared with a non-SDB control group [174]. In summary, there is strong evidence based on high-quality epidemiological data that even a small degree of SDB causes elevation of blood pressure and systemic hypertension.

Physiology/pathophysiology

A number of pathophysiological mechanisms have been identified by case-control studies. They all suggest that SDB may cause sustained elevation of blood pressure [87]. Briefly, hypoxia and repetitive arousal from sleep are well-documented factors that cause an overall increase of sympathetic activity in patients with SDB [60]. Furthermore, changes in the renin-angiotensin system as well as in blood volume regulation are shown in OSA patients. Recent work has pointed out that vascular function is altered in OSA. It has been shown that the pressor response to hypoxia and to a given amount of angiotensin II is increased in OSA patients as compared with controls. In contrast, dilatory vascular response to the application of nitric oxide or to intra-arterial vascular β -2 receptor stimulation is attenuated in patients with SDB. However, it remains unclear whether altered vascular function is a cause or consequence of elevated blood pressure in SDB patients. In summary, there is pathophysiological plausibility and strong experimental evidence that SDB may cause systemic hypertension.

Impact on clinical practice

SDB is common in hypertensive patients (30–80%). In particular, OSA has been observed in up to 80% of patients with therapy-resistant hypertension [38, 124].

Therapeutic intervention

Treatment of SDB with CPAP results in a significant decrease in daytime and night-time blood pressure values in hypertensive patients [16, 43, 86, 137, 143, 146, 162, 175, 189, 230], indicating a causal relationship between the two conditions. High blood pressures or elevated heart rates at baseline – indicators of an increased sympathetic activity – may be predictors of a beneficial effect of CPAP therapy on blood pressure [204, 258]. Under CPAP therapy, also normotensive patients experience a decrease in blood pressure. On the other hand, not all hypertensive SDB patients show a blood pressure reduction in response to CPAP.

Diagnostic recommendations

Acute rises in blood pressure caused by SDB can be documented during sleep by invasive or noninvasive techniques. When daytime hypertension is suspected, blood pressure should be measured at least three times during two separate examinations. Blood pressure values above or equal to 140/90 mm Hg are considered hypertensive. Ideally, the diagnosis of hypertension should be verified by noninvasive ambulatory 24-h blood pressure monitoring or self-measurement. Given the epidemiological data, SDB proved to be the most common secondary cause of hypertension. Thus polysomnography should be performed in all patients with hypertension of unknown origin (so-called ‘idiopathic hypertension’), especially in the absence of a nocturnal blood pressure dip [54].

Therapeutic recommendations

Usually, there is no association between the degree of blood pressure decrease with CPAP and polysomnographic parameters indicative of the degree of SDB improvement. This could be explained by the fact that hypertension – even if induced by SDB – might subsequently be perpetuated by

vascular remodelling or some secondary renal response to chronic preglomerular vasoconstriction and altered perfusion. Furthermore, SDB is probably not the only cause of hypertension in these patients. For that reason, CPAP treatment can rarely replace medical treatment of systemic hypertension completely [118].

Conclusions and future perspectives

Hypertension and SDB are frequently associated: Approximately one-third of hypertensive patients have OSA, whereas about 50% of OSA patients are hypertensive. Epidemiological studies of the last years have documented that there is a causal relationship between these two conditions – independent of other known risk factors. Consequently, CPAP therapy has a significant blood pressure-lowering effect in a subgroup of hypertensive patients with OSA.

These data emphasize the need to consider OSA as a potential cause or aggravating factor in hypertensive patients, especially if hypertension is difficult to control. Furthermore, blood pressure monitoring should be performed in patients suspicious of OSA, and patients with ‘idiopathic’ arterial hypertension should be evaluated by full polysomnography, especially in the absence of a nocturnal blood pressure dip.

Coronary Artery Disease – Acute Myocardial Infarction

S. Andreas, U. Koehler, R. Staats

Introduction

Coronary artery disease (CAD), also named ischaemic heart disease, is defined as the manifestation of atherosclerosis in the coronary arteries. CAD may lead to coronary stenosis with flow limitation and consequently to an imbalance of myocardial oxygen supply and demand. Severity and duration of ischaemia determine the clinical manifestation as asymptomatic, stable or unstable angina pectoris, myocardial infarction, arrhythmias, and sudden cardiac death.

Epidemiology

Today, CAD is the most common, chronic, life-threatening disease. According to data from the MONICA study, cardiovascular mortality in Germany affects 428 men and 272 women per 100 000 persons per year, with a slight decrease from 1993 to 1996 [252]. More than 60% of the overall cardiovascular mortality is attributed to CAD and >30% to cerebrovascular disease. There were 380 acute myocardial infarctions per 100 000 persons in the age group of 35–64 years. Similarly, the Physicians’ Health Study revealed 440 cases of acute myocardial infarction (AMI) per 100 000 physicians per year [227]. Risk factors, life style, and socioeconomic circumstances are probably the most important explanations for a large regional variation [252].

Obstructive sleep apnoea and coronary artery disease

In a large study on the prevalence of OSA in CAD [149], 142 men with CAD verified by angiography were investigated by polysomnography using a pressure-sensitive bed. Thirty-seven per cent of patients had an AHI of 10 or more, which was significantly higher than that of age-matched controls [149]. A number of studies on patients with CAD who were

slightly overweight with a mean body mass index of 27 kg/m² yielded similar results, with an incidence of OSA between 35% and 50% [6, 41, 113, 148, 171, 214]. In one study, 101 unselected males aged less than 66 years were investigated by polysomnography 24 days (mean value) after they survived an acute myocardial infarction (AMI) [97]. About 30% of these patients had an apnoea index (AI) >5/h. Mean AHI in the patients was 12.7/h, while 53 male subjects of similar age but without evidence of ischaemic heart disease had an AHI of 3.7/h [97]. In an Italian study, the prevalence of apnoeas, chiefly of the central type, soon after clinical stabilization of unstable angina and following AMI, was similar and higher than that in stable CAD [152]. In 440 patients with OSA proven by polysomnography, CAD was demonstrated by angiography in 24.6% [203]. This high prevalence might be explained by a referral bias because the institution has a local reputation for CAD. The key question of public health importance is: Is OSA a risk factor for CAD? Although most studies found an association of OSA with CAD, they were of limited value because they were either hospital based with a selection bias, small in number, or lacked a control group. Cross-sectional associations from the baseline examination of the Sleep Heart Health Study [217] in 6424 individuals are compatible with modest to moderate effects of OSA on various manifestations of CVD within a range of AHI values that is considered normal or only mildly elevated. SDB was associated more strongly with self-reported heart failure and stroke than with CAD: The relative odds ratio for CAD was 1.27 (0.99–1.62 upper vs. lower AHI quartile) [217].

