Eur Respir J 2013; 41: 523–538
DOI: 10.1183/09031936.00226711

ERS/ESH TASK FORCE REPORT

Recommendations for the management of patients with obstructive sleep apnoea and hypertension

Gianfranco Parati, Carolina Lombardi, Jan Hedner, Maria R. Bonsignore, Ludger Grote, Ruzena Tkacova, Patrick Lévy, Renata Riha, Claudio Bassetti, Krzysztof Narkiewicz, Giuseppe Mancia and Walter T. McNicholas on behalf of the EU COST Action B26 members

ABSTRACT: This article is aimed at addressing the current state-of-the-art in epidemiology, pathophysiology, diagnostic procedures and treatment options for appropriate management of obstructive sleep apnoea (OSA) in cardiovascular (in particular hypertensive) patients, as well as for the management of cardiovascular diseases (in particular arterial hypertension) in OSA patients. The present document is the result of work performed by a panel of experts participating in the European Union COST (Cooperation in Scientific and Technological research) Action B26 on OSA, with the endorsement of the European Respiratory Society and the European Society of Hypertension. In particular, these recommendations are aimed at reminding cardiovascular experts to consider the occurrence of sleep-related breathing disorders in patients with high blood pressure. They are also aimed at reminding respiration experts to consider the occurrence of hypertension in patients with respiratory problems at night.

KEYWORDS: Arterial hypertension, continuous positive airway pressure treatment, guidelines, hypertension treatment, obstructive sleep apnoea

AFFILIATIONS
For a full list of author affiliations, please refer to the Acknowledgements.

CORRESPONDENCE
G. Parati
Dept of Cardiology
S. Luca Hospital
Istituto Auxologico Italiano IRCSS
Piazza Brescia 20
Milan 20159
Italy
E-mail: gianfranco.parati@unimib.it

Received:
Dec 27 2011
Accepted after revision:
Aug 23 2012

This article is aimed at addressing the current state-of-the-art in epidemiology, pathophysiology, diagnostic procedures and treatment options for appropriate management of obstructive sleep apnoea (OSA) in hypertensive patients, as well as for the management of arterial hypertension in OSA patients. The present document is the result of work performed by a panel of experts from different European countries participating in the European Union COST (Cooperation in Scientific and Technological research) Action B26 on OSA, with the endorsement of the European Respiratory Society and the European Society of Hypertension (ESH). For the readers' convenience, additional material is provided as online supplementary material.

The present recommendations have been prepared following a careful methodological approach, the details of which are also summarised in online supplementary material.

ASSOCIATION OF OSA WITH HYPERTENSION AND HYPERTENSION WITH OSA

Sleep-related breathing disorders include habitual snoring, OSA, central sleep apnoea (CSA), obstructive sleep apnoea syndrome (OSAS), *i.e.* OSA accompanied by daytime symptoms, Cheyne–Stokes breathing and sleep hypoventilation syndrome [1]. Obstructive breathing alterations during sleep are listed in table 1.

Since the first polysomnographic descriptions, OSA events at night are known to be accompanied by acute changes in cardiovascular parameters. These acute effects mainly include the occurrence of wide swings of blood pressure (BP) and heart rate, as a result of alternating obstructive apnoea and hyperventilation episodes during sleep [2].

OSA has been linked to long-term consequences. Untreated OSA not only increases the risk for car

For editorial comments see page 505.
This article has supplementary material accessible from www.erj.ersjournals.com

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

TABLE 1 Definitions of breathing alterations during sleep

Apnoea	Obstructive breathing event with complete upper airways obstruction (residual air flow <20% of the preceding period of stable breathing, *i.e.* reduction in air flow >80%)
	Each event should last at least 10 s
Hypopnoea	Obstructive breathing event with a reduction of airflow between 70% and 20% of the preceding period of stable breathing
	Each event should last at least 10 s
RERA: **respiratory effort related arousal**	Events characterised by increased respiratory effort during sleep caused by flow limitation in the upper airways which is terminated by an arousal from sleep
	These events are typically not associated with significant hypoxaemia
AHI: apnoea/hypopnea index	Number of apnoeas and hypopneas per hour of sleep:
	Mild OSA: AHI 5–15 events·h^{-1}
	Moderate OSA: AHI 15–30 events·h^{-1}
	Severe OSA: AHI >30 events·h^{-1}
RDI: **respiratory disturbance index**	Summarises both the AHI and the RERA indices together
Snoring	A noise induced by vibration of the upper airways
	It is a symptom reflecting a compromised air flow in the upper airways and is complex to assess in a quantifiable manner
OSAS: obstructive sleep apnoea syndrome[#]	The combination of at least five obstructive breathing episodes per hour during sleep (apnoea, hypopnoea and RERA events) and the following diagnostic criteria (A and/or B to be fulfilled)
	A: Excessive daytime sleepiness that is not better explained by other factors
	B: Two or more of the following symptoms that are not better explained by other factors:
	Choking or gasping during sleep
	Recurrent awakenings from sleep
	Unrefreshing sleep
	Daytime fatigue
	Impaired concentration

