

SERIES 'SLEEP AND BREATHING'
Edited by W. De Backer

Manifestations and consequences of obstructive sleep apnoea

J.H. Peter, U. Koehler, L. Grote, T. Podszus

Manifestations and consequences of obstructive sleep apnoea. J.H. Peter, U. Koehler, L. Grote, T. Podszus. ©ERS Journals Ltd 1995.

ABSTRACT: Over the last two decades the diagnostic tools used in sleep medicine have developed enormously, making it possible to study the interaction of sleep-related breathing disorders (SRBD) with cardiovascular function and the autonomic nervous system, as well as the effects of SRBD on a variety of physiological processes during wakefulness. Different modes of nasal ventilation are now available, allowing all forms of SRBD to be treated. If early diagnosis and treatment are provided, the acute and long-term sequelae of SRBD can be prevented.

In addition to the care and treatment of patients with severe obstructive sleep apnoea syndrome (OSAS), future patient management will need to focus on patients with milder forms of obstructive sleep apnoea (OSA). In particular, the consequences of SRBD on cardiac arrhythmias, arterial hypertension and hypersomnolence are discussed, considering epidemiological, clinical, diagnostic and therapeutic aspects.

Some economical issues arising from SRBD are also discussed, and the authors conclude that a Europe-wide programme for early detection, treatment and prevention of SRBD is required. This could make a large contribution to the reduction of cardiovascular morbidity and mortality and also reduce the incidence of "human error catastrophes" due to hypersomnolence.

Eur Respir J., 1995, 8, 1572-1583.

Klinikum der Philipps-Universität, Zentrum für Innere Medizin, Abteilung Poliklinik, Schlafmedizinisches Labor, Marburg, Germany.

Correspondence: J.H. Peter
Schlafmedizinisches Labor
Klinikum der Philipps-Universität Marburg
Zentrum für Innere Medizin
D-35033 Marburg
Germany

Keywords: Arterial hypertension
cardiac arrhythmia
hypersomnolence
obstructive sleep apnoea

Received: April 13 1995
Accepted for publication May 24 1995

Obesity, hypertension, sudden cardiac death, cardiac failure, and accidents caused by sleepiness or "human error" are among the most important issues in medical research, and are all linked to obstructive sleep apnoea (OSA). Numerous books and review articles that deal with the symptoms and features of obstructive sleep apnoea syndrome (OSAS) have been published. It would make no sense, therefore, to add another purely retrospective article with the title "Manifestations and Consequences of OSA". Instead, this article will focus on hypersomnolence as the key symptom of OSA and also as a major risk factor contributing to accidents. Arterial hypertension and cardiac arrhythmias - the most important cardiovascular effects of OSA - will also be discussed. For each of these issues, we will try to describe the challenges, from our perspective, for future patient management and care in sleep medicine.

Over the last 15 yrs we have evaluated and treated more than 10,000 patients with suspected sleep-disordered breathing. During this period, a huge technological evolution has taken place in the field of diagnostics. Several monitoring devices that continuously measure a variety of parameters, such as pulse oximetry, inductive plethysmography, continuous noninvasive blood pressure monitoring (finger photoplethysmography),

small oesophageal pressure sensors, and sensors for other cardiorespiratory parameters have become widely available for general use outside specialized research institutions [1]. Such devices now enable us to routinely assess sleep and sleep-related pathological conditions in large numbers of patients. Other major improvements have been made in areas such as the surgical treatment of OSA (maxillo-mandibular advancement), and even more importantly in the field of nasal ventilation. Our ability to detect impaired daytime function caused by the disruptive effect of autonomic dysfunction during sleep (*i.e.* apnoeas) on sleep quality and architecture (frequent arousal *etc.*), even in an early stage, has improved. Circadian variation of parameters such as arterial blood pressure and the subsequent effects of treatment can now be studied both during sleep and wakefulness.

In the past, sleep-induced upper airway obstruction (UAO) had been typically described as OSAS in obese middle-aged males suffering from loud and irregular snoring, impaired daytime vigilance, and cardiovascular and cardiopulmonary disorders (arterial and pulmonary hypertension, heart failure, arrhythmias). OSAS is associated with increased morbidity and mortality. Whilst in the past, the term OSAS was helpful to focus on a combination of symptoms and findings in patients with

sleep-related breathing disorders, this narrow focus is no longer adequate today. The evaluation and treatment of patients with upper airway obstruction during sleep has clearly shown that parameters such as apnoea or respiratory disturbance index are insufficient to assess the severity of the disorder [2]. Usually, patients with a high apnoea index (>40 episodes \cdot h $^{-1}$) present with a combination of symptoms and features sufficient to use the term "syndrome". However, patients may be oligo- or even asymptomatic. Recognition and intervention can prevent long-term sequelae due to UAO in these patients. To adhere to the term "syndrome" and to limit treatment only to patients who show the full-blown syndrome would mean withholding successful treatment from many patients [3]. Treatment should ideally start in the early stages of the disorder rather than waiting for the development of the full-blown syndrome and possibly irreversible sequelae.

The most relevant long-term consequences of SRBD arise from the effects on the cardiovascular system and from "human error" caused by hypersomnolence. Accordingly, this article addresses the effect of sleep induced upper airway obstruction on arterial hypertension, cardiac arrhythmias, daytime sleepiness and the effects of treatment.

Hypersomnolence and OSA

Normal sleep fulfils a restorative function, and is typically characterized by a regular pattern of 4–5 sleep cycles during the sleep period. Each cycle contains several distinct stages of sleep that are classified according to standard criteria based on electroencephalographic (EEG), electro-oculographic (EOG) and electromyographic (EMG) signals. The two main categories of sleep include rapid eye movement (REM) and non-REM (NREM) sleep, which are distinguished on these grounds [4]. NREM sleep, which accounts for approximately 75% of total sleep time, consists of the sleep stages 1, 2, 3 and 4. Stages 1 and 2 are characterized by a relatively low arousal threshold. SRBD are usually associated with a disturbed sleep architecture, in particular an increase in the quantity and proportion of stage 1 and 2 sleep.

Stages 3 and 4 NREM sleep are characterized by high amplitude slow waves in the EEG and a reduction in muscle tone. Autonomic function is relatively stable. Young healthy individuals will spend 20% of their sleep in stages 3 and 4 NREM, predominantly at the beginning of the night. A reduction in the quality of stage 3 and 4 NREM is typically associated with tiredness and impaired daytime performance.

REM sleep is characterized by bursts of rapid eye movements and a further reduction of muscle tone. Regulation of autonomic functions, such as temperature, heart rate, blood pressure, and breathing and upper airway stability, becomes unstable, even in healthy subjects, during REM. In OSA, apnoeic events and oxygen desaturation are more severe during REM-sleep. Twenty to twenty five percent of the total sleep time is normally spent in REM-sleep. The duration of each REM period

tends to increase over the course of a night's sleep. Interestingly, the early morning is the time of the day when human mortality peaks [5].

Since 1991, there has been a provisional International Classification of Sleep Disorders (ICSD) [6]. The two clinically most important groups of disorders are dys-somnias (intrinsic and extrinsic) and parasomnias. OSA is the most common intrinsic dyssomnia leading to hypersomnia. However, insomnia may be a manifestation in OSA, and approximately 5% of our patients, usually with mild to moderate OSA, report this symptom.

In the early 1980s, the report of COLEMAN *et al.* [7] surprisingly demonstrated that patients presenting to sleep laboratories complaining of hypersomnia were equally as frequent as those who presented with the complaint of insomnia. The prevalence of obstructive SRBD is approximately 8% in male subjects aged 40–65 yrs [8, 9]. We estimate that the major symptom in one third of these patients is hypersomnia. Upper airway obstruction during sleep induces central nervous activation, the so-called arousal, which is usually not noticed by the patient (fig. 1). The more severe the sleep fragmentation, the more likely that daytime somnolence will be reported.

As a consequence of arousal, muscle tone, heart rate, blood pressure and ventilation will increase. Hyperventilation following an apnoea will usually restore normal blood gases. Patients with severe OSA, but also those with partial upper airway obstruction causing frequent arousal without clear-cut apnoeas, may present with excessive daytime sleepiness. Arousal due to upper airway obstruction is thought to be a major factor causing hypertension in these patients.

As the apnoea index (AI) increases, the amount of REM-sleep and the amount of stages 3 and 4 NREM sleep decreases (fig. 2).