Physiology/pathophysiology – impact on clinical practice

In order to analyse the association of SDB, especially OSA, and ischaemic heart disease with its different manifestations such as chronic stable CAD and acute coronary syndrome (e.g. unstable angina and myocardial infarction), it is noteworthy to differentiate between acute effects and long-term effects of SDB with possible causal relationships. In general, myocardial ischaemia occurs as a result of diminished oxygen supply or increased oxygen demand in the case of inappropriate coronary reserve. Heart rate is an important determinant of myocardial oxygen consumption, especially during sleep without physical activity *Quyyumi et al.* [181] found episodes of ST-segment depressions in Holter ECG recordings preceded by an increase in heart rate as a result of arousal, lightening of sleep, body movements, and REM sleep in patients with CAD and nocturnal angina without evidence of OSA. Experimental data from animal studies exhibited an increase in coronary blood flow in REM sleep due to an increased sympathetic drive to the heart [42]. In the case of experimental coronary artery stenosis, the coronary blood flow was diminished in phasic REM sleep as a result of a mismatch between the increase in heart rate and diastolic perfusion [42]. In these circumstances, myocardial ischaemia is promoted by REM sleep, which was described first by *Nowlin* and coworkers in 1965 [165]. In OSA, myocardial oxygen supply is diminished by apnoea-associated hypoxaemia. Besides the effects of oxygen desaturation on myocardial ischaemia, OSA may reduce myocardial blood flow supply and/or increase oxygen demand by acute changes in heart rate and elevations of blood pressure-induced left ventricular after-load at the resumption of breathing at each apnoea termination. In addition, interventricular septum shift leads

to an impediment of the diastolic function of the left ventricle. The frequency and clinical impact of nocturnal myocardial ischaemia in patients with OSA is unclear because of a lack of systematic studies. Asymptomatic ST-segment depressions during sleep were observed in seven of 23 patients with OSA without evidence of CAD by Holter ECG [79] *Franklin et al.* [63] found OSA in nine of 10 patients with nocturnal angina pectoris. During treatment of OSA with CPAP, nocturnal angina diminished and the number of nocturnal myocardial ischaemic events was reduced. In a study of 21 patients with OSA, *Schäfer et al.* [209] found asymptomatic nocturnal ST-segment depressions reflecting myocardial ischaemia only in those patients with angiographically proven CAD and in one patient with diffuse coronary vessel defects. The vast majority of these episodes was associated with apnoea-related oxygen desaturations and occurred predominantly in REM sleep. Microstructure of sleep was disturbed to a greater extent in ischaemic episodes than in control episodes. Ischaemic episodes led to more and severer arousals than control episodes, correlating with the extent of oxygen desaturation. In a more recent study, *Peled et al.* [172] investigated 51 patients with OSA and CAD and a control group of 17 patients with OSA without CAD (only 15 of the total had coronary angiography). Nocturnal ST-segment depression occurred in 10 patients with CAD, and no events were seen in the control group. The exacerbation of ischaemic events during sleep in OSA and CAD may be explained by the combination of increased myocardial oxygen consumption and decreased oxygen supply due to oxygen desaturation, with peak haemodynamic changes during the rebreathing phase of obstructive apnoea. Treatment with CPAP significantly ameliorated nocturnal ischaemia [172]. With regard to the different manifestations of ischaemic heart disease in selected subjects without risk factors for OSA, the frequency and extent of sleep apnoea was higher after an AMI or unstable angina than in stable CAD [152]. Moreover, in stable CAD, apnoeas were of obstructive type, whereas in unstable CAD the central type of apnoea was predominant without any correlation to left ventricular function. The increased sympathetic drive in unstable CAD [132] may have an inhibitory effect on respiratory drive as a possible cause of apnoea in these patients [152]. The sympathetic activation and coagulation disorders associated with OSA make it reasonable to believe that acute coronary syndromes with or without ST-segment elevation can be triggered by OSA. Treatment of AMI is focussed on the rapid reopening of the infarct-related artery, as detailed in national and international guidelines. To reduce angina, anxiety and oxygen consumption, morphine is used in the acute setting. This may lead to sleep and apnoeas when angina ceases. One study reports a high incidence of SDB in patients recovering from AMI [97]. In another study of AMI, patients' OSA was related to premature ventricular contraction but not to major complications of AMI [133]. Despite the greater incidence of cardiac arrhythmias during AMI in OSA patients, these patients have the same clinical course in hospital and mortality rate as non-OSA patients [133]. Whether patients with OSA and CAD are at increased risk of 'dying in their sleep' is not clear, although in general the frequency of AMI is highest in the early morning [153] due to increased sympathetic drive and changes in rheological factors. In patients with AMI occurring at night, the respiratory disturbance index (RDI) was significantly higher than in patients with AMI during wakefulness [114]. Besides the

acute effects of OSA on myocardial and cardiovascular physiology, a number of mechanisms link OSA and vasculopathy, leading to atherosclerosis and CAD in the long-term (see chapter on atherosclerosis).

Therapeutic intervention

Shahar et al. revealed that even an RDI considered normal or mildly elevated might enhance the risk of developing CVD including CAD, thus commencing the discussion of when to start OSA treatment [88, 217]. Though it is appealing that screening for OSA with the intention to treat patients with known CAD will reduce cardiovascular mortality, no study has specifically addressed this question. Some problems should therefore be mentioned: Since patients with CAD do not present to the medical system with complaints directly related to OSA, compliance with CPAP treatment is likely to be lower than that in a typical population of OSA patients [147, 170]. This might improve when OSA is considered to be a modifiable risk factor for CVD by all physicians involved in the treatment of patients with CAD. Related to this question is the problem of whether the treatment effect on blood pressure, sympathetic activity, endothelial function, etc., of OSA patients with an AHI >10/h and without significant daytime sleepiness will be as good as that in the published studies on 'classic' OSA patients with daytime sleepiness [49, 175]. However, since the underlying pathophysiology of the OSA-related cardiovascular complications and positive CPAP effects are clearly related to nocturnal apnoeas and oxygen desaturation [48, 175], the positive effects of CPAP on the cardiovascular system are unlikely to be influenced by daytime symptoms. There are several studies investigating the effects of CPAP therapy on CAD symptoms and risk factors of CVD in OSA patients. In OSA patients who also suffered from CAD, ECG recordings revealed ST-segment depression and therefore significant ischaemic events, often accompanied by nocturnal angina. CPAP therapy ameliorated the nocturnal ST-segment depression time and nocturnal angina [63, 79]. Venous vascular reactivity to bradykinin was found to be blunted in OSA patients as compared to controls. This effect was reversed with CPAP therapy [48]. In a recent study, *Imadojemu* and coworkers analysed the reactive hyperaemic blood flow and described an impaired arterial vasodilator response in OSA patients. CPAP therapy improved vascular function and decreased muscle sympathetic nerve activity [99]. Two studies detected decreased circulating NO levels in patients suffering from OSA. Serum level of NO increased significantly after overnight CPAP therapy [100, 213]. The relationship between OSA and hypertension is discussed in another part of this paper.