[#]: it is important to distinguish between obstructive sleep apnoea (OSA) as a laboratory diagnosis and OSAS which represents the combination of OSA and symptoms as a fully established clinical syndrome.

accidents and worsens quality of life, mood and cognitive performance, but is also proposed as an additional and independent risk factor for cardiovascular diseases.

Indeed, OSA has been acknowledged as a novel, frequent and modifiable cause of systemic arterial hypertension in both European and US guidelines for the management of arterial hypertension. Scientific data and clinical awareness about the interaction between OSA and hypertension are continuously increasing. In particular, there is increasing evidence that diagnosis of an association between OSA and hypertension, as well as the need of their combined treatment, should be considered in patients with refractory hypertension and non-dipping profile [3–5].

Because of its potential prognostic importance [6], the association between OSA and hypertension has been investigated through several study designs, such as cross-sectional [7–12] and longitudinal [13–15] studies in the general population, cross-sectional studies in OSA patients [16, 17], case–control studies [18] and questionnaire-based surveys in snorers [19–25]. Although part of such an association may be mediated by co-existing risk factors, such as obesity, a large body of evidence supports an independent role of OSA in the pathogenesis of daytime hypertension, even if this issue is still a matter of debate [13–15]. Prevalence of hypertension in OSAS patients ranges from 35% to 80%, and appears to be influenced by OSA severity. Over 60% of subjects with a respiratory disturbance index >30 were found to be hypertensive. Conversely, approximately 40% of hypertensive patients are diagnosed with OSA [26].

Several factors may affect the relationship between BP and OSA, including age and sex [27, 28]. OSA is associated with hypertension more strongly in young to middle-aged adults (<50 yrs of age) than in older adults [13, 29], as confirmed by population-based cross-sectional [7] and longitudinal [13] studies. A significant role of OSA on BP regulation in children has been also suggested, although the body of evidence is still limited compared to data in adults [30–32].

A specific condition for which an association has been suggested between high BP and sleep-disordered breathing is pregnancy-related hypertension, but the studies on this issue suffer from some methodological limitations (small sample size and few polysomnographic studies) [33–35]. Thus, further studies on this issue are needed. In this context, a recent study on 220 pregnant females has shown that OSA (although identified only using Berlin and Epworth scales) is related to hypertension independently of obesity. In this study among non-obese (body mass index (BMI) <30 kg·m^{-2}) pregnant females, frequency of pre-eclampsia was significantly higher among those with OSA (adjusted OR 6.58, 95% CI 1.04–38.51; p=0.035) [36].

The pathogenetic link between obstruction of upper airway during sleep and hypertension during pregnancy is also supported by the positive effects of continuous positive airway

pressure (CPAP) on BP levels in pregnant hypertensive females [37, 38]. Accordingly, treatment of OSA in pregnant females should be undertaken along the same lines as for non-pregnant patients, although treating pre-eclampsia with CPAP cannot be recommended as a routine procedure.

MECHANISMS OF INCREASED CARDIOVASCULAR RISK IN OSA PATIENTS

Given the independent link between OSA and hypertension described above, it is important to define the mechanisms that might be responsible for it, as well as for the relationship between OSA and target organ damage and for the increased cardiovascular risk reported in these patients. Among the possible mechanisms, the following should be considered with particular attention.

Autonomic alterations

OSA patients are characterised by a derangement in autonomic cardiovascular regulation both during the night and during the day. During apnoeic episodes an increase in efferent sympathetic neural activity occurs, as shown by microneurographic studies in humans and by experimental studies in animals [39]. This increase in sympathetic activity is largely due to chemoreflex stimulation, triggered by the reduction in arterial oxygen pressure and by hypercapnia occurring during each apnoeic episode, and represents one of the major factors responsible for the increases in BP and heart rate that accompany resumption of ventilation after each apnoeic episode.