This effect is disproportionate, in that stage 3/4 NREM sleep may be totally absent in severe OSA, whilst some REM-sleep is usually maintained. The short daytime naps of these patients, however, may contain quantities of stage 2 NREM and even of REM sleep. During nasal

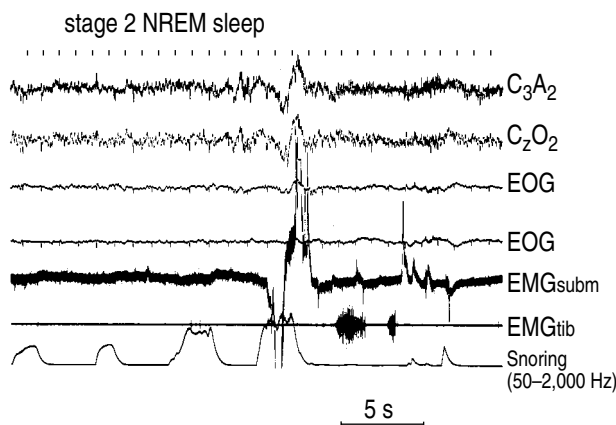


Fig. 1. – Arousal caused by snoring during stage 2 non-rapid eye movement (NREM)-sleep. The figure shows two electroencephalogram (EEG) leads (C_3-A_2 ; C_2-O_2), two electro-oculogram (EOG) leads, submental and leg electromyographic activity (EMG_{subm} and EMG_{tib} , respectively), and integrated snoring activity.

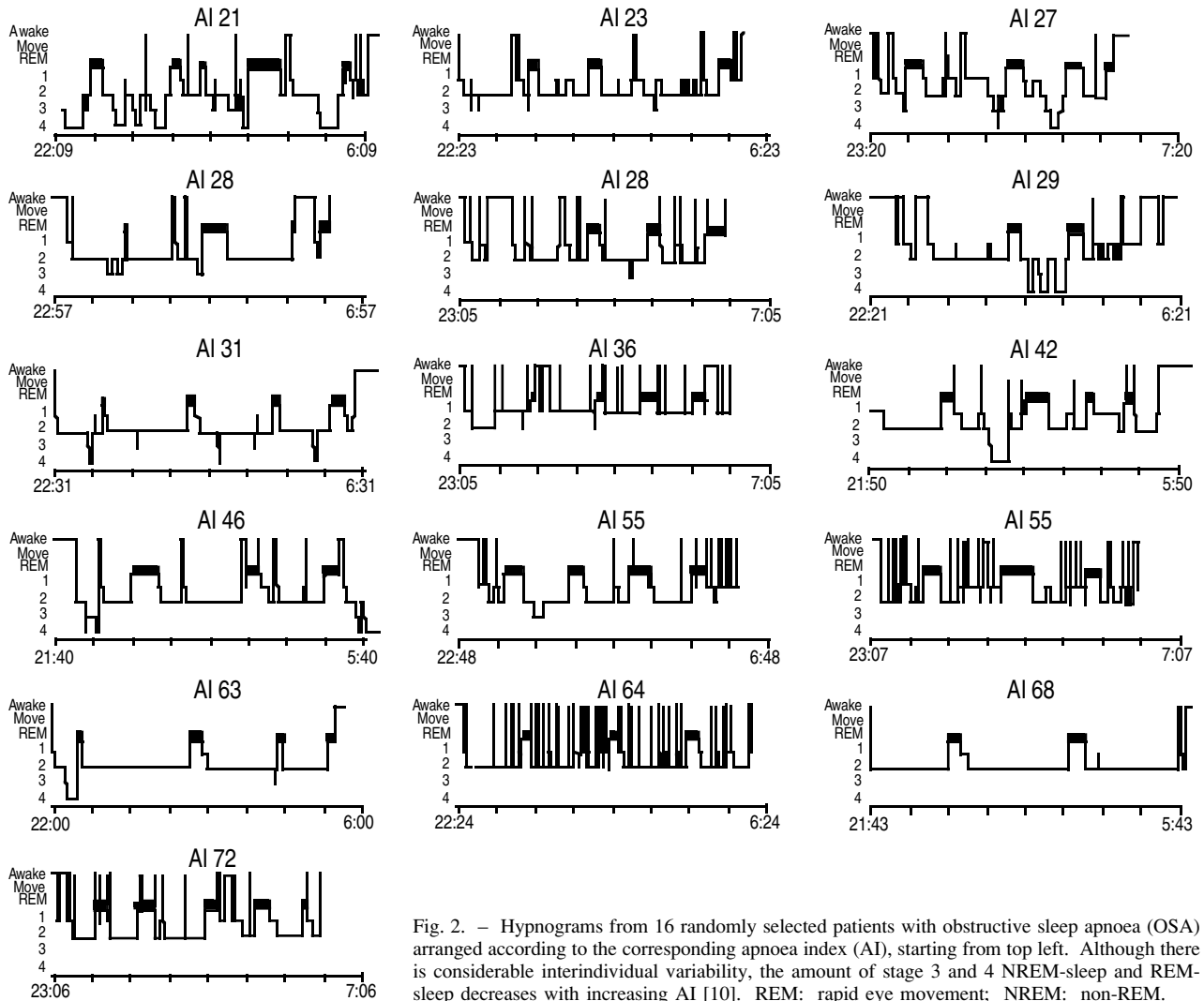


Fig. 2. – Hypnograms from 16 randomly selected patients with obstructive sleep apnoea (OSA) arranged according to the corresponding apnoea index (AI), starting from top left. Although there is considerable interindividual variability, the amount of stage 3 and 4 NREM-sleep and REM-sleep decreases with increasing AI [10]. REM: rapid eye movement; NREM: non-REM.

continuous positive airways pressure (nCPAP) therapy, the total amount of stage 3/4 NREM sleep is increased, and this increase occurs mainly during nocturnal sleep (fig. 3).

A flattening of the circadian body core temperature rhythm in OSA may be a further important pathophysiological factor in this disorder. This is reversible with nCPAP therapy [11] (fig. 4).

The degree of excessive daytime sleepiness and reduced vigilance due to sleep fragmentation in OSA may vary widely. Initially, the normal rhythmic circadian tendency to fall asleep will be more pronounced. In severe cases, however, sleep onset can be rapid and uncontrollable for the patient, even to the point where a diagnosis of narcolepsy is erroneously made. A detailed sleep-waking history should be obtained. We have developed a diary as a part of a simple, but very efficient questionnaire to assess daytime sleepiness [12]. The Multiple Sleep Latency Test (MSLT) [13], Maintenance of Wakefulness Test (MWT) [14], and vigilance tests are used to objectively measure sleepiness. All of these tests have the limitation of being influenced by the subject's motivation to perform the test, and are also performed in a "nonrealistic" test situation. However, these tests

are useful in documenting impairment before therapy and changes during treatment (fig. 5). In OSA patients effectively treated by nCPAP, the performance in vigilance tests is normalized along with a restitution of normal breathing pattern and sleep structure [15]. There are only limited data on the effect of "fighting to stay awake" on blood pressure in hypersomnolent OSA patients. During vigilance testing in hypersomnolent OSA patients, arterial blood pressure shows marked phasic increments following a false or delayed reaction to a task. This response is very similar to the blood pressure increase seen following arousal after an apnoeic event during sleep [16].

Hypersomnolence, sleep fragmentation and sleep deprivation will interfere with control of breathing and lower hypercapnic and hypoxic ventilatory responsiveness. The effect of changes in vigilance on cardiovascular and respiratory function has long been known. These findings are of enormous clinical relevance and should be taken into account more often in patient management.