CPAP therapy positively influenced platelet aggregability, fibrinogen level, superoxide release, and cell adhesion molecule expression [21, 24, 33, 34, 206, 211]. Hence, future studies will disclose whether public awareness of a possible association between OSA and CAD will improve therapy compliance in non-sleepy patients with OSA. In patients unable to tolerate CPAP, however, alternative therapy strategies are required. Although less effective than conventional CPAP therapy, oral appliance (OA) devices proved to be beneficial with rare serious side effects in patients unable to maintain CPAP therapy and, when correctly indicated, as first choice therapy in selected OSA patients with low RDI [20, 71, 89, 183, 190]. Patients with AMI are usually monitored on an intensive care unit (ICU). If OSA in this setting leads to severe surges in blood pressure and/or myocardial ischaemia, treatment of

OSA should be initiated even on the ICU, but there are no studies available supporting this hypothesis.

Diagnostic recommendations

Clinical examination in patients with CAD is directed by the underlying heart disease itself as well as cardiovascular risk factors and significant comorbidity. As detailed above, OSA is common in patients with CAD and is a significant and modifiable risk factor for CVD [129, 147, 217]. Therefore, OSA should be included in the diagnostic work-up of patients with CAD. If the CAD patient's medical history is positive regarding excessive daytime sleepiness, nocturnal angina pectoris, witnessed snoring, or apnoeas, polysomnography is recommended.

Therapeutic recommendations

A consensus statement published in 1999 recommended CPAP therapy in any OSA patients with an RDI exceeding 30/h or at a minimal threshold of 5/h if the patient is suffering from either excessive daytime somnolence, impaired cognition, mood disorders, insomnia, or documented cardiovascular disease [129]. The recommendation to treat non-sleepy patients with low RDI and CAD is further supported by cross-sectional results of the Sleep Heart Health Study [217]. In patients with AMI, CPAP treatment should be initiated on the ICU if OSA in this setting leads to severe surges in blood pressure or myocardial ischaemia, but there are no data supporting this hypothesis.

Conclusions and future perspectives

There is growing evidence suggesting that OSA is an independent risk factor for CAD. While studies with randomized therapeutic intervention are unlikely to be performed in the near future, it seems prudent to advocate CPAP therapy in patients with CAD and moderate to severe OSA even if they do not suffer from excessive daytime sleepiness.

Heart Failure

S. Andreas, I. Fietze, V. Töpfer

Introduction

Heart failure is defined by symptoms *and* objective evidence of cardiac dysfunction [186]. Symptoms may be breathlessness, ankle swelling, signs of venous distension, and fatigue. The severity of heart failure is classified by the New York Heart Association (NYHA), but there is a poor relationship between symptoms and cardiac dysfunction as well as prognosis. The underlying causes of heart failure are CAD and arterial hypertension, valvular disease, and idiopathic dilated cardiomyopathy. Clearly evidenced guidelines for the treatment of heart failure exist [186]. The prevalence of symptomatic heart failure in the general European population is 0.4–2% and increases rapidly with age [186]. The prognosis of heart failure is poor, albeit significant improvements in treatment have been gained. Still, about half of the patients diagnosed with chronic heart failure (CHF) will die within 4 years [186]. Recently, diastolic heart failure has been noticed to be common especially in the elderly population and

carries a prognosis nearly as grim as heart failure with systolic dysfunction [55].

Epidemiology

Javaheri et al. reported on 81 ambulatory male CHF patients with an left ventricular ejection fraction (LVEF) <45% [105]. The authors noted that 51% of their patients had an AHI >15/h. Most of the patients had Cheyne–Stokes respiration (CSR), but some more obese patients had obstructive apnoeas. Similar findings were made in a comparable CHF group [225] and in patients on a waiting list for heart transplantation [127]. In patients with an LVEF <45% investigated 1 month after an episode of pulmonary oedema, an AHI >15/h was reported in about 80% of 34 consecutive patients. Again, OSA was less common (25%) than CSR (75%) and was chiefly observed in the more overweight patients [239]. CSR seems to be more common in men [220], which might be explained by the higher ventilatory drive in men. It is our impression that presently the prevalence of SDB in appropriately treated CHF patients is less than 30%. This is likely the result of the increased prescription of β -blockers and probably their direct influence on central controller gain (see Pathophysiology). There is insufficient knowledge about SDB in patients with diastolic heart failure. In one study, 11 out of 20 patients with diastolic heart failure had an AHI >10/h with mainly obstructive apnoeas [29]. Furthermore, there was an independent association between abnormal diastolic ventricular relaxation pattern and nocturnal oxygen desaturations in 68 patients with OSA [66].

Physiology/pathophysiology

In patients with impaired LVEF, a fundamental characteristic of SDB is the central origin of the disorder. Periodic breathing (CSR) with or without apnoea, central sleep apnoea, as well as other respiratory disorders such as hypopnoea and hypoventilation, all characterize the syndrome of SDB in CHF patients. The main factor leading to SDB in CHF patients, especially during sleep onset, is a fall in carbon dioxide (PaCO_2) tension below the apnoea threshold, with a consecutive decrease of central nervous outflow to respiratory muscles [104]. Engaged in this phenomenon are: carbon dioxide receptors in the medulla, the carotid body and the aortic arc; oxygen receptors located in the medulla and carotid body; ergoreceptors of the respiratory muscles; and central mechanisms regulating the sleep–wake rhythm. In CHF patients with CSR, hypocapnia is more pronounced than in CHF patients without CSR [223]. PaCO_2 levels are consequently only 1–3 mm Hg above the apnoea threshold during sleep in CSR patients, in comparison with healthy subjects, among whom this difference is 3–5 mm Hg. An increase of CO_2 in inhaled air to the level of 4% during sleep increases PaCO_2 and prevents occurrence of apnoea in CHF patients [128].

PaCO_2 in CHF patients with CSR is inversely correlated with pulmonary capillary wedge pressure (PCWP). An increase in PCWP leads to activation of pulmonary vagal afferent pathways, followed by hyperventilation and a fall in PaCO_2 [223]. Another mechanism possibly involved in generation of apnoea is enhanced peripheral and central chemoreceptor sensitivity. This corresponds to enhanced respiratory response, which is in turn correlated with the amount of CSR [7] and daytime hyperventilation [159]. Although the role of hypoxaemia in the genesis of CSR is not

well known, it is possible that hypoxaemia elicits arousals that provoke hyperventilation.

