Obstructive sleep apnoea: clinical signs, diagnosis and treatment

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Normal and disturbed sleep

Humans spend one-third of their lifetime sleeping. It has only been ~50 years since it was recognized that sleep is not simply a passive state characterized by the absence of wakefulness, but rather a condition that has a typical structure with electrophysiologically, clearly distinguishable phases that follow one another according to a characteristic pattern in healthy subjects. Using electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG), sleep is classified as rapid eye movement (REM) sleep or one of four different non-REM sleep stages. Altogether, one spends ~20–25% of the total sleep time in deep sleep and REM sleep, respectively, and ~50% in light sleep. After the age of 50, the percentage of deep and REM sleep decreases, whereas light sleep and periods of wakefulness during the night increases.

During the night, 4–6 sleep cycles are completed lasting 70–90 min and consisting of an initial period of light sleep, followed by deep sleep and finally REM sleep. Whereas deep sleep is predominantly present during the first hours of sleep, there is an increase in REM sleep in the second half of the night, often accompanied by dreaming.

Breathing during sleep and sleep-disordered breathing

The transition from wakefulness to sleep is characterized by marked changes in all aspects of ventilation in healthy subjects. Upper airway resistance more than doubles, due to a reduction in pharyngeal muscle tone. Ventilatory drive as well as the ventilatory response to hypercapnia and hypoxia decreases. Minute ventilation decreases by ~10%, and as metabolic demand also decreases, arterial PCO₂ only increases by between 2 and 4 mmHg.

Sleep apnoea

Four different patterns of sleep-disordered breathing can be determined: apnoeas, hypopnoeas, hypoventilation and respiratory events that do not fulfill the criteria of apnoeas and hypopnoeas but cause arousal from sleep. An airflow reduction by ≥90% for ≥10 s is called apnoea, and an airflow reduction of ≥50% to <90% for at least 10 s that causes oxygen desaturation of ≥4% is called hypopnoea. Hypoventilation is defined as a reduction in ventilation for at least 5 min with an increase in PCO₂ of >50 mmHg or a desaturation of <85% according to the most widely used definition.

These respiratory events can be of the obstructive type with persisting breathing efforts or of the central type without any respiratory movements [1]. Clinically, mixed apnoeas are often present, in which the initial central apnoea develops into an obstructive one, but from a therapeutic point of view, mixed apnoeas are treated like obstructive ones, and therefore mixed apnoeas are part of obstructive sleep apnoea. To quantify breathing disorders, the mean number of apnoeas and hypopnoeas per hour of sleep, the apnoea–hypopnoea index (AHI), is calculated. More than five episodes of disturbed breathing per hour of sleep are considered pathological, because in epidemiological studies the risk of cardiovascular disorders started to increase from an AHI of 5.

Apnoeas, hypopnoeas and other respiratory events are terminated by a central nervous alarm reaction (arousal) that increases pharyngeal muscle tone (in obstructive events) and leads to the resumption of breathing. Snoring is characteristic in patients with an obstructive and mixed disorder and indicates resumption of respiratory airflow in a still obstructed upper airway. Physiological sleep structure is disturbed by frequent arousals, and deep sleep as well as REM sleep is markedly reduced or even completely missing. Well-known risk factors for the development of obstructive sleep apnoea are male gender and obesity of the abdominal type—~50% of obstructive sleep apnoea (OSA) patients are obese. Many patients have upper airway abnormalities such as retrognathia, anatomically narrow airways or large tonsils.
Symptoms suggestive of sleep apnoea

Sleep disorders typically result in impaired daytime function. Excessive daytime sleepiness, defined as the tendency to fall asleep in inadequate situations despite adequate sleep duration, is the leading symptom of these patients. Frequently, patients successfully overcome their desire to fall asleep by being active and report about falling asleep unintentionally as soon as they encounter monotonous situations such as reading, watching television or driving a car. However, often patients consult a doctor because of symptoms that are not characteristic at all, ranging from irritability, impaired memory and concentration or tiredness and lack of energy to headaches or impotence. As the symptoms develop gradually, they are hardly recognized by the patient and are often attributed to the ageing process. That is why the symptoms often need to be elaborated by asking specific questions about falling asleep unintentionally in monotonous situations, about snoring and witnessed apnoeas. In many cases, high blood pressure, which is a consequence of sleep apnoea in ~30% of hypertensives, leads the patient to his or her doctor, and in this case, it is important to consider sleep apnoea as the cause of hypertension.