In an industrialized society, vehicle operating tasks and the control and monitoring of complex processes have become part of working and everyday life. Most

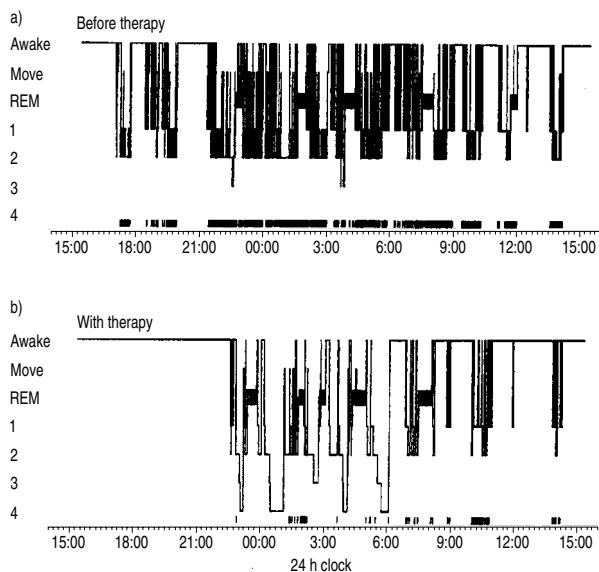


Fig. 3. — Twenty four hour hypnogram: a) before therapy, and b) with nCPAP treatment in a patient with OSA. The occurrence of apnoeas is shown above the time scale, where one small line represents one apnoea (obstructive, mixed or central). With nCPAP the quantity of stage 3 and 4 NREM-sleep increases markedly during the 24 h period and the episodes of sleep during daytime are considerably reduced. nCPAP: nasal continuous positive airway pressure. For further abbreviations see legend to figure 2.

importantly, these tasks depend on alertness and an ability to react to infrequently occurring, unexpected events. While tasks arising at regular intervals can even be performed at decreased levels of vigilance fulfilling the criteria of light sleep [17, 18], this is not the case for unexpected tasks or events. Official statistics in Germany attribute only 0.5% of all traffic accidents to tiredness and sleepiness [19]. However, this contrasts with other estimates that up to 9% of all traffic accidents are due to the above mentioned factors [20]. In those car accidents in which sleepiness was the obvious cause, the rate of deaths was three times as high as in other accidents. Falling asleep whilst driving seems to be the cause of 3% of the accidents causing material damage, 20% of the accidents causing injuries, and 50% of the accidents causing death [21]. Falling asleep whilst driving is the most frequent cause of lethal car accidents on the German "Autobahn", causing 24% of the accidents according to a recent survey by insurance companies [22]. LEGER [23] estimates that the cost of road accidents due to sleepiness ranged between 43–54 billion US\$ in the USA in 1988.

With the prevalence rate of OSA in males aged 40–60 yrs being as high as 10%, there would seem little doubt that OSA is the most important medical cause for hypersomnolence. FINDLEY *et al.* [24] found a threefold increased risk for road accidents in OSA patients (apnoea/hypopnoea index (AHI) >5 episodes·h⁻¹) compared to the overall risk of all drivers. Compared to a control group of 35 subjects without OSA, the accident risk was increased by sevenfold. The performance in a driving simulator was significantly reduced in OSA patients compared to subjects without OSA [25]. CASSEL *et al.* [15] demonstrated impaired performance in objective vigilance tests

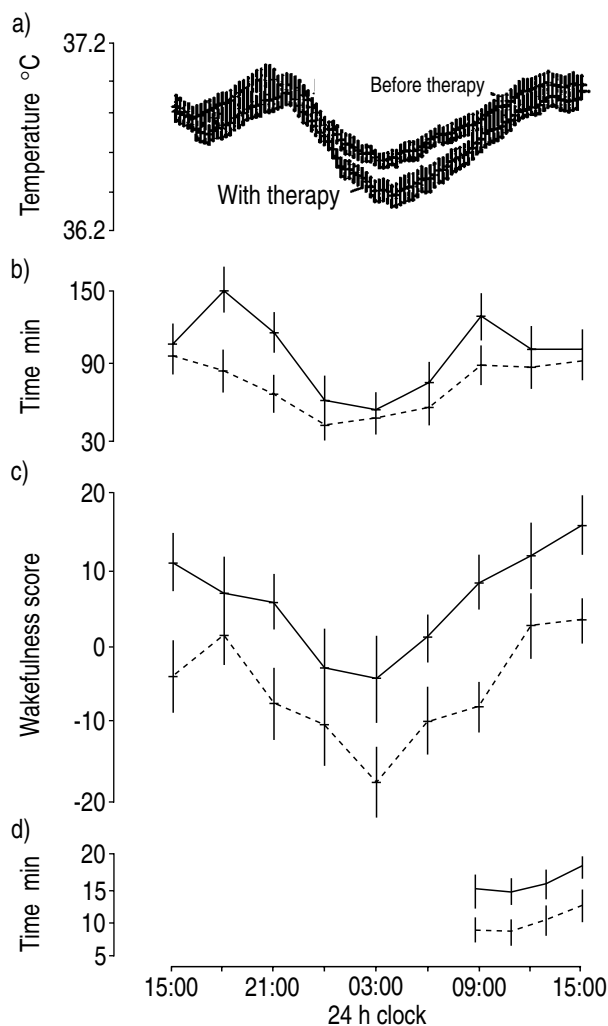


Fig. 4. — a) Body core temperature; b) latency to sleep stage 2; c) subjective wakefulness; and d) latency to sleep stage 2 in the MSLT in 12 patients over a 24 h period. Values are presented as mean \pm SEM. —: with therapy; - - -: before therapy. Following the reversal of apnoeic episodes with nCPAP, a normalization of circadian body core temperature rhythm occurs. Subjective and objective measures of sleepiness improve [11]. MSLT: Multiple Sleep Latency Test. For

untreated OSA patients, which was almost completely reversible during nCPAP treatment. Using a questionnaire, they revealed that falling asleep whilst driving was markedly reduced after one year of nCPAP therapy. Also, a significant improvement was observed in sleep latency (MSLT) and in sustaining concentration [15].

Cardiac arrhythmias and OSA

With the introduction of the Holter-electrocardiogram (ECG) as a routinely used diagnostic tool, it became obvious that serious heart rhythm disturbances may be present during sleep. There are only limited data concerning the causes of sleep-related cardiac arrhythmias. This is partly because, until recently, there was a lack of simple diagnostic tools available for continuous recording of parameters such as respiration, arterial and pulmonary artery pressure, EEG *etc.* Polysomnography

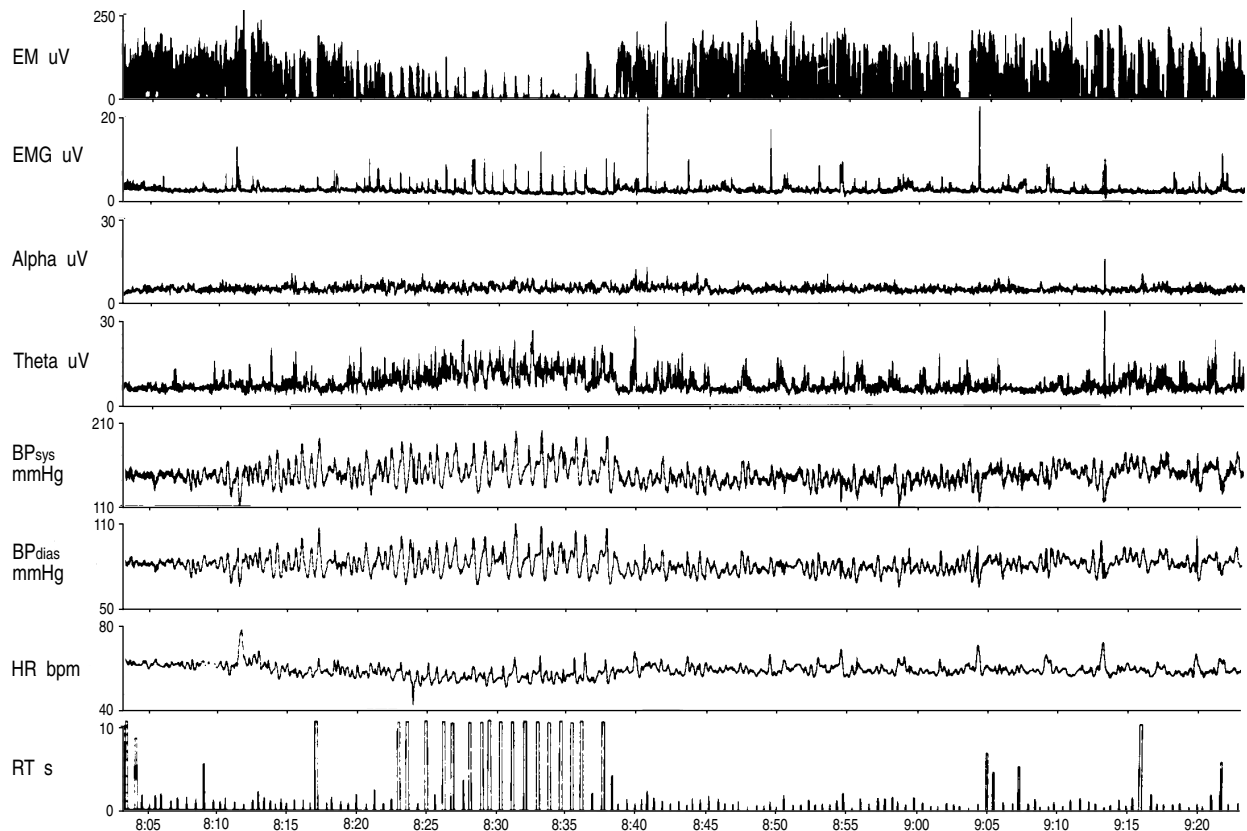


Fig. 5. — Eye movements (EM), mean activity of electromyogram (EMG), amount of alpha and theta wave activity in the EEG frequency analysis, systolic and diastolic blood pressure (BP_{sys} , BP_{dias}), heart rate (HR) and reaction time (RT) during a vigilance test. Between 8.20 and 8.37 a.m. the amount of theta wave activity increases, showing that the patient is very sleepy. During that time, muscle tone and heart rate decrease, whilst average systolic and diastolic blood pressure increase with marked variability in BP. As seen in the RT, the patient completely misses several tasks. bpm: beats·min⁻¹.

established the important role of sleep-disordered breathing in the pathogenesis both of bradycardia and tachycardia nocturnal arrhythmias.