During sleep, the extent of CSR is also evidently a function of sleep stage. Sleep-stage differences are based on the degree of impaired arousability in REM sleep, during which CSR is less common than in NREM sleep. One effect of an arousal-related stage shift is that the sleeper suddenly detects PaCO_2 as excessively high, which can in turn lead to hyperventilation. Further mechanisms responsible for CSR in CHF patients are increased blood circulatory time, enhanced sympathetic nerve activity, decreased body oxygen and CO_2 stores, upper airway instability, impaired LVEF, and respiration pattern preceding CSR [4, 77, 90, 109, 116, 124, 128, 156]. A correlation has been established, for example, between the cyclic length of periodic breathing and the degree of LVEF [77]. Changes in blood gas tension may provoke instability (underdamping) of the respiratory system, accompanied by exaggerated gas changes during CSR [116]. CSR is accordingly an expression of oscillations in feedback regulation of respiration by the above-stated disturbance variables, which prevent damping or physiological counter-regulation.

The question arises: Is there a relationship between central and obstructive apnoeas in CHF patients? Obstructive apnoea may provoke acute nocturnal decompensation with interstitial lung oedema, which in turn decreases functional residual capacity (FRC) [161] and leads to the above-stated changes in blood gas stores Tkacova et al. described a possible shift from OSA to CSR under conditions of progressively rapidly falling PaCO_2 and rising blood circulatory time, owing to deterioration in cardiac function [237]. Conversely, it is feasible that periodic breathing leads to instability in the upper airway due to pharyngeal oedema. It is also possible that obstructive breathing is followed by reduced respiratory drive during the waning phase of periodic breathing, with greater reduction of drive to the pharyngeal dilatator muscle than to the diaphragm. CSR has also been described for CHF patients during the day, as a symptom of disturbed autonomic regulation and poor survival outcome. Augmented chemoreceptor sensitivity [178], impaired autonomic control, and baroreflex inhibition [179] are possible mechanisms involved in the genesis of daytime CSR.

Impact on clinical practice

Clinical markers that indicate CSR among CHF patients are as follows: episodic hypoxaemia, numerous arousals during sleep, sleep fragmentation, daytime sleepiness [80], and heart rhythm disorders correlating with falls in PaCO_2 [98]. Other phenomena include nocturnal heart rate and blood pressure changes due to arousals, changes in sympathetic nerve activity [90, 160, 241], increased chemoreceptor sensitivity, and altered heart rate variability [164, 256].

Therapeutic intervention

Treatment options can be broadly divided into four groups: intensive heart failure treatment, pharmacological therapy, oxygen, and various forms of positive airway pressure such as CPAP, bilevel pressure ventilation, and adaptive pressure support servo-ventilation.

Intensive heart failure treatment

The first consideration is to optimize the heart failure therapy. Cardiovascular drugs improve left ventricular function,

decrease PCWP and favourably influence neuroendocrine activation. Recent studies have reported a decrease in central sleep apnoea (i.e. CSR) caused by heart failure treatment [37, 243]. Thus, before any specific therapy for CSR is undertaken, appropriate utilization (including dose adjustments) of cardiovascular drugs to optimize cardiovascular function should be undertaken [103].

Pharmacological therapy

Theoretically, respiratory-drive stimulants such as theophylline and acetazolamide can alleviate CSR beyond optimizing CHF by cardiovascular drugs [40, 53, 106]. In a study by *Javaheri et al.* [106], use of theophylline was associated with a significant reduction in AHI, but a reduction in the frequency of arousals or improvements in sleep structure were not documented. Theophylline did not lead to any improvement of cardiac function. Theophylline is problematic because it could increase minute ventilation in CHF patients with CSR whose minute ventilation is already elevated, and because of its potentially dangerous effects on cardiac output by causing cardiac arrhythmias. The effect of acetazolamide [18, 238, 250] on CSR has not been systematically evaluated in patients with CHF *Sakamoto et al.* [200] found that acetazolamide did not consistently reduce the frequency of respiratory events in patients with central sleep apnoea. In summary, theophylline or acetazolamide are not recommended for treatment of CSR in patients with CHF.

Oxygen

The rationale for using oxygen is that it increases oxygen and carbon dioxide stores and suppresses peripheral chemoreceptor drive, thereby dampening the respiratory control system and making it more stable *Hanly et al.* [78] investigated the effect of oxygen administration and demonstrated a significant decrease in AHI, arousal index, and degree of oxyhaemoglobin desaturation. In a subsequent randomized placebo-controlled study of intranasal oxygen given for 1 week, *Andreas et al.* [5] also documented a modest decrease of central apnoeas and hypopnoeas in patients with CSR. In addition, these patients experienced a significant increase in peak oxygen consumption during exercise without a change in the duration of exercise, peak heart rate, or quality of life. Furthermore, the hypercapnic ventilatory response (HCVR) was reduced by nocturnal oxygen [8]. More recently, *Staniforth et al.* [226] documented significant reductions in AHI and in overnight urinary norepinephrine excretion in patients with stable CHF and CSR while they were treated with nocturnal oxygen over a 4-week period. Similar acute effects were noticed in patients with chronic hypoxaemia due to chronic obstructive pulmonary disease [90]. More effective suppression of CSR may be achieved by adding carbon dioxide to oxygen therapy. Therefore, *Andreas et al.* [9] performed a study that evaluated the effects of nocturnal oxygen plus carbon dioxide on CSR, sleep, and sympathetic activation. Nocturnal combination of oxygen plus carbon dioxide reduced the duration of CSR and increased arterial oxygen saturation as well as mean transcutaneous carbon dioxide tension but markedly increased sympathetic activation.

Forms of positive airway pressure

Continuous positive airway pressure

CPAP is the most extensively studied therapy for CSR in patients with CHF and has been shown to alleviate this breathing disorder in association with substantial beneficial

effects on cardiovascular function [253] *Takasaki et al.* [233] were the first to study the effects of CPAP in patients with CHF and CSR in a controlled trial in 1989. Application of CPAP was associated with a highly significant reduction in AHI, an increase in nocturnal SaO₂ and improvements in sleep structure [158]. These initial observations of beneficial effects of CPAP on CSR were confirmed by *Naughton et al.* [160] in a controlled trial of CPAP in patients with stable CHF and CSR. The group treated with CPAP experienced a decrease in the frequency of central events, associated with a reduction in minute ventilation and an increase in transcutaneous PCO₂. A randomized trial of CPAP was undertaken by *Naughton et al.* [160], with LVEF as the primary outcome measure. There was a greater improvement of LVEF in the CPAP group than in the control group. In another study, *Naughton et al.* [157] demonstrated that CHF patients with CSR had higher overnight urinary and daytime plasma norepinephrine concentrations than CHF patients without CSR. By using CPAP, there was a 40% reduction in overnight urinary norepinephrine and a 24% reduction in daytime plasma with a significant decrease in heart rate. The largest and longest randomized clinical trial of CPAP therapy for CHF involved 29 patients with and 37 without CSR [221]. Over a follow-up period of up to 5 years, patients in the CSR group who complied with CPAP therapy experienced a reduction in the combined rate of mortality and cardiac transplantation rate. In contrast, CHF patients without CSR but randomized to CPAP therapy did not experience any significant decrease in the mortality or cardiac transplantation rate.