Obstructive sleep apnoea and cardiovascular diseases

Thirty to sixty percent of OSA patients suffer from arterial hypertension. However, the question for many years was whether OSA was an independent risk factor for arterial hypertension, or the increased prevalence of hypertension was simply a result of the high prevalence of other risk factors like obesity, physical inactivity or diabetes. Many studies have now confirmed the fact that OSA is an independent risk factor for arterial hypertension [2–8]. Young et al. [2], accounting for all known confounders, demonstrated an increased prevalence of hypertension with increasing OSA severity as measured by the apnoea–hypopnoea index. In a longitudinal survey of the study participants, Peppard et al. [3] demonstrated that the incidence of newly diagnosed arterial hypertension in a 4-year follow-up period increased with the AHI at baseline: after the adjustment for known risk factors for hypertension, there was still a twofold risk increase for subjects with an AHI of 5–15/h and a threefold increase for subjects with an AHI >15 as compared to subjects without breathing disorders at baseline. It is important to note that even mild OSA in the AHI range of 5–15/h will substantially increase the risk for hypertension. It seems important to detect sleep apnoea in hypertensives in order to provide causal treatment of hypertension in these patients. Therefore, sleep apnoea has been included in the recommended work-up of hypertensive patients [9].

OSA has been shown to be an independent risk factor for many cardiovascular diseases like coronary artery disease, myocardial infarction, heart failure and stroke [10,11]. Twenty percent of OSA patients have (generally mild) pulmonary hypertension at rest or upon exertion. Right heart failure, polycythaemia or nocturnal bradyarrhythmas are present in 5–10% of the cases [12,13].

The underlying mechanisms have been the subject of substantial research over the last few years. Intermittent hypoxia with consecutive normoxia is believed to promote the production of reactive oxygen species (ROS). Several studies repeatedly, yet not uniformly, indicated increased oxidative stress in OSA patients. Comorbidities not accounted for could be responsible for conflicting results [14,15].

In OSA patients, levels of derivatives of nitric oxide (NO) are decreased, indicating decreased levels of NO itself. Continuous positive airway pressure (CPAP) therapy increased these values significantly [16,17]. Accordingly, endothelium-mediated systemic and pulmonary vasodilatation is reduced in OSA [18–20]. Improvement could be shown after CPAP therapy [18,19]. Dysregulation of NO pathways may contribute to the increased incidence of cardiovascular complications [21].

Dysregulation of vasomotor activity could also be shown for pathways involving endothelin-1, the endothelin-A receptor and intracellular calcium sensitivity [22].

Markers of inflammation are increased in OSA, including CRP, TNF-α and other cytokines. Granulocytes, CD4 and CD8 T cells show signs of activation; their interaction with the endothelium, in which adhesion molecules are upregulated, may promote atherogenesis [14]. Inflammation in turn contributes to oxidative stress by enhancing granulocyte superoxide production, an effect reversible by CPAP therapy [23].

Furthermore, hypoxia, via stimulation of peripheral chemoreceptors, leads to increased sympathetic activity, which in patients with intermittent nightly hypoxia persists during the day. Resulting activation of the renin–angiotensin–aldosterone system contributes to hypertension [22]. Nightly sympathetic activation is reversible by CPAP therapy immediately, whereas daily activation only after treatment over a period of 6 months or more [24].

Increased levels of fibrinogen involved in inflammation lead to increased blood viscosity as a co-factor for vascular complications [25]. Platelet activation and silent brain infarction have been described in OSA as risk factors for stroke [26]. Systemic and pulmonary hypertension lead to left and right ventricular hypertrophy, respectively. The role and mechanisms of direct hypoxia-mediated changes in myocardial function are subject of further studies [15].