The reported prevalence of heart block in sleep apnoea patients varies considerably in the literature, most probably because of the differences in the patient groups studied (table 1). In two reports on 15 and 25 patients by TILKIAN and co-workers [26, 27], bradycardia <30 beats·min⁻¹ was seen in 40 and 36% of the patients, sinus arrest (>2.5 s) in 33 and 36%, and II° and III° atrioventricular (AV) conduction block in 13 and 16%, respectively. In a retrospective analysis of 400 patients with obstructive sleep apnoea, sinus bradycardia (<30 beats·min⁻¹) was seen in 7%, sinus arrest (>2.5 s) in 11% and II° AV conduction block (Mobitz II) in 8% of the patients [29]. Our own data shows a somewhat lower prevalence of bradyarrhythmias. In 178 OSA patients, sinus arrest (>2 s) was present in 6%, II° AV-block in 5% and III° AV block in 2% [32]. In a study by BECKER and co-workers [36], 17 out of 239 OSA patients (7%) were diagnosed as having a total number of 1,575 episodes of heart block (sinus arrest, II° and III° AV block) during sleep. The prevalence of heart block may be similarly high in young, healthy subjects [37, 38], however, it is very rare in healthy subjects of comparable age to the OSA patients studied [39].

Heart block is to be expected in morbid obesity and severe OSA; out of 239 consecutive OSA patients the

lowest respiratory disturbance index (RDI) in those 17 patients with heart block was 59 episodes·h⁻¹ and the mean body mass index (BMI) was 39 kg·m⁻² [36].

The mortality of untreated patients with moderate and severe OSA (apnoea index (AI) >20 episodes·h⁻¹) is markedly increased compared to patients with an AI of less than 20 episodes·h⁻¹ [20]. This difference in mortality was most pronounced in patients less than 50 yrs of age. The comparison of two age- and weight-matched groups of OSA patients with and without nocturnal heart block revealed a higher apnoea and hypopnoea index (AHI) (48 ± 24 vs 32 ± 20 episodes·h⁻¹) ($p < 0.001$) in the heart block group, but no significant differences in the number of cardiovascular diagnoses, blood gas results, or lung function values between the two groups [40].

Besides severe OSA (AHI >50 episodes·h⁻¹) and morbid obesity (BMI >30 kg·m⁻²), REM-sleep and the severity of desaturation during apnoeas are further independent factors contributing to the occurrence of heart block in OSA. More than 80% of heart block episodes occurred during REM-sleep, and the likelihood of heart block increased significantly if the apnoea associated desaturation exceeded 20% [36, 41]. In a study by GUILLEMINAULT *et al.* [29] heart block occurred exclusively at an arterial oxygen saturation (S_{a,O_2}) below 72%.

Figure 6 shows a Holter-ECG in a patient both with apnoea-related heart block and premature ventricular contractions. The polysomnographic recording, in combination

Table 1. – Prevalence of bradycardic and tachycardic arrhythmias in OSA

First author [Ref.]	Year	Patients n	Sinus arrest %	II° AV block %	III° AV block %	Complex PVCs %	VT %
TILKIAN [26, 27]	1977–1978	15	33	13	0	67	13
MILLER [28]	1982	23	36	16	0	NR	8
MILLER [28]	1982	23	9	4	0	9	0
GUILLEMINAULT [29]	1983	400	11	8	0	NR	3
BOLM-AUDORFF [30]	1984	20	0	0	0	36	15
SHEPARD [31]	1985	31	10	6	0	55	3
KOEHLER/ZINDLER [32, 33]	1993	178	6	5	2	14	0
FLEMONS [34]	1993	76	5	1	0	1	0
HOFFSTEIN [35]	1993	214	Sinus arrest, AV block, junctional rhythm (2–3%)			NR	3
BECKER [36]	1995	239	6	3	1	NR	NR

OSA: obstructive sleep apnoea; [Ref.]: reference number; II° and III°: second and third degree; AV: atrioventricular; PVCs: premature ventricular contractions; VT: ventricular tachycardia; NR: not reported.

with the ECG shown in figure 7 demonstrates the occurrence of repetitive episodes of III° AV conduction block of up to 14.1 s towards the end of the apnoeic episodes.

To our knowledge there are no data on the influence of oxygen therapy on heart block in OSA; probably, since O₂ may markedly prolong apnoeas and hypopnoeas, these studies have not been performed. ZWILLICH *et al.* [42] reported a reduction of apnoea-induced bradycardia during oxygen breathing, despite the overall lengthening of apnoeas with O₂ supplementation.

As the *i.v.* application of atropine eliminates heart block but has no effect on apnoea, an increased vagal tone has been postulated as the cause of nocturnal heart block in OSA. Hypoxia in the absence of respiratory movements seems to be the most important vagal stimulus. Upper airway obstruction might also play an important

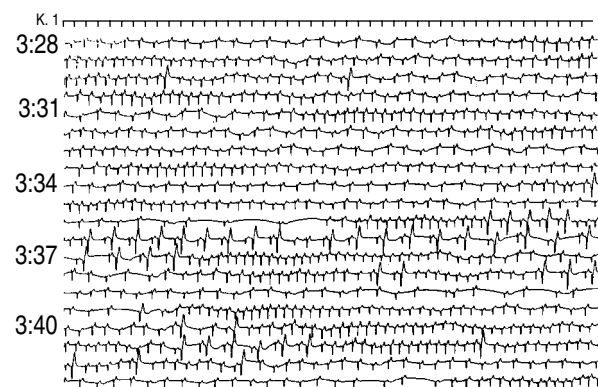


Fig. 6. – Part of a Holter electrocardiogram (ECG) recording (one channel) in an obstructive sleep apnoea (OSA) patient showing both heart block and premature ventricular contractions (PVCs) during apnoea. One line represents 45 s.

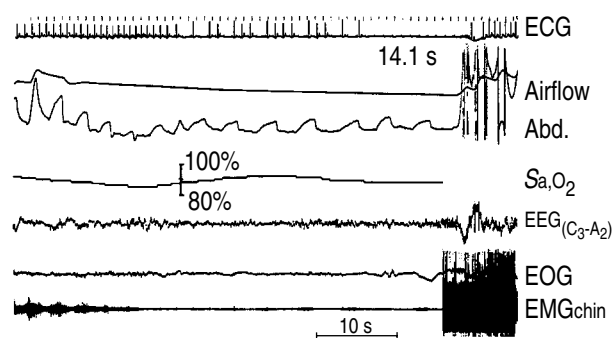


Fig. 7. – Part of a polysomnographic recording in a patient with severe obstructive sleep apnoea (OSA) (RDI 67 episodes·h⁻¹) showing intermittent complete AV conduction block during an obstructive apnoea. Abd: abdominal respiratory movements; Airflow: oronasal airflow; RDI: respiratory disturbance index; Sa₂O₂: arterial oxygen saturation. For further abbreviations see legends to figures 5 and 6.

role. The negative intrathoracic pressure resulting from continuing effort to breathe against the closed upper airway increases with apnoea duration, thus directly increasing vagal tone. Furthermore, this also indirectly stimulates the vagus *via* a volume-change induced alteration of heart rate, blood pressure and stroke volume, triggered by baroreceptors and intracardiac mechanoreceptor reflexes.

In OSA patients, heart block does not occur during wakefulness, an important criterion to distinguish these arrhythmias from heart block in patients with heart disease. Furthermore, less than 10% of our OSA patients with heart block also had coronary artery disease [40]. Electrophysiological studies were normal in most of the patients studied [43], suggesting that vagally-mediated reflexes, and not cardiac disease, are responsible for heart block in OSA patients.