Bilevel pressure ventilation

Willson et al. [254] recently reported preliminary data showing that CSR was abolished and sleep improved with noninvasive nasal ventilation using a time-cycled volume preset ventilator. In these studies, the prolonged use of noninvasive ventilation was also associated with a reduction in the AHI, a decrease in arousal index, and an improvement in cardiac function.

Adaptive pressure support servo-ventilation

Adaptive pressure support servo-ventilation (ASV) is a new approach to the treatment of CSR, in which a small but varying amount of ventilatory support is provided. The intention is to provide the hydrostatic benefits of low levels of CPAP while directly suppressing CSR and attendant sleep disturbance without causing overventilation. In a recent study by *Teschler et al.* [234], the acute effect of ASV on quality of sleep and breathing was compared with nasal oxygen, nasal CPAP, and bilevel spontaneous/time (ST) mode nasal ventilation. The authors described a better improvement in sleep and breathing with ASV than either nasal CPAP/bilevel ventilation or 2 L/min nasal oxygen. The authors concluded that sleep and breathing were better during 1 night of ASV therapy than during 1 night of oxygen or CPAP/bilevel pressure ventilation. Long-term studies of the effect of ASV on quality of life and cardiovascular function are presently under way.

Diagnostic recommendations

As detailed above, CSR, and to a lesser degree OSA, is common in CHF and is independently related to impaired left ventricular performance and increased mortality [81, 120, 217, 221]. Therefore, CSR and OSA have to be included in the diagnostic work-up of patients with CHF. Although OSA

often has a characteristic history, this seems to be much less the case for CSR in the setting of CHF [3, 225]. Full polysomnography is recommended in patients with CHF in order to analyse breathing patterns, arousals, and sleep structure, especially if nocturnal angina, excessive daytime sleepiness, witnessed snoring, or apnoeas are present.

Therapeutic recommendations

Of paramount importance is maximal conservative CHF treatment. It seems necessary to find the right method of treatment of CSR on an individual basis. However, we recommend trying oxygen therapy initially because it is effective and simple to use. In case of an insufficient therapeutic effect of oxygen, the next option is to use CPAP. CPAP is the most extensively studied therapy for CSR and is shown to alleviate this breathing disorder in association with substantial beneficial effects on cardiovascular function. The most effective suppression of CSR in patients with CHF is achievable with ASV. In severe cases of CSR with a high AHI or in cases where other options were ineffective, treatment with ASV is recommended. Using ASV, however, is not as simple as CPAP or oxygen, because special equipment and software is needed.

Conclusions and future perspectives

In conclusion, there is good evidence suggesting that CSR is common in CHF and is the cause of impaired sleep and sympathetic activation with concomitant unfavourable effects on left ventricular function and survival. However, large controlled studies are needed to test the hypothesis that successful treatment of CSR will reduce the high mortality of CHF.

Pulmonary Hypertension in Obstructive Sleep Apnoea Syndrome

W. Randerath, K.-H. Rühle, B. Sanner, H. Schäfer

Introduction

Pulmonary hypertension (PH) can be defined by a sustained elevation of the mean pulmonary artery pressure (PAP) to ≥ 20 mm Hg or of the systolic pressure to ≥ 30 mm Hg [74]. PH results from increases in resistance of blood flow in pulmonary venous drainage (e.g. elevated left ventricular diastolic pressure), in the pulmonary vascular bed (e.g. obstructive or restrictive pulmonary diseases) or from resistance of flow itself (e.g. thromboembolism). Syndromes associated with hypoventilation, namely the obesity–hypoventilation syndromes, OSA or neuromuscular disorders, are thought to lead to pulmonary hypertension. However, PH might be secondary due to hypoxic pulmonary vasoconstriction [74]. Other potential mechanisms are hypoxia-induced vascular endothelial dysfunction [56], pulmonary vascular remodelling [199], intrathoracic pressure changes, and autonomic reflexes.

Epidemiology

The prevalence of PH in OSA without underlying pulmonary disease is still controversial. Early studies reported prevalence rates between 20% and 80%. However, these investigations included patients with lung disorders, especially chronic obstructive pulmonary disease. According to these

studies, impairment of lung function and hypoxaemia seemed to correlate best with PH. However, recent studies in patients without pulmonary disease also showed prevalence rates of about 30% of PH in OSA [11]. Studies in which pulmonary pressure was measured invasively found a prevalence of about 20%, whereas studies based on the noninvasive Doppler technique showed figures of 40% [119, 197]. One may conclude that PH can be found in OSA patients without pulmonary disease, which however can aggravate PH.

Physiology/pathophysiology

Increases in PAP have been described both acutely during a single apnoeic event and chronically in the course of the OSA. In NREM sleep, PAP reaches its maximum during the postapnoeic hyperventilation period, whereas in REM sleep, even long apnoeas are not necessarily associated with pressure increases [177].

While intravascular PAP decreases during apnoea and increases at the resumption of breathing, transmural pulmonary artery pressure (PAP_{tm}, i.e. the correction for intrathoracic pressure swings) tends to increase progressively throughout an apnoea, with a maximum during the final occluded efforts and sustained during the early phase of hyperventilation [134]. Analysis of apnoea episodes in NREM sleep revealed a progressive increase in systolic mean PAP_{tm} of 10 mm Hg towards the end of apnoea [208]. Among the underlying mechanisms of the acute changes, alveolar hypoxia was suggested to play an important role [134]. However, oxygen administration affected neither mean PAP_{tm} nor the amplitude of pressure swings in most patients [135]. Other factors contributing to PAP_{tm} changes are mechanical events caused by intrathoracic pressure swings with increased right ventricular preload and output or due to increased left ventricular afterload.

Beat-by-beat analysis of the underlying factors showed that hypoxia was a major determinant of the slow changes of PAP_{tm} over the whole course of an apnoea and rapid changes in PAP_{tm} were synchronous with intrathoracic pressure changes [136]. Analysing the contributing factors, Schäfer et al. [208] found hypoxaemia and intrathoracic pressure swings both independently associated with an increase of PAP_{tm}. The authors did not find any association of arterial blood pressure as a rough estimate of left ventricular afterload with the changes in PAP_{tm} in this study. According to the time course of pulmonary haemodynamics during the night, Schäfer et al. [208] did not find a progressive increase in PAP, in contrast to another study, which showed a trend towards a small progressive increase in PAP throughout the night [216]. The authors concluded that this increase reflects the cumulative effects of repetitive apnoeas and hypoxaemia. However, apnoea duration increased throughout the night in this study.