Sleep apnoea and chronic kidney disease

Nocturia, increased sodium excretion, an increase in ANP and a decrease in renin secretion at night, in patients with no clinical overhydration, are accepted findings in patients with SAS [27–29]. The increased sympathetic activity caused by hypoxia leads to increased glomerular filtration in OSA, which is ameliorated by CPAP therapy [30]. Increased renal resistance indices (RI) as a marker of parenchymal renal damage could be shown in mild to moderate SAS, but surprisingly, not in severe SAS in comparison to hypertensive controls without OSA. In mild to moderate sleep apnoea, RI correlates with AHI after correction for age [31]. One study shows elevated creatinine and decreased endogenous creatinine clearance in OSA [32]. Intermittent hypoxia leads to increased urinary...
uric acid excretion, which decreases after CPAP therapy [33]. The debate on proteinuria associated with OSA is still open [32,34–36]. Glomerular hypertrophy may lead, together with the frequently coexisting obesity and hypertension, to changes of the glomerulus, described as focal segmental glomerulosclerosis [37,38]. While clinical range proteinuria seems to be rare in OSA and warrants further nephrologic check-up, new data suggest that OSA, independently of hypertension or diabetes, leads to mild albuminuria, increasing with AHI, and indicating renal endothelial dysfunction [39].

Among patients with terminal renal failure, 16–80% showed symptoms of SAS [40,41]. Predictors include high BMI, elevated BUN and creatinine, and acidosis [42]. As possible aetiological factors, metabolic acidosis, overhydration, anaemia or the accumulation of respiratory depressant substances were suggested [43–46]. Erten et al. showed higher levels of cytokines in patients with end-stage renal disease (ESRD) with sleep apnoea compared to those without sleep complaints. Whether SAS is the cause or the result of cytokine elevation in these patients is not known [47]. OSA in these patients may also be related to enhanced chemoreflex responsiveness to hypcapnia [48]. Recently, new data indicated the association of ESRD and pharyngeal narrowing [49]. Extracellular fluid overload and impaired left ventricular function could cause upper airway oedema as demonstrated by patients with heart failure [50]. In these patients, diuretic therapy reduced OSA, but the relationship between fluid removal, OSA and upper airway diameter has not been examined until now [50]. Furthermore, upper airway muscle tone could be reduced by increased mechanoreceptor sensitivity and myopathy due to uraemic neuropathy.

In comparison to conventional haemodialysis (HD) or CAPD, intensified HD or nocturnal peritoneal dialysis improves the SAS [46,51–53]. Vice versa, the transition from nocturnal peritoneal dialysis to CAPD increased the AHI significantly [46]. On the other hand, in patients on conventional HD, no difference was found between polysomnographic findings on days with and without HD [47,53,54].

Nocturnal dialysis corrected total body water and hydration significantly better than intermittent dialysis at day [46]. Conversion from intermittent daytime HD to nocturnal HD reduced chemoreflex responsiveness and increased upper airway calibre. Nevertheless, the change in diameter alone did not correlate with the change in OSA [49]. Therefore, it seemed to be possible that multifactorial mechanisms, such as improvement of extracellular fluid control, enhanced clearance of uraemic toxins and reduction of hypocapnea by correction of metabolic acidosis, are responsible for the improvement of OSA in nocturnal dialysis. A trend towards lower KT/V was observed in dialysis patients with OSA; however, the difference was not statistically significant and could be attributable to the generally higher body weight in this group [55]. Whether renal transplantation contributes to an improvement of the condition has not yet been completely clarified [56]. While there are several case reports of healing sleep apnoea by transplantation, Beecroft et al. found a marked improvement in only 3 out of 11 patients with OSA receiving renal transplantation despite near normal renal function [57]. The prevalence of OSA is still high in patients after renal transplantation and does not differ from patients on a waiting list, by male gender, older age, lower educational status, worse kidney function, use of hypnotic drugs and comorbidity being independent risk factors [58].