The apnoea-related bradycardia leads to a reduction of oxygen consumption, whilst the increase in diastolic time improves myocardial O₂ supply. Therefore, bradycardia during apnoea can be regarded as an oxygen-saving mechanism. However, extreme bradycardia may impair myocardial perfusion, as the perfusion gradient drops during prolonged diastole. Relative coronary ischaemia might arise and lead to ventricular flutter or fibrillation. In this context, the question of a cardiac pacemaker should be discussed. The indication for a pacemaker depends on the type of arrhythmia, the patients symptoms and concomitant diseases. However, the standard criteria for pacemaker implantation [44] are of little use in OSA patients, as: 1) patients usually do not report arrhythmia-related symptoms; 2) patients are comparatively young and do not have concomitant cardiac disease; 3) most of the OSA patients do not require digitalis treatment; 4) there are no data suggesting that heart block constitutes a major factor contributing to the increased mortality risk; and 5) these patients have no episodes of heart block during wakefulness.

In more than 90% of these patients, heart block can be prevented by the use of nCPAP [36]. However, a pacemaker may be indicated in addition to nCPAP, in patients with persistent heart block despite nCPAP or in circumstances of poor compliance with nCPAP, as the arrhythmias will recur after interruption of the treatment [45].

Before implanting a pacemaker three hitherto unanswered problems should be considered:

1. Do bradycardic arrhythmias contribute to the increased cardiac risk or should they be seen as the extreme form of a protective oxygen saving mechanism'?
2. Are patients more at risk from tachycardic arrhythmias evolving from hypoxia-induced bradycardia?
3. Might the stimulation of the hypoxaemic and vulnerable myocardium by a pacemaker induce dangerous premature ventricular contractions (PVC)?

There are no data comparing the mortality of patients with OSA and heart block with or without a pacemaker, nor is there any information on the natural course or evolution of heart block in this group. Prospective studies in a large patient sample are needed to define these risks. Furthermore, the mechanisms involved need to be clarified. Why do some patients with severe OSA develop heart block but the majority of patients who are equally affected and matched for age, BMI and degree of desaturation do not? If a pacemaker is indicated, we use a dual chamber pace-maker (DDD) system with an AV interval programmed to 250 ms, thus enabling an atrial demand pacemaker with ventricular stimulation to be used when required.

There are differing results concerning the prevalence of tachycardic arrhythmias during sleep in OSA patients (table 1). Most authors have found an increase in PVCs during sleep [26, 27, 29, 30]; however, one has reported a decrease in these events [28]. Again, hypoxia seems to be a crucial aetiological factor. SHEPARD *et al.* [46] reported a significant increase in PVCs in OSA at a Sa_o₂ below 60%. In three out of the 16 patients bigeminy developed at Sa_o₂ values below this threshold [46].

In a large prospective study in patients with suspected OSA, PVCs were found in 58% of patients with OSA (AHI >10 episodes·h⁻¹) vs 42% of those without OSA [35]. PVCs were shown in 82% of patients with a mean nocturnal Sa_o₂ below 90%, but in only 40% of patients with a Sa_o₂ above 90%. If the AHI was >40 episodes·h⁻¹, the prevalence of PVCs was 70%, but only 42% if the AHI was <10 episodes·h⁻¹. Ventricular tachycardia was seen in six OSA patients but in none of the non-OSA patients.

Our data and that of FLEMONS *et al.* [33, 34] suggest that PVCs are increased in obese patients with severe OSA and concomitant cardiovascular disease.

In OSA patients, nocturnal myocardial ischaemia, demonstrated by ST-wave depression, was seen exclusively if the patients also had coronary artery disease (CAD). Ischaemic episodes occurred predominantly during long apnoeas with profound hypoxia in REM-sleep, and were unaffected by nitrates. PVCs were not recorded during the ischaemic phases. Concomitant OSA did not seem to increase the frequency of complex PVCs in 78 patients with CAD, shown by coronary angiogram [49]. RDI was >10 episodes·h⁻¹ in 27 of the 78 patients, but there was no difference in PVCs, both qualitatively and quantitatively during wakefulness or sleep, in patients with or without OSA.

Summarizing these findings, the pathophysiological mechanisms involved in the generation of PVCs are complex in OSA patients. The prevalence data from early studies seem high when compared with more recent work.

Severe OSA with marked desaturation may constitute an additional risk factor for complex PVCs in patients with concomitant CAD. Whereas, the role of severe hypoxaemia is undisputed, the influence of sleep state, haemodynamic changes, and cardiovascular disease has to be further evaluated.

Arterial hypertension and OSA

Arterial hypertension is common and is a major risk factor for the development of cardiovascular diseases, including myocardial infarction, stroke and heart failure. In 95% of hypertensive patients, no obvious cause for the blood pressure elevation can be found [50]. Twenty four hour blood pressure monitoring demonstrates that "non-dippers", patients without the physiological nocturnal decrease in blood pressure (BP), have an increased morbidity and mortality compared to "dippers". "Non-dipping" has long been recognized in patients with secondary arterial hypertension (AHT). A significant proportion of patients with essential AHT also demonstrate "non-dipping" on 24 h BP monitoring [51]. As most of the time during the night is spent sleeping, the effects of sleep on BP, as described by COCCAGNA *et al.* [52], is certainly of great importance. Studies looking at the effect of sleep-disordered breathing, especially OSA, on nocturnal blood pressure, have shown the profound influence of OSA on BP [53]. In a large number of patients, hypertension is caused by OSA. Increased

(cardiovascular) morbidity and mortality have been shown to be long-term consequences of OSA [20, 54–56].

The San Marino study represents the first demonstration of a link between snoring (as a symptom of OSA) and arterial hypertension [57]. Further studies have revealed that OSA is present in at least 30% of hypertensive patients [58–61]. Our own data and those of others demonstrate that approximately 45% of patients with OSA also have arterial hypertension [62]. Some researchers have argued against the role of OSA as an independent factor causing hypertension [63, 64]. However, the strongest evidence in favour of OSA as a cause for hypertension is the significant decrease or even normalization in blood pressure during nCPAP treatment [65], without changes in weight or medication.

Alterations in circadian blood pressure profile are of considerable diagnostic value, as several studies have demonstrated increased morbidity and mortality in "non-dippers" compared to "dippers" [66]. The risk for stroke was 24% in "non-dippers" vs 3% in "dippers" [51]. Left ventricular muscle mass index was elevated only in "non-dippers" and significantly higher in "non-dippers" compared to "dippers", despite the fact that there were no differences in daytime blood pressure [66]. Fifty percent of 140 patients studied after a stroke were "non-dippers", and in 25% of these patients nocturnal blood pressure was higher than diurnal [67]. In our opinion, the epidemiological data show that OSA represents an additional risk factor contributing to cardiovascular disease and may dramatically influence blood pressure in the individual patient (fig. 8).

Numerous haemodynamic changes occur during sleep and these changes are sleep stage dependent [52, 68, 69]. In REM-sleep haemodynamic parameters are more variable while blood pressure rises [53]. The marked

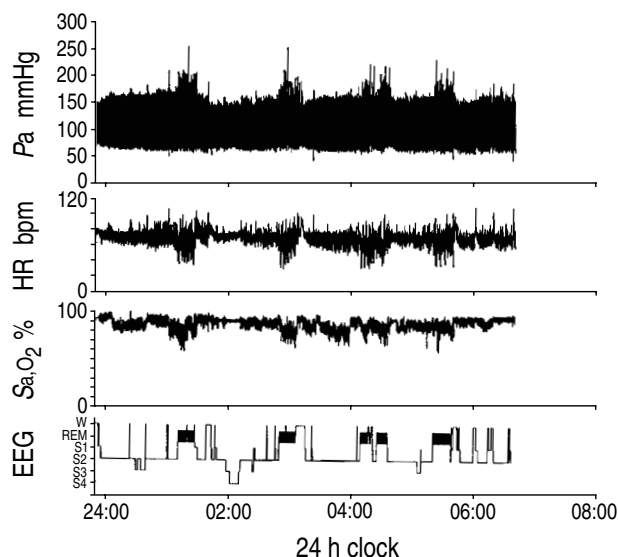


Fig. 8. – Continuously recorded arterial blood pressure (P_a); measured invasively, heart rate (HR) and Sa_{O_2} together with the hypnogram from midnight to 6.30 a.m. in an untreated obstructive sleep apnoea (OSA) patient (AI 54 episodes·h⁻¹). During REM-sleep periods, blood pressure and heart rate variability, as well as oxygen desaturation are more pronounced than during NREM periods (S1 to S4) or wakefulness (W). bpm: beats·min⁻¹; EEG: electroencephalogram. For further abbreviations see legend to figures 2 and 7.