In 40% of OSA patients without overt CVD, Sajkov et al. described a slightly elevated PAP at rest, which rose significantly when pulmonary blood flow was increased [199]. Patients with or without sustained PH did not show any differences in the severity of SDB, lung function or body mass index. However, in patients with PH, the authors found more pronounced ventilation–perfusion mismatch and resting hypoxia. PH in these patients was thought to be the result of structural narrowing of the pulmonary vessels. The authors speculated that this remodelling may be caused by an increased pulmonary vascular pressure response to hypoxia or an increased small airways closure with regional lung hypoxaemia. In a more recent study, the same authors found

a decreased hypoxic pulmonary constrictor response, which was measured as the difference in PAP under hypoxic and hyperoxic conditions [198]. This might result from an impaired pulmonary vascular endothelial function, which is responsible for the vascular tone [10, 19, 56]. Moreover, *Sajkov* et al. described a reduction in the hypoxic pulmonary vascular reactivity under treatment with CPAP. They concluded that intermittent nocturnal hypoxia might cause pulmonary vascular endothelial dysfunction [198]. Recent studies suggest that genetic factors determine the link between hypoxia and manifestation of PH [47, 52].

Impact on clinical practice

In general, PH can lead to dyspnoea and right heart failure. It is often difficult or impossible to differentiate whether OSA or other pulmonary diseases are responsible for these symptoms. If present, the degree of daytime PH is mild in most patients with OSA alone. Hence, specific clinical symptoms of PH are rarely described in these patients. Although an association of OSA with PH has been shown conclusively, there is no correlation between the severity of OSA as measured by AHI and the severity of PH. Right ventricular failure and PH define, in part, one subtype of SDB, the pickwickian syndrome.

Diagnostic recommendations

The sensitivity of ECG or radiographic findings in the diagnosis of PH is unsatisfactory. *Sanner* et al. demonstrated pulmonary wedge pressure and time spent below 90% SaO₂ during the night as independent predictors for PH when coexisting pulmonary disease was excluded. Other parameters of lung function or PaO₂ were not predictive for PH [205]. There are controversial results concerning the predictive value of resting PaO₂, AHI, or lung function. PAP can be evaluated invasively using right heart catheterization and noninvasively by using Doppler echocardiography [150, 196]. Invasive pressure measurement is the diagnostic gold standard, although *Sajkov* et al. described a good correlation ($P = 0.96$) between catheter and Doppler techniques in the investigation of PAP [196].

Therapeutic intervention – therapeutic recommendations

An early investigation in OSA patients treated with tracheostomy reported an improvement in PAP and right ventricular function [62]. In several studies, CPAP did result in a long-term improvement of PAP in patients with OSA [31, 215]. *Chaouat* et al., for example, did not exclude patients with chronic obstructive pulmonary diseases, which might influence the level of PAP [31]. In contrast, *Sajkov* et al. studied the effects of CPAP in 20 patients without lung or cardiovascular disorders. Five of these subjects showed an elevation in mean PAP at baseline. The authors found that CPAP improved daytime PAP and total pulmonary vascular resistance, and the greatest improvement was shown in patients with sustained daytime PH [198]. *Alchanatis* et al. described a sample of 21% of patients with PH out of 29 patients with OSA but without further CVD. In both groups, pulmonary hypertensive and normotensive, PAP fell significantly under treatment with CPAP for 6 months [2]. Though indicative of positive effects of CPAP therapy on PH in OSA, the therapeutic studies mentioned above have to be regarded with caution, as there was no control group.

Conclusions and recommendations

Mild PH is present in 20–40% of patients with OSA, but there is no correlation between the severity of OSA and the occurrence of PH. Although the pathophysiological background is still unclear, vascular endothelial dysfunction associated with increased vascular reactivity might be one important aspect. There is some evidence for the positive effect of long-term treatment with CPAP on PH in patients with OSA.

Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

W. Randerath, K. Rasche, K.-H. Rühle

Introduction

Chronic obstructive pulmonary disease (COPD) is often associated with nocturnal (i.e. sleep-related) hypoventilation, ventilation–perfusion mismatching, and consecutive O₂ desaturations [58]. As a consequence of the Euler–Liljestrand reflex and other mechanisms, pulmonary arterioles in the pulmonary circulation constrict and vascular resistance increases [36]. In the following, the pathophysiological mechanisms leading to an increase in pulmonary artery pressure will be discussed and the consequences for therapy elucidated.

Epidemiology

COPD is often diagnosed in patients with chronic cigarette abuse. The disease can be defined by clinical symptoms such as exertional dyspnoea, chronic cough and sputum production, and by lung function tests with reduced Tiffeneau index. COPD can be diagnosed in about 50% of all smokers older than 60 years [188]. In the daytime-hypoxic blue-bloater type of COPD, we often observe SDB and oxygen desaturations. In 30% of patients with COPD and daytime PO₂ values between 60 and 70 mm Hg, oxygen desaturations during sleep are diagnosed [185]. OSA and COPD are independent diseases, both possibly leading to PH [187, 244] (see chapter on pulmonary hypertension in obstructive sleep apnoea syndrome).

Physiology/pathophysiology

Most patients with COPD present with moderate or severe daytime hypoxaemia. During sleep onset, alveolar ventilation decreases slightly due to changes of the set point for CO₂. Especially during REM sleep, there is a further fall in ventilation with marked O₂ desaturations [45]. The two major causes of hypoventilation are a reduction in ventilatory effort, caused by an altered central nervous stimulation and a relaxation of thoracic muscles during REM sleep, whereas diaphragmatic ventilatory drive is blunted for anatomical reasons in COPD, especially in emphysema. The reduced central drive can be documented by reduced swings in the oesophageal pressure being observed mainly during periods of REM sleep with frequent eye movements. This decrease in ventilation is not counterbalanced by a hypoxic and hypercapnic ventilatory response because REM sleep mechanisms are blunting chemosensitivity. There is also a mild increase of upper airway resistance caused by the relaxation of the oropharyngeal airway. As a consequence of these mechanisms, O₂ saturation decreases dependent on

the resulting ventilation–perfusion mismatch. The duration of these episodes last as long as 10–20 min and can easily be discriminated from the apnoea-induced short desaturations with durations of 10–100 s. As a consequence of the sleep-induced O₂ desaturations, pulmonary artery pressure increases during these periods. In one study, integrated pulmonary artery mean pressure increased from 29.6 ± 10 mm Hg during wakefulness to 41.2 ± 14.4 mm Hg [194]. Besides the alveolar vascular reflex, the increase of cardiac output plays a role in the increase of pulmonary artery pressure [61]. It is controversially discussed whether the extent of nocturnal hypoxaemia is an additional factor contributing to the degree of PH. In patients with isolated sleep-associated hypoxaemia without severe daytime hypoxaemia, it was shown that despite nocturnal oxygen therapy, no significant change in daytime PAP could be observed compared with a control group breathing room air [30]. If COPD is combined with repetitive upper airway obstructions, i.e. OSA, the resulting hypoxaemia and pulmonary hypertension are more severe and the patients are more likely to develop right heart failure [23, 92, 95, 187, 228, 244].