The hypoxic and hypercapnic reflexes triggered by apnoeic events, through involvement of central autonomic neural mechanisms, generate an increase of sympathetic nerve activity and cyclical changes in parasympathetic cardiac modulation, as documented by the increases in noradrenaline plasma levels and muscle sympathetic nervous activity during wakefulness and sleep, as well as by the increase in the spectral components of heart rate variability that reflect sympathetic activations and by the decrease of spontaneous baroreceptor reflex sensitivity in severe OSA patients.

The repeated occurrence of OSA and of the associated intermittent hypoxemia over prolonged time-periods are known to chronically activate the sympathetic nervous system through the resulting chemoreflex activation, and are also associated with a blunting of cardiovascular reflexes with afferent fibres stemming from baroreceptor or pulmonary receptors. In particular, the sensitivity of baroreflex control of the heart has been shown to be depressed in OSAS during different sleep stages [40], an alteration that is secondary to the chemoreflex activation by intermittent hypoxia, and contributes to both the acute and chronic increases in BP and heart rate observed in OSA patients. The reduction of baroreflex sensitivity in OSA has been shown to improve after chronic treatment with CPAP [41]. The degree of autonomic impairment occurring at night in OSA may also have an impact on daytime symptoms and has been proposed as a marker of excessive daytime sleepiness [42].

Altered mechanics of ventilation: acute physiologic effects of negative intrathoracic pressure

In patients with sleep-disordered breathing, ineffective inspiratory efforts are a hallmark of obstructive events. The interruption of airflow, despite persisting vigorous respiratory efforts against the occluded airway, leads to abrupt progressive decreases in intrathoracic pressure, which may have important effects on ventricular loading conditions as well as on autonomic cardiac modulation (due to stimulation of vagal thoracic afferent).

Renin–angiotensin–aldosterone system and sleep apnoea

There are very limited data trying to correlate OSA with various markers of renin–angiotensin–aldosterone system activity, based on studies of insufficient size [43, 44]. It has also been claimed that OSA might increase aldosterone secretion, and that this might be one of the mechanisms of the resulting resistant hypertension [26]. However, a recent paper suggests that antagonism of mineralcorticoid receptors by spironolactone reduces the apnoea/hypopnoea index (AHI), affecting the number of both central and obstructive events [45]. Whether increased aldosterone levels may help explain the interactions between OSA and resistant hypertension is an important question, and one that has been explored by CALHOUN *et al.* [26]. In a study utilising polysomnographic diagnosis of sleep apnoea, they reported that there was a positive correlation between plasma aldosterone concentrations and OSA severity, but that this was only true for patients with resistant hypertension. No relationship between plasma aldosterone and sleep apnoea severity was noted in normotensive control subjects [46]. Thus, whether sleep apnoea plays a role in increasing aldosterone levels *per se* remains to be ascertained. In general, more evidence is needed on the relationship between the activity of the renin–angiotensin–aldosterone system and OSA.

Endothelial dysfunction

Endothelial dysfunction has also been shown to occur in OSA patients in studies that assessed forearm vascular flow, intima-media thickness, carotid–femoral pulse-wave velocity, number of circulating endothelial progenitor cells and vascular endothelial growth factor. A role for this dysfunction in the pathogenesis of cardiovascular complications in OSA has been supported by various experimental studies carried out with proper methodology [47]. Several studies have also suggested hypercoagulability in patients with OSA, but these investigations were generally limited by small numbers and/or inadequate control for potential confounding variables such as obesity and smoking [48, 49]. However, the functional importance of these potential changes in OSA patients remains unknown, and it cannot be excluded that the observed cardiovascular changes might be unrelated to endothelial dysfunction.

Inflammation

The current interest in inflammatory components of cardiovascular risk has stimulated studies showing that in OSA patients there is an activation of reactive oxygen species. Apnoea-induced cyclic hypoxia and re-oxygenation in OSA generate reactive oxygen species and oxidative stress, increase circulating levels of adhesion molecules and also preferentially activate nuclear factor-κB and related cytokines, such as tumour necrosis factor-α and interleukin-8, thus promoting inflammation [47]. This may contribute to the increased cardiovascular risk typical of OSA patients, given the suggested role of inflammation in the development of atherosclerosis. However, studies focusing on

whether blocking the inflammatory reactions might also reduce the cardiovascular complications of OSA would be required.