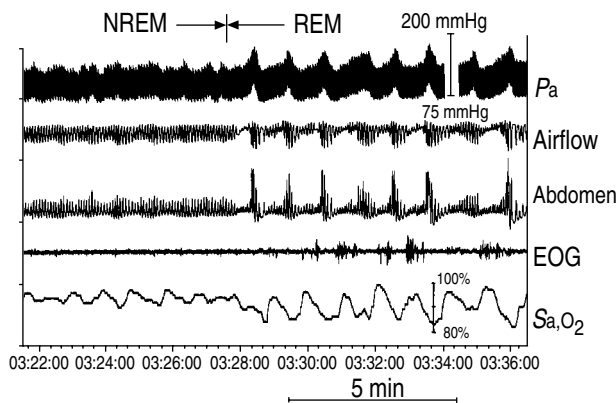


Fig. 9. – Transition from NREM- to REM-sleep. During REM-sleep, the systolic and diastolic arterial blood pressure (P_a) measured invasively, increase. Furthermore, with the longer apnoeic episodes and more pronounced oxygen desaturation seen in REM-sleep, blood pressure is much more variable. EOG: electro-oculogram. For further abbreviations see legends to figures 2 and 7.

increase in blood pressure during REM compared to NREM is demonstrated in figure 9 in an OSA patient.

In OSA, hypoxia increases sympathetic tone *via* chemo- and baroreflex activation [31, 70], thus increasing blood pressure. Increased negative intrathoracic pressure causing increased venous return [71–73], and arousal from sleep in association with apnoeic events [74] also contributes to the rise in blood pressure seen in OSA.

Although an increase in muscle sympathetic nerve activity (MSA) has been demonstrated towards the termination of an apnoeic event [75], the mechanism causing a tonic increase in MSA both during wakefulness and at the transition from NREM to REM sleep in OSA remains unclear. Changes in pulsatile secretion of the renin-angiotensin system and atrial natriuretic peptide, which are vital hormones in regulating blood volume, have been demonstrated. These changes are reversed by nCPAP treatment [76–78].

Our own experience from invasive arterial blood pressure recordings shows that there is no uniform blood pressure profile both during wakefulness and sleep in OSA patients. Besides influencing short-acting regulatory mechanisms, long-acting control systems will be disturbed by OSA, which may lead to a change in the target value of the central control and an impaired response to physiological stress. Long-term effects of hypoxia, repetitive arousal and sleep fragmentation, along with changes in volume regulating hormones and the sleep-wake cycle, are of special importance. Further efforts are necessary to define the long-term effects of OSA on haemodynamics and to evaluate the preventive effects of early treatment.

Surprisingly, despite increasingly convincing evidence, the diagnostic guidelines for hypertension [79], do not consider the potentially important contribution of sleep-related breathing disorders. As OSA is common and because effective therapy is available, we feel it should be normal clinical practice to, at least, ask hypertensive patients about symptoms suggestive of OSA (snoring, apnoeas and daytime sleepiness). Because a lack of symptoms does not exclude the presence of OSA, objective

measurements may be required, especially in patients with other cardiovascular diseases, such as myocardial infarction or cerebrovascular disease.

The following findings are often due to OSA and should lead either to diagnostic polysomnography or recordings using ambulatory monitoring devices: 1) left ventricular hypertrophy on echocardiogram; 2) absent nocturnal blood pressure dip on 24 h BP monitoring (*i.e.* a fall of more than 10% of the systolic and/or diastolic blood pressure); and marked sinus arrhythmia on Holter-ECG monitoring.

If arterial hypertension does not respond to treatment and other secondary causes have been excluded, OSA may often be the cause [80].

We have demonstrated that blood pressure treatment without knowing the effect of treatment on blood pressure during sleep has a limited value. Treatment with antihypertensive medication should consider concomitant disease, including OSA. Drugs should be evaluated as to their suitability in patients with OSA and hypertension. Many frequently used drugs, such as reserpine and clonidine, may increase sleepiness. Beta-blockers may aggravate bradycardia and heart block, and it has been shown that metoprolol, for example, has no effect on blood pressure during REM-sleep [81]. We therefore do not use these drugs in OSA patients as antihypertensives. The choice of an adequate antihypertensive drug is especially important in patients with mild OSA, who are treated by a combination of behavioural measures and therapy for any concomitant disease. If nCPAP is used, patients should be followed up closely at the beginning of the treatment, as antihypertensive medication can be terminated in some patients and reduced in others with successful nCPAP treatment.

State of the art antihypertensive treatment should aim at sustained blood pressure normalization at rest and during exercise, as well as during sleep. Left ventricular hypertrophy should be reversed, the medication should have no relevant side-effects, and any concomitant metabolic disease should not be aggravated by their use. Long-acting drugs are desirable, particularly with respect to nocturnal action and for the benefits of increased compliance likely with single dose medication. Our own studies using Cilazapril in patients with OSA and hypertension revealed that this long-acting angiotensin-converting enzyme (ACE) inhibitor lowered blood pressure effectively during the daytime and during all sleep stages [82]. OSA is an important factor in patients with arterial hypertension and should be considered both in terms of diagnosis and treatment.

Summary and conclusions

In the early 1980s apnoea-induced cardiac arrhythmias were thought to play a major role in the increased mortality risk of OSA patients. However, the prevalence of severe rhythm disturbances today seems confined to cases of more severe OSA. Across the full spectrum of OSA, the overall incidence of apnoea-induced arrhythmia is lower than was originally suspected. Electrophysiological

studies in OSA patients with heart block are usually normal, supporting the hypothesis of TILKIAN and GUILLEMINAULT and co-workers [26, 27, 29, 83] of an increased vagal tone causing heart block in these patients. Predominantly nocturnal heart block or an increase in PVC during sleep should be considered a symptom suggestive of sleep-disordered breathing, and the appropriate diagnostic tests should be performed.

In contrast to cardiac arrhythmias, the relationship between OSA, snoring and arterial hypertension have attracted considerable attention in recent years. Cardiovascular disease remains the major cause of death in industrialized countries. Arterial hypertension is considered to be the "number one killer". It is evident that even patients with mild OSA, and snorers who do not have the symptoms and features of "full-blown" OSAS, experience phases of elevated blood pressure during sleep. Mechanisms by which the nocturnal increase in blood pressure, caused by sleep-disordered breathing, leads to daytime hypertension have been reported. The fact that treatment of OSA with nCPAP can normalize arterial blood pressure adds further evidence to the aetiological role of OSA in arterial hypertension.

Antihypertensive medication in OSA and in hypertensive snorers should fulfil the requirements of sufficiently lowering blood pressure, not only during wakefulness but also during sleep, and of not aggravating OSA and sleepiness. The enormous potential benefits of preventing and treating OSA, particularly with respect to the prevention of cardiovascular morbidity and mortality, should lead to the implementation of the investigation and management of SRBD as a routine in cardiovascular prevention programmes. The fact that, *e.g.* in 1980, 15% [65] of the resources in the German health system were spent on the treatment of cardiovascular diseases, emphasizes that the integration of sleep medicine into prevention and treatment programmes will certainly be of great economical benefit.

Accidents are a further area in which huge amounts of health resources (13% in Germany in 1980) [84] are spent. As hypersomnolence is one of the major causes for single driver accidents, which especially affect young people, this area holds considerable potential for improvement with the treatment of OSA and snoring. In industrialized nations, physical requirements in the workplace are reduced, but high levels of vigilance are needed in order to fulfil control tasks in the automated working environment. Lack of vigilance may, therefore, cause severe and even catastrophic damage. Most vulnerable are the areas of transport, chemical industries, power plants, and other highly automated production processes. Once again, integration of sleep medicine is necessary and beneficial from both a medical and economical point of view.

Sleep-disordered breathing should also be considered more widely in andrology (impotence), endocrinology (obesity, acromegaly, hypothyroidism), haematology (polycythaemia) and anaesthetics (prevention of complications following anaesthesia). In cardiology, apart from patients with arrhythmias and arterial hypertension, those with heart failure should also be investigated for possible links

with sleep-disordered breathing in certain clinical circumstances. In kyphoscoliosis, restrictive chest wall disorders and neuromuscular disease, diagnosis and treatment of sleep-related breathing disorders (SRBD) are of critical importance in the management of the primary disease. In paediatrics SRBD are not only important in the spectrum "near miss for sudden infant death" children or for the Pickwickian type of children, but also in children with growth retardation, enlarged tonsils or adenoids. The same is true for patients with craniofacial malformation [85], especially if the upper airway is involved. In psychiatry and psychosomatic medicine, not only the classical sleep-wake disorders but also dementing processes and other psychiatric illnesses, such as depression, should give rise to consideration of a role for SRBD in the disease process.