Impact on clinical practice

COPD promotes development of PH by different pathophysiological mechanisms. Concerning sleep, both COPD-associated nocturnal hypoxaemia and additional OSA lead to significant rises in PAP. The severity of COPD-associated hypoxaemia during sleep can be predicted with sufficient precision by blood gas measurements in the evening before sleep onset, because according to one study, PO₂ values higher than 55 mm Hg during daytime combined with O₂ desaturations during sleep do not contain clinically important prognostic information concerning the development of PH [32].

Therapeutic intervention

In most patients with COPD and nocturnal hypoxaemia, nocturnal O₂ saturation (SaO₂) is increased to values above 90% by insufflation of O₂ through a nasal cannula at a flow rate of 2 L/min. Thus, total sleep time can be prolonged and sleep quality improved. In COPD patients, mean PAP fell significantly from 29.5 ± 12.7 to 24.9 ± 9.7 mm Hg in the first night of O₂ therapy [194]. Long-term oxygen therapy applied during 15–18 h/day led to a significant reduction in pulmonary artery pressure from 28.0 ± 7.4 to 23.9 ± 6.6 mm Hg after 31 months of therapy [245]. In a more recent study, Raeside et al. diagnosed a mean nocturnal PAP comparable to their PAP at exercise in 10 patients with COPD. This elevated nocturnal PAP could be reversed with oxygen [182]. The decrease in PAP could mainly be attributed to a decrease in pulmonary vascular resistance. The expectation that patients with resting hypoxaemia and hypercapnia treated with supplemental oxygen might develop progressive nocturnal hypercapnia as a consequence of reduced ventilatory drive caused by hypoxaemia could not be confirmed. In patients with stable COPD without OSA, transcutaneously measured PCO₂ did not increase more than 6 mm Hg [69]. In COPD patients with predominantly ventilatory failure, i.e. elevated levels of PaCO₂, (non-)invasive ventilator therapy may be necessary [139]. For COPD patients with additional OSA, see the chapter on pulmonary hypertension in obstructive sleep apnoea syndrome.

Diagnostic recommendations

Measurements of oxygen saturation during the night do not yield any additional value in the decision-making of whether oxygen therapy is indicated or not. Daytime arterial blood gas measurements are of sufficient prognostic value. Additional polysomnographic measurements are usually not indicated in COPD. However, polysomnography should be performed in COPD patients with a suspicion of coexisting OSA or in patients with unclear symptoms and findings such as daytime sleepiness, polycythaemia, cor pulmonale, or morning headaches.

Therapeutic recommendations

Daytime hypoxaemia in COPD is nearly always associated with hypoventilation and ventilation–perfusion mismatching during sleep and should be treated by supplemental oxygen therapy during the night. It has been shown that 14–16 h per day of oxygen therapy is superior to only nightly treatment with oxygen. In COPD patients with predominantly ventilatory failure, i.e. elevated levels of PaCO₂, (non-)invasive ventilator therapy may be necessary [139]. In COPD patients with additional OSA, both diseases should be treated consequently because these patients are likely to develop PH.

Conclusions and future perspectives

There is only a moderate correlation between nocturnal O₂ desaturation, hypercapnia severity and PH. Additional factors responsible for the development of PH, such as OSA, should be identified [184]. O₂ therapy reduces right-heart strain and improves life expectancy, but the work of breathing is only slightly improved. With intermittent positive pressure ventilation, the diaphragm can be unloaded in patients with ventilatory failure. Thus physical performance during the day can be ameliorated. However, especially in patients with COPD, noninvasive ventilation is not well tolerated and compliance after 6 months is only about 50%. We therefore need more intelligent ventilator devices with servo-ventilation to avoid sleep disturbances induced by mask and machine. Pharmacological therapy of PH with nitric oxide donors or endothelin receptor antagonists have to be studied in COPD patients first, before they can be considered as a further treatment option in future [92, 94, 228, 236, 244].

Sleep-Disordered Breathing and Cerebrovascular Disease

P. Clarenbach, A. Nachtmann, T.E. Wessendorf

Introduction – epidemiology

The high prevalence of SDB among patients with stroke has been confirmed in numerous studies, although methodological differences regarding patient age, time after stroke, or diagnostic methods somehow reduce the power of a general conclusion [14, 50, 83, 144, 145, 168, 207, 240, 247]. Most of the authors come to the following conclusions:

- 1 The overall prevalence rate of SDB in acute stroke patients is in the range of 40–60%.
- 2 OSA is the leading type of SDB; true central sleep apnoea is comparatively rare.

- 3 There is no correlation between stroke location and the diagnosis of coexisting SDB apart from a tendency of Cheyne–Stokes respiration to be more common in infratentorial strokes.

The Sleep Heart Health Study, a large population-based epidemiological study, confirmed an increased prevalence of stroke in SDB; the odds ratio for the highest AHI quartile (AHI >11/h) was 1.6 times (confidence interval [CI] 1.02–2.46) higher than that of the lowest quartile (AHI <1.4/h) [217]. In earlier studies using subjective questionnaires for evaluating snoring history, an even stronger association between snoring and stroke had been found [169, 224]. The fact of a similar prevalence of SDB in patients with transient ischaemic attacks (TIA) [13] and of similar anthropometric data in SDB [240, 247] with stroke as in SDB without stroke suggests that OSA preceded the event in most cases. This is further underlined by the observation that obstructive events tend to persist after stroke, whereas central apnoeas improve [168]. It should be noted that the vast majority of epidemiological studies investigating the relationship between SDB and cerebrovascular disease have been performed in patients suffering from TIA/stroke. In contrast, there is a paucity of data concerning the prevalence of TIA/stroke in patients with OSA. So far, only one retrospective survey addressed this question and found a prevalence rate of 8% [212].

Physiology/pathophysiology

Hypertension is regarded as the most important risk factor for stroke: The link between SDB and hypertension is now accepted as independent of other confounding factors (see above). However, there is evidence of other possible links apart from hypertension: Cerebral blood flow is impaired by SDB: During obstructive, but not central, events there is a significant decline in cerebral blood flow followed by an increase of up to 216% [12, 163]. Flow reduction correlates with severity of oxygen desaturation, which would be of particular relevance during REM sleep when cerebral blood flow and oxygen demands are normally highest, but when apnoeas are accompanied by the greatest degrees of hypoxia [110]. In patients with OSA, cerebrovasodilator reserve seems to be diminished, which can be restored with CPAP [44]. Patients with lesions in the intra- and extracranial circulation could therefore be at higher risk of stroke during respiratory events [1].