Cardiovascular morbidity due to OSA in patients with ESRD is suggested by findings that nocturnal deoxygenation is associated with coronary calcification measured by computer tomography [59] as well as left ventricular hypertrophy [60]. Mean nocturnal SaO2 <95% is associated with an increase in cardiovascular events, but not all-cause mortality, in a study including 50 dialysis patients [61]. Mean blood pressure is elevated in dialysis patients with OSA compared to otherwise matched controls [62]. Excess mortality in patients with OSA, while repeatedly demonstrated in the general population, has so far not been shown for persons with ESRD. In a prospective study including 270 HD patients, using a questionnaire to assess risk for OSA, no excess mortality was observed by the authors in the high or intermediate risk groups, though the authors concede that the study may have been underpowered [55]. Mortality studies of a sufficient sample size and using polysomnography rather than substitute methods to diagnose OSA are still missing. In contrast to the general population, there are no prospective controlled trials investigating a difference in outcome after CPAP therapy in nephrology patients.

**Diagnostic procedures**

Medical history, especially when patients are questioned about excessive daytime sleepiness, snoring and witnessed apnoeas, is the most important diagnostic tool. A number of questionnaires are available to screen for patients at risk for OSA [63]; however, none of these have been explicitly validated for patients with ESRD. If there are symptoms suggestive of sleep apnoea, then there are easily usable portable multi-channel recorders of respiration during sleep that can be used in the patient’s home (Figure 1A,B).

In patients with disorders that are often related to sleep apnoea, but with no or only mild symptoms suggestive of sleep apnoea, medical history and ambulatory multi-channel recording of nocturnal breathing seem to be adequate and economical ways of ruling out sleep apnoea. In patients with more severe symptoms, and if nasal positive pressure therapy is needed (see below), a complete diagnostic work-up in a sleep laboratory is recommended [64]. During polysomnography, the standard diagnostic procedure in the sleep laboratory, EEG, EOG and EMG, respiratory parameters and ECG or heart rate are continuously monitored during an entire night (Figure 2). An additional video recording during sleep documents movement disturbances, sleep walking and nocturnal epilepsy [65].

**Interventions with obstructive sleep-related breathing disorder (SRBD)**

Building blocks for making therapeutic decisions are the severity of sleep apnoea detected in the sleep laboratory,
Fig. 1. (A) and (B) Recording example of a four-channel ambulatory recording of breathing parameters during the night. (A) Four hours of recording and (B) four 10-min episodes. The recordings show repetitive desaturations, snoring with intermittent periods without noise and cyclic variation of heart rate in patients with severe obstructive sleep apnoea.

Fig. 2. Typical obstructive sleep apnoeas during REM sleep with blood pressure increase towards the end of the apnoeas and even more pronounced after the resumption of breathing. Invasively measured blood pressure at the radial artery. Air flow = oro-nasal airflow; RC = rib cage movements; Abd. = abdominal movements; SaO₂ = arterial oxygen saturation; EOG = electrooculogram; Part = arterial pressure.

the patient’s age, the intensity of the symptoms and concomitant diseases. With low risk, initially general measures and pharmacotherapy of possible concomitant diseases are carried out. An AHI of >30–40/h represents a high risk, as do relevant concomitant diseases or special occupations, such as those involving passenger transport or work-related use of a car. In the presence of a high risk and severe symptoms, nasally applied CPAP (nCPAP) therapy should be initiated immediately.

**General measures**

Obesity increases an existing sleep apnoea or leads to its manifestation. Loss of weight can reduce the number of apnoeas and alleviate the symptoms [66]. Alcoholic drinks and tranquilizer use induce or intensify an obstruction of the pharyngeal airways [67,68]. Thus, substances that by themselves contribute to daytime sleepiness should be avoided, also in the management of concomitant diseases (clonidine and reserpine). Beta-adrenergic blockers can be used, as long as no bradycardiac arrhythmias are present. The administration of oxygen to treat OSA can be a threat for the patient, because apnoea periods may be prolonged under oxygen application.

The collapse of the upper airways is aggravated in the supine position, because the tongue dropping backwards narrows the pharynx more than in the lateral and abdominal position. Sleep position training involving the use of aids that help to maintain a lateral or abdominal sleeping position can reduce obstructive sleep apnoea in these cases.

Commercially available ‘anti-snoring devices’ that, according to the manufacturer information, sense snoring and induce arousal using various mechanisms (noise, electric shock or vibrations) and consequently make the patient change his body position are contraindicated, because the additional sleep structure disturbance may increase the breathing disorder.