Nasal ventilatory support is usually administered by respiratory physicians who have expertise in the increasingly complex field of noninvasive ventilation. Close collaboration with other medical disciplines, particularly neurology and psychiatry, will further aid the respiratory physician in dealing with the full spectrum of SRBD. Such a "team approach" is the most beneficial for the patient. The key to understanding SRBD and upper airway obstruction for the respiratory physician is that only a small part of the complex subject can be elucidated by classical diagnostic tools in respiratory medicine, such as blood gas analyses and lung function. The role of diagnostic evaluation of breathing during sleep is critical.

References

1. Penzel T. Non-EEG variables as a tool to analyze the sleep-wakefulness cycle. *In: Kumar VN, Mallick HN, Nayar U, eds. Sleep-Wakefulness. New Delhi Wiley Eastern Ltd, 1993; pp. 221-227.*
2. American Thoracic Society. Sleep Apnoea, Sleepiness, and Driving Risk. *Am J Respir Crit Care Med* 1994; 150: 1463-1473.
3. Stammnitz A, Becker H, Schneider H, Fus E, Peter JH. Fortschritte in der nasalen Ventilationstherapie schlafbezogener Atmungsstörungen (SBAS). *WMW* 1994; 144 (Sonderheft): 83-87.
4. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility and concomitant phenomena during sleep. *Science* 1953; 118: 273-274.
5. Mitler MM. Two peak 24 hour patterns in sleep, mortality, and error. *In: Peter JH, Penzel T, Podszus T, von Wichert P, eds. Sleep and Health Risk. Berlin, Heidelberg, New York, Springer, 1991, pp. 65-77.*
6. American Sleep Disorders Association. ICSD - International Classification of Sleep Disorders. Diagnostic and coding manual 1990; Diagnostic Classification Steering Committee. Thorpy MJ, Chairman. Rochester, Minnesota.
7. Coleman RM, Roffwarg HP, Kennedy SJ. Sleep-wake disorders based on a polysomnographic diagnosis: a national co-operative study. *J Am Med Assoc* 1982; 247: 997-1003.
8. Peter JH, Fuchs E, Köhler U, et al. Studies in the prevalence of sleep apnea activity: evaluation of ambulatory screening results. *Eur J Respir Dis* 1986; 69 (Suppl. 146): 451-458.
9. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230-1235.
10. Penzel T. Zur Pathophysiologie der Interaktion von Schlaf, Atmung und Kreislauf-Konzepte der kardiorespiratorischen Polysomnographie. (In preparation).
11. Vogel M, Moog R, Hildebrandt G, Peter JH. Chronobiologische Aspekte des OSAS. *In: Peter JH, Penzel T, Cassel W, von Wichert P, eds. Schlaf-Atmung-Kreislauf. Berlin, Heidelberg, New York, Springer-Verlag, 1993; pp. 95-105.*
12. Kemeny C, Ploch T, Schultze B, Teßmann W, Cassel W, Gärtner D. Screeningfragebögen, Risikoabschätzung und Dokumentation. *In: Peter JH, Penzel T, Cassel W, von Wichert P, eds. Schlaf-Atmung-Kreislauf. Springer, Berlin, Heidelberg, New York, 1993; pp. 199-206.*
13. Carscadon MA. Guidelines for the Multiple Sleep Latency Test (MSLT): a standard measure of sleepiness. *Sleep* 1986; 9(4): 518-524.
14. Mitler MM, Gujavarty KS, Browman CP. Maintenance of Wakefulness Test: a polysomnographic technique for evaluating treatment efficiency in patients with excessive somnolence. *Electroenceph Clin Neurophysiol* 1982; 53: 658-661.
15. Cassel W, Ploch T, Becker C, Dugnus D, Peter JH, von Wichert P. Risk of traffic accidents in patients with sleep-disordered breathing: reversal with nasal CPAP? (In preparation).
16. Värri AO, Grote L, Penzel T, Cassel W, Peter JH, Hasan J. A new method to study blood pressure, heart rate and EEG as a function of reaction time. *Meth Inform Med* 1994; 33: 64-67.
17. Peter JH, Fuchs E, Langanke K, Pfaff U. The SIFA train function safety circuit. I. Vigilance and operational practice in psychophysiological analysis. *Int Arch Occup Environ Health* 1983; 52: 329-339.
18. Peter JH, Fuchs E, Langanke K, Pfaff U. The SIFA train function safety circuit. II. Inefficiency of a paced secondary task as a vigilance monitor. *Int Arch Occup Environ Health* 1983; 52: 341-352.
19. Statistisches Bundesamt Wiesbaden (Ed). Fachserie 8 Verkehr. Reihe 7 Verkehrsunfälle. Kohlhammer, Stuttgart, Mainz, 1992.
20. He JH, Kryger MH, Zorick FJ, Conway W, Roth T. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. *Chest* 1988; 94: 9-14.
21. Hoag OJ, Pack A. Drive alert arrive alive. WFSRS news letter. 1994, Vol. 3, No. 1.
22. HUK-Verband, Büro für Kfz-Technik München. "Struktur der Unfälle mit Getöteten auf Autobahnen im Freistaat Bayern im Jahr 1991. 1994.
23. Leger D. Cost of sleep-related accidents. *Sleep* 1994; 17(1): 84-93.
24. Findley LJ, Unverzagt ME, Suratt PM. Automobile accidents involving patients with obstructive sleep apnea. *Am Rev Respir Dis* 1988; 138: 337-340.
25. Findley LJ, Fabrizio MJ, Knight H, Norcross BB, Laforte AJ, Suratt PM. Driving simulator performance in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1989; 140(2): 529-530.
26. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Sleep-induced apnea syndrome: prevalence of cardiac arrhythmias and their reversal after tracheostomy. *Am J Med* 1977; 63: 348-358.
27. Tilkian AG, Motta J, Guilleminault C. Cardiac arrhythmias in sleep apnea. *In: Guilleminault C, Dement WC,*