Metabolic factors

OSA and metabolic syndrome and/or type 2 diabetes frequently co-exist and potentially interact metabolically and haemodynamically. Solid evidence suggestive of impaired glucose tolerance in OSA is available, dealing mainly with insulin resistance [49, 50]. Moreover, it has been suggested in a smaller number of studies that OSA patients also show a higher degree of leptin resistance compared with non-OSA subjects. However, the possibility of an independent relationship of leptin and other adipocytokines (such as adiponectin and ghrelin) with OSA requires further investigation [49, 51, 52].

Genetic aspects of hypertension in OSA

The genetic contribution to differences in BP is thought to amount up to 30–40%. From family and epidemiological studies it is clear that a complex interplay between heritable and environmental factors such as dietary sodium intake, alcohol consumption, stress and body weight results in final expression of hypertension [53, 54]. Limited data on the genetic contribution to the association between OSA and hypertension is available. The presence of gene polymorphisms potentiating hypertension may or may not be shared between patients with OSA and those with essential hypertension. Candidate gene studies have only been performed to date in the OSA population; they are generally small, the patients have been poorly phenotyped and most results have not been replicated. A summary of these studies has recently been published [55].

CARDIOVASCULAR EVENTS AND ORGAN DAMAGE IN OSA PATIENTS

Severe untreated OSA (AHI >30 events·h^{-1}) has been linked to fatal and nonfatal cardiovascular events, and all-cause mortality. This association is not convincing in the subgroup of subjects with mild OSA. Moreover visceral fat volume contributes to cardiovascular risk even after controlling for BMI and waist circumference. Thus, despite efforts to control for obesity as a covariate, there is the lingering concern that there could be differences in the degree of visceral obesity between those with OSA who died and those who did not [56–60].

Ischaemic heart disease

Published prospective and cross-sectional reports suggest an association between OSA and coronary artery disease and that untreated OSA may adversely influence prognosis in patients with coronary artery disease. However, the interpretation of these data is still controversial because the link between OSA and coronary artery disease could be related to age and obesity. In the Sleep Heart Health study, after adjustment for multiple risk factors, OSA was a barely significant predictor of incident coronary heart disease (myocardial infarction, revascularisation procedure, or coronary heart disease death) in males up to 70 yrs of age (adjusted HR 1.10, 95% CI 1.00–1.21; per 10-unit increase in AHI) but not in older males or in females of any age [61, 62].

Sleep apnoea and stroke

In a Swedish cohort (182 middle-aged males), severe OSA was associated with a very high cardiovascular risk (>10 yrs), 14% of this group were predicted to experience a stroke and 23% a myocardial infarction (36% combined risk) [63].

Prospective data in a larger population confirmed that in a community-based sample of middle-aged and older adults (5,422 participants without a history of stroke at the baseline examination and untreated for sleep apnoea, who were followed for a median of 8.7 yrs), incident cardiovascular disease, including stroke, was significantly associated with sleep-disordered breathing in males [64].

A survey on 6,424 patients of the Sleep Heart Health Study showed a relative stroke risk of 1.58 for patients with an AHI >10 events·h^{-1} compared to patients without sleep apnoea [65]. Moreover, in another prospective cohort study, patients with an AHI >10 events·h^{-1} had an increased relative combined stroke and death risk of 1.97 in 3-yr follow-up, increasing to 3.3 when AHI was >36 events·h^{-1} [60].

Finally, a recent evidence-based study has concluded that OSA increases the risk of stroke independently of other cerebrovascular risk factors [66].

Congestive heart failure

Recent studies show that untreated sleep apnoea may promote left ventricular dysfunction, disease progression, and increased mortality in heart failure patients [67]. In the Sleep Heart Health Study the presence of OSA conferred a 2.38 relative risk in the likelihood of having heart failure, independent of other known risk factors [61]. However, since most data were obtained in elderly patients, the role of OSA in increasing the risk for heart failure in relatively young patients is uncertain.