**Therapy with positive ventilation pressure**

The nasally administered therapy nCPAP is the therapy of choice in moderate and severe sleep apnoea. A blower generates an air flow that is directed via a tube and a soft nose mask to the airways of the patient. By means of a valve,
the individual pressure required can be adjusted between 3 and 20 cm H2O. This pressure extends into the airways and acts as a passive splint in the pharyngeal muscular tub and consequently prevents it from collapsing. The effective treatment pressure required by each patient is identified by continuous polysomnographic recordings in the sleep laboratory. In the course of at least one complete treatment night, the pressure is adjusted in such a way that in all sleep stages in the supine position the obstructive breathing disturbances completely disappear.

**BiPAP, PPAP and automatic nCPAP**

Up to 20% of the patients poorly tolerate conventional nCPAP, especially because the expiration against the positive pressure is experienced as being unpleasant. There are three modifications of nCPAP therapy available for those patients: a ‘bilevel positive airway pressure’ (BiPAP®; Fa. Respironics, USA) administers during inspiration a higher and during expiration a 3–5 cm H2O lower pressure. Proportional positive airway pressure (PPAP) works with a basic pressure that prevents the collapse of the upper airways in resting end-expiratory position. Proportional to the inspiration efforts of the patient, the pressure is increased or, during expiration, decreased. Automatic nCPAP devices adjust the treatment pressure to the respective requirements automatically.

**Risks and side effects**

As acute side effects, prolonged hypoventilation and acute cardiac insufficiency were reported [69,70]. Furthermore, dyspnœa due to airway obstruction in the presence of a soft epiglottis may occur in rare cases. These rare side effects require a continuous monitoring of the patient in the sleep laboratory during the first treatment night.

Rhinitis is a harmless side effect that, however, occurs in up to 25% of the patients and is treated with topical therapeutic products or, in severe cases, with a humidifier with a heating system. Problems with pressure sores caused by the nose mask or with the noise of the nCPAP devices are of minor importance today because of technical advances.

**Effects**

In the sleep laboratory, nCPAP has been shown to be an effective therapy for SBAS with obstruction of the upper airways in ~95% of patients. The increased tendency to fall asleep during daytime is already markedly reduced or has completely disappeared after 2–3 nights of treatment. Therapy of the recurrent episodes of hypoxia, arousal and intrathoracic pressure variations, among other things, leads to the disappearance of the apnoea-associated increases in systemic and pulmonary arterial blood pressure, as well as the bradycardiac arrhythmias during sleep. With consequent nCPAP therapy, the daytime arterial blood pressure is reduced by ~10 mmHg [30]. In the case of regular follow-ups with at least annual examinations, the long-term acceptance is ~70–80% in European therapy centres.

In unselected patients with OSA, meta-analysis of randomized controlled trials showed a trend towards lower blood pressure under CPAP therapy, but no significant decrease. However, including only studies with patients with AHI >30, a significant decrease in blood pressure under CPAP therapy could be shown [71]. Remarkably, in the study including the patients with the highest mean AHI [63,8], the greatest decrease in blood pressure was found (~10 mmHg) [72]. Therefore, one can speculate that reduction in AHI correlates with reduction in blood pressure.

Data from randomized controlled trials showing an effect of CPAP on mortality are still missing [73]. A retrospective cohort study stratifying CPAP-treated patients according to compliance showed significantly higher 5-year mortality in noncompliant patients [74]. Another historical cohort study comparing untreated with treated patients with severe OSA (mean AHI: 55) showed similar results [75]. In a 10-year observational study, Marini et al. found a higher incidence of fatal as well as non-fatal cardiovascular events in untreated patients with severe OSA than in mild-moderate OSA or treated patients [76].

In conclusion, nCPAP therapy improves quality of life and effectively reduces daytime sleepiness. Especially in patients with high cardiovascular risk and severe sleep apnoea syndrome, CPAP holds the potential to reduce the rate of cardiovascular incidents. Whether this is true for the highly selected group of patients with chronic renal failure remains to be proven.

Conflict of interest statement. None declared.

(See related article by Y.-L. Chiu et al. Higher systemic inflammation is associated with poorer sleep quality in stable haemodialysis patients. Nephrol Dial Transplant 2009; 24: 247–251.)

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