- eds. Sleep apnea syndromes. New York, AR Liss Inc., 1978; pp. 197–210.
28. Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome: prevalence and significance. *Am J Med* 1982; 73: 317–321.
 29. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol* 1983; 52: 490–494.
 30. Bolm-Audorff U, Koehler U, Becker E, et al. Nächtliche Herzrhythmusstörungen bei Schlafapnoe-Syndrom. *Dtsch Med Wschr* 1984; 109: 853–856.
 31. Shepard JW. Gas exchange and hemodynamics during sleep. *Med Clin North Am* 1985; 69: 1243–1264.
 32. Koehler U, Fett I, Hay J, et al. Bradycarde Herzrhythmusstörungen im Schlaf-Das Morbiditätsspektrum bei Patienten mit Schlafapnoe und nächtlichen bradycarden Herzrhythmusstörungen. In: Peter JH, Cassel W, Penzel T, von Wichert P, eds. Schlaf-Atmung-Kreislauf. Berlin, Heidelberg, New York, Springer, 1993; pp. 374–383.
 33. Zindler G, Koehler U, Fett I, et al. Tachycarde Herzrhythmusstörungen im Schlaf-Das Morbiditätsspektrum bei Patienten mit Schlafapnoe und nächtlichen tachycarden Herzrhythmusstörungen. In: Peter JH, Cassel W, Penzel T, v. Wichert P, eds. Schlaf-Atmung-Kreislauf. Berlin, Heidelberg, New York, Springer, 1993; 358–373.
 34. Flemons WW, Remmers JE, Gillis AM. Sleep apnea and cardiac arrhythmias. *Am Rev Respir Dis* 1993; 148: 618.
 35. Hoffstein V, Mateika S. Cardiac arrhythmia, snoring, and sleep apnea. *Chest* 1993; 106: 466–471.
 36. Becker H, Brandenburg U, Peter JH, v. Wichert P. Reversal of sinus arrest and atrioventricular conduction block in patients with sleep apnea during nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 1995; 151: 215–218.
 37. Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. *Am J Cardiol* 1977; 39: 390–395.
 38. Sobotka PA, Mayer JH, Bauernfeind RA, Kanakis C, Rosen KM. Arrhythmias documented by 24 hour continuous ambulatory electrocardiographic monitoring in young women without apparent heart disease. *Am Heart J* 1981; 101: 753–759.
 39. Bjerregaard P. Mean 24 hour rate, minimal heart rate and pauses in healthy subjects 40–79 years of age. *Eur Heart J* 1983; 4: 44–51.
 40. Koehler U, Wetzig T, Peter JH, Ploch T, Schäfer H, Stellwaag M. Morbidität und Letalität bei Schlafapnoe und nächtlichen Bradyarrhythmien. *Dtsch Med Wschr* 1994; 119: 1187–1193.
 41. Becker H, Brandenburg U, Conradt R, et al. Einfluß der nCPAP-Therapie auf bradycarde Herzrhythmusstörungen bei Schlafapnoe (SA). *Pneumologie* 1993; 47: 706–710.
 42. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea: characteristics and mechanism. *J Clin Invest* 1982; 68: 1286–1292.
 43. Grimm W, Hoffmann J, Koehler U, Peter JH, von Wichert P, Maisch B. Invasive electrophysiologic evaluation of patients with sleep apnea associated ventricular asystole: methods and preliminary results. *J Sleep Res* 1995; (in press).
 44. Breithardt G, Luderitz B, Schlepfer M. Empfehlungen für die Indikation für permanenten Schrittmacherimplantation. *Z Kardiol* 1989; 78: 212–217.
 45. Koehler U, Becker H, Faust M, et al. Nächtliche bradycarde Herzrhythmusstörungen bei schlafbezogener Atmungsstörung-Ist eine Herzschrittmachertherapie indiziert? *Internist* 1989; 30: 819–822.
 46. Shepard JW, Garrison MW, Grither DA, Dolan GF. Relationship of ventricular ectopy to oxyhemoglobin desaturation in patients with obstructive sleep apnea. *Chest* 1988; 3: 335–340.
 47. Koehler U, Dübler H, Glaremin T, et al. Nocturnal myocardial ischemia and cardiac arrhythmia in patients with sleep apnea with and without coronary heart disease. *Klin Wschr* 1991; 69: 474–482.
 48. Koehler U, Glaremin T, Cassel W, et al. Nächtliche ventrikuläre Arrhythmien bei Patienten mit Schlafapnoe und Verdacht auf koronare Herzerkrankung. *Med Klin* 1993; 88: 684–690.
 49. Schäfer H, Koehler U, Ploch T, Peter JH. Coronary heart disease and upper airway obstruction. *J Sleep Res* 1995; (in press).
 50. Williams GH. Hypertensive Vascular disease. In: Isselbacher KJ, Martin JB, Braunwald E, Fauci AS, Wilson JD, Kasper DL, eds. Harrison's Principles of Internal Medicine. McGraw Hill, Inc. 1994; pp. 1116–1130.
 51. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988; ii: 397.
 52. Coccagna G, Mantovani M, Brignani E, Manzini A, Lugaresi E. Arterial pressure changes during spontaneous sleep in man. *Electroenceph Clin Neurophysiol* 1971; 31: 277–281.
 53. Coccagna G, Mantovani M, Brignani F, Parchi C, Lugaresi E. Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. *Bull Physiopathol Respir* 1972; 8: 1159–1172.
 54. Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients. *Chest* 1988; 94: 1200–1204.
 55. Koskenvuo M, Partinen M, Sarna S, Kaprio J, Laginvainio H, Heikkilä K. Snoring as a risk factor for hypertension and angina pectoris. *Lancet* 1985; 1: 893–896.
 56. Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikkilä K, Sarna S. Snoring as a risk factor for ischaemic heart disease and stroke in men. *Br Med J* 1987; 294: 16–19.
 57. Lugaresi E, Cirignotta F, Coccagna G, Piana C. Some epidemiological data on snoring and cardiocirculatory disturbances. *Sleep* 1980; 3: 221–224.
 58. Peter JH, Bolm-Audorff U, Becker E, et al. Schlafapnoe und essentielle Hypertonie. *Verh Dtsch Ges Innere Med* 1983; 89: 1132–1135.
 59. Kales A, Bixler EO, Cadieux RJ, et al. Sleep apnea in a hypertensive population. *Lancet* 1984; 3: 1005–1008.
 60. Lavie P, Ben-Yosef R, Rubin A. Prevalence of sleep apnea syndrome among patients with essential hypertension. *Am Heart J* 1984; 108: 373–376.
 61. Fletcher EC, De Behnke RD, Lovoi MS, Gorin AB. Undiagnosed sleep apnea in patients with essential hypertension. *Ann Intern Med* 1985; 103: 190–195.
 62. Levinson PD, McGravey ST, Carlisle CC, Eveloff SE, Herbert PN, Millman RP. Adiposity and cardiovascular risk factors in men with obstructive sleep apnea. *Chest* 1993; 103: 1336–1342.
 63. Hoffstein V, Chan CK, Slutsky AS. Sleep apnea and systemic hypertension: a causal association review. *Am J Med* 1991; 91: 190–196.
 64. Stradling JR. Sleep apnoea and systemic hypertension. *Thorax* 1989; 44: 984–989.

65. Mayer J, Becker H, Brandenburg U, Penzel T, von Wichert P. Blood pressure and sleep apnea: results of long-term nasal continuous positive airway pressure therapy. *Cardiology* 1991; 79: 84–92.
66. Verdecchia P, Schillaci G, Guerrieri M, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 1990; 81: 528–536.
67. Doutheil A, Schrader J, Holzgraefe M, et al. Häufung und Bedeutung einer nächtlichen Hypertonie bei Patienten mit zerebralen Insulten. *Nieren- und Hochdruckkrankheiten* 1992; 21: 492–494
68. Snyder F, Hobson JA, Morrison FM, Goldfrank F. Changes in respiration, heart rate and systolic blood pressure in human sleep. *J Appl Physiol* 1964; 19: 417–422.
69. Bristow JD, Honour AJ, Pickering TG, Sleight P. Cardiovascular and respiratory changes during sleep in normal and hypertensive subjects. *Cardiovasc Res* 1969; 3: 476–485.
70. Hedner J, Wilcox I, Laks L, Grunstein RR, Sullivan CE. A specific and potent pressor effect of hypoxia in patients with sleep apnea. *Am Rev Respir Dis* 1992; 146: 1240–1245.
71. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures, and the normal venous return curve. *Am J Physiol* 1957; 189: 609–615.
72. Podszus T, Feddersen O, Peter JH, von Wichert P. Cardiovascular risk in sleep-related breathing disorders. In: *Sleep and Cardiovascular Control*. Eds. Gaultier C, Escourrou P, Curzi-Dascalova I. Colloque INSERM 1991; Vol. 217: pp. 177–186.
73. Podszus T, Greenberg H, Scharf SM. Influence of sleep state and sleep-disordered breathing on cardiovascular function. In: Saunders NA, Sullivan CE, eds. *Sleep and Breathing*. New York, Marcel Dekker, 1994; pp. 257–310.
74. Ringler J, Basner RC, Shannon R, et al. Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. *J Appl Physiol* 1990; 69(6): 2143–2149.
75. Hedner J, Ejjnell H. Is high and fluctuating muscle sympathetic nerve activity in the sleep apnea syndrome of pathogenetic importance for the development of hypertension? *J Hypertens* 1988; 6 (S4): 529–531.
76. Brandenberger G, Follenius M, Simon C, Ehrhart J, Libert JP. Nocturnal oscillations in plasma renin activity and REM-NREM sleep cycles in humans: a common regulatory mechanism? *Sleep* 1988; 11: 242–250.
77. Ehlenz K, Peter JH, Kaffarnik H, von Wichert P. Disturbances in volume regulating hormone system: a key to the pathogenesis of hypertension in obstructive sleep apnea syndrome. *Pneumonologie* 1991; 45: 239–245.
78. Krieger J, Follemuis M, Sforza E, et al. Effects of treatment with nasal continuous positive airway pressure on atrial natriuretic peptide and arginine vasopressin release during sleep in patients with obstructive sleep apnea. *Clin Sci* 1991; 80: 443–449.
79. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993; 153: 154–183.
80. Serrato JF, Black HR. Refractory hypertension. *N Engl J Med* 1992; 327/8: 543–547.
81. Mayer J, Weichler U, Herres-Mayer B, Schneider H, Marx U, Peter JH. Influence of metoprolol and cilazapril on blood pressure and on sleep apnea activity. *J Cardiovasc Pharmacol* 1990; 16: 952–961.
82. Grote L, Heitmann J, Schneider H, et al. Twenty four hour blood pressure control: effect of cilazapril on continuous arterial blood pressure during sleep and physical and mental load in patients with sleep apnea. *J Cardiovasc Pharmacol* 1994; 24: 78–82.
83. Guilleminault C, Eldridge F, Dement WC. Human pathology: sleep-induced apnea and cardiovascular changes. *Bull Physiopathol Respir* 1974; 10: 244–247.
84. Henke, Behrens. The economic cost of illness in the FRG, 1980. *Health Policy* 1986; No. 5.
85. Hochban W, Brandenburg U, Peter JH. Surgical treatment of obstructive sleep apnea by maxillo-mandibular advancement. *Sleep* 1994; 17(7): 624–629.