The link between atherosclerosis and OSA has been discussed above. An increased intima-media thickness as well as a higher prevalence of stenosis of the extracranial arteries has been confirmed in stroke patients [154, 219, 255]. Patients with ischaemic stroke and coexisting OSA have increased fibrinogen plasma levels [248], and the level of fibrinogen correlates with the severity of SDB. The consequences for increased blood viscosity and coagulability may further add to the increased risk of thrombotic events *Chin* et al. observed a reduction in overnight fibrinogen levels in OSA patients [34]. An effective treatment of OSA, e.g. with CPAP, can in fact improve other vascular risk factors beyond blood pressure, so that the risk/benefit ratio calculated from blood pressure changes may underestimate the true benefit [175].

Impact on clinical practice

There are only few data about the course of SDB after stroke: However, in most patients, SDB tends to persist at

least for a 3-month period [123, 168] but shows a tendency to improve during the first 6–9 weeks [83]. Using a screening device without discrimination between obstructive and central events, *Szucs* et al. found persistent events in ischaemic but not in hemorrhagic stroke after 3 months [231]. Using pulse oximetry, *Good* et al. showed a worse functional outcome after 3 and 12 months in patients with higher desaturation indices [70]. This could not be confirmed in recent studies [101, 123], although *Iranzo* et al. found early neurological worsening associated with OSA. It has been speculated that some of the neuropsychological sequelae observed after stroke – and regarded as a consequence of the event – could in fact be partially due to coexisting SDB. OSA in elderly stroke patients is associated with delirium, depressed mood, latency in reaction and in response to verbal stimuli, and impaired ADL (activities of daily living) ability [202]. The evidence of an effect of SDB on morbidity and mortality is weak in patients with stroke, as no study has addressed this point in particular, and the original strong association between a positive history of snoring and short-term survival in acute stroke reported by *Spriggs* et al. [224] has not been confirmed by others *Good* et al. reports a correlation between mortality and oxygen saturation [70] and *Dyken* et al. found a mortality of 21% within 4 years in their stroke patients with OSA, but 0% in patients without OSA [50]. Mortality data in patients with CAD and SDB indicate a higher risk of stroke within the following 5 years [147].

The importance of central sleep apnoea (CSA) in stroke patients is an open question: Whereas CSA in heart failure has been associated with increased mortality, its relevance in stroke patients is not known. As these patients often have cardiac disease, too, the question remains whether CSA is a sign of underlying cardiac dysfunction. No study has addressed this point so far.

Therapeutic intervention

The role of treatment of SDB in stroke has yet to be determined: In a consecutive series of patients, *Wessendorf* et al. showed that CPAP is an option with an acceptance rate of up to 66% but with the need for intensive coaching during rehabilitation after stroke. CPAP was effective without increasing concomitant central apnoeas, but aphasia and functional disability predicted negative compliance. In case of acceptance, better subjective fitness and improved blood pressure control were observed [249]. This primary compliance rate could not be achieved in every setting [82], but *Milanova* et al. reported an acceptance rate of 50% in acute stroke [140]. One could speculate that treatment may be particularly important in the acute phase, when the survival of the penumbra is critical.

Among elderly stroke patients, in whom CPAP could not be initiated, oxygen treatment (3 vs. 0.5 L/min) for 8 days improved some cognitive symptoms in up to 53% of patients [65]. In a randomized treatment study, *Sandberg* et al. investigated the effects of CPAP in stroke rehabilitation and found positive effects on depression but not on functional outcome after 4 weeks of treatment. Compliance was a particular problem in patients with delirium and cognitive impairment [201] *Hui* et al. reached primary CPAP acceptance in 16 of 34 stroke patients with OSA, but only four proceeded to home treatment, with an overall low compliance after 3 months [96].

Diagnostic/therapeutic recommendations – conclusions and future perspectives

The high prevalence of SDB observed after stroke justifies a screening for SDB in stroke patients [144]. As milder forms of SDB, e.g. the upper airway resistance syndrome, are not of concern in this clinical setting of mostly elderly patients, simple forms of screening with a portable device or simple pulse oximetry may be sufficient [246]. Polysomnography, however, is the only diagnostic method to safely diagnose SDB and initiate adequate therapy. But one may argue that as long as the clinical consequences of treatment are not clear, diagnosis is useless. Therefore, randomized studies are needed to answer the important question about treatment relevance. Such studies are currently under way.

Conclusion

There is rapidly accumulating evidence for OSA being an important cardio- and cerebrovascular risk factor independent of confounding factors such as diabetes mellitus, hyperlipidaemia, and smoking. In particular, OSA is associated with a dose-dependent increase in systemic arterial blood pressure. Effective treatment of OSA with CPAP therapy lowers blood pressure values not only while asleep but also during daytime. Although somewhat less clear, OSA probably enhances atherosclerosis and thereby contributes to the emergence of vaso-occlusive disease such as CAD and TIA/stroke. Pulmonary hypertension and nocturnal cardiac arrhythmias are further features of OSA-related cardiovascular morbidity; however, they are usually less clinically important. CSR is frequently observed in the setting of advanced CHF (in earlier series in up to 50% of patients with an LVEF below 40%). It mainly occurs in elderly males and constitutes an adverse prognostic sign. Treatment options for CSR include medical stabilization of CHF, administration of nasal oxygen, and various forms of noninvasive ventilatory support. Another possible consequence of SDB (especially OSA, pulmonary diseases, or both) is PH, which leads to dyspnoea and right-heart failure. Depending on the causal type of SDB, administration of nasal oxygen or various forms of ventilatory support is recommended in these patients.

Based on the complexity of the interaction of sleep, SDB, and CVD, an exact diagnosis is important in order to initiate adequate therapy. Concerning diagnosis of SDB, full polysomnography is the only tool, besides the medical history, with which to simultaneously detect and analyse sleep structure, nocturnal arousals, disordered breathing, ECG and oxygen saturation in patients with CVD. These are the relevant facts physicians need to precisely define the underlying type of SDB. Nonlaboratory monitoring systems (NLMS) may help in risk-stratifying patients with suspected SDB, but often cannot precisely analyse the underlying sleep disorder, especially in the complex setting of a patient with CVD. As detailed above, adequate therapy of SDB can improve the outcome of CVD and is thus of great medical and socioeconomic importance.

Based on this review paper, some proposals for future research on the relationship between SDB and CVD can be made. First, the pathophysiological basis for the emergence of CVD in OSA needs to be further clarified. Second, the role of OSA in the development of atherosclerotic disease has to be studied further. Third, the long-term effects of CPAP therapy on cardio- and cerebrovascular end points have to be

investigated. Fourth, the prevalence of Cheyne–Stokes respiration in chronic heart failure has to be evaluated. Finally, significant work needs to be done to stratify the value of different treatment options available for CSR/CHF. In the near future, at least some of these questions will be addressed by the members of the working group ‘Kreislauf und Schlaf’ of the German Sleep Society.

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