Target organ damage

Strong evidence has been obtained on the crucial role of target organ damage in determining the cardiovascular risk of individuals with high BP. Methods for evaluating organ damage are mentioned in detail in the recent ESH/European Society of Cardiology (ESC) hypertension guidelines and reappraisal [3, 4]. Data are also available showing that OSA may favour appearance of hypertension-related organ damage.

Blood vessels

OSA and hypertension are independently associated with increased stiffness of large arteries that may contribute to left ventricular (LV) remodelling. Subjects with OSA were shown to have higher values of aortic stiffness, and lower large artery distensibility than controls. However, given the cross sectional nature of most available observations, it is still to be clarified whether an increased arterial rigidity in OSA is the result of OSA-related hypertension or, on the contrary, whether an increased arterial stiffness contributes to BP elevation in this condition. A blunted endothelium-dependent dilatation, increased carotid intima-media thickness and increased aortic stiffness, all known early signs of atherosclerosis, have been observed in patients with OSA [68].

Heart

Compared with normotensive subjects without OSA, left atrial diameter, interventricular septal thickness, LV posterior wall thickness, LV mass index and prevalence of LV hypertrophy were increased to a similar extent in normotensive patients

with OSA and in patients with hypertension without OSA, with a significant further increase in subjects affected by both OSA and hypertension [69, 70].

Both right ventricular and LV systolic and diastolic functions are impaired in patients with OSA with or without hypertension [71]. Thus, OSA, independently of obesity and of hypertension, may induce cardiac changes that could predispose to atrial fibrillation and heart failure [70].

Cardiovascular diseases leading to pacemaker implantations are suspected of being associated with a high rate of undiagnosed OSA [72]. After treatment with CPAP, significant improvements were observed in cardiac symptoms and in haemodynamic parameters, as well as in left and right ventricular morphology and function [73–75].

Urinary albumin excretion

The prevalence of OSA in patients with chronic kidney diseases is higher than in the general population, and an association between OSA and proteinuria, as well as an improvement of proteinuria after OSA treatment, have been described previously. However, whether such a link is independent of BMI and BP values is still controversial. Thus, the relationship between proteinuria and OSA warrants further evaluation [76, 77].

Retina

Alterations in retinal vascular function resulting from OSA and arterial hypertension can impair optic nerve function, leaving it vulnerable to ischaemic events. Some eye disorders may occur in association with OSA including: non-arteritic anterior ischaemic optic neuropathy; papilledema secondary to raised intracranial pressure; and an optic neuropathy with an associated visual field defect that may mimic glaucoma. There is conflicting evidence as to whether an association exists between OSA and glaucoma [78, 79].

SLEEP-RELATED BREATHING DISORDERS IN PATIENTS WITH CARDIO- AND CEREBROVASCULAR DISEASES

Congestive heart failure

The sleep-related breathing disorder commonly linked to heart failure is CSA [80] but the prevalence of OSA in congestive heart failure patients is relatively high (between 10% and 25%), possible due to upper airway narrowing by fluid accumulation in the neck while supine [81]. Prevalence of OSA in congestive heart failure is likely to increase because of the emerging epidemics of obesity [82]. Untreated OSA is associated with an increased risk of death independently of confounding factors in patients with congestive heart failure [83].

Stroke

Prevalence of breathing alterations during sleep is higher in patients with acute ischaemic stroke or transient ischaemic attacks (50–70%) than in the general population [84, 85], both because stroke may favour occurrence of OSA and because OSA may be a risk factor for stroke. This should be considered when assessing and treating stroke patients.

CSA and central periodic breathing or Cheyne–Stokes breathing may appear in up to 30–40% of acute stroke patients [84–87], reflecting a new-onset stroke-associated condition. In the transition from the acute to the sub-acute phase of stroke sleep apnoea tends to improve, but >50% of patients still exhibit an AHI $\geqslant$10 events·h^{-1} 3 months after the acute event [87–90], because obstructive events improve less than central ones [87].

Little is known about the clinical relevance of OSA in the acute phase (first few days) of ischaemic stroke, and the limited information available suggests an association between OSA severity and stroke severity [86, 91]. Considering the evolution in the weeks/months following stroke, sleep-related disordered breathing was shown to be associated with duration of hospitalisation [91, 92], increased mortality [93–95] and poor functional outcome [91, 96].

DIAGNOSTIC ASPECTS

Diagnosing OSA in patients with hypertension

The diagnosis of OSA(S) is based on the composite of symptoms, clinical findings and an overnight recording of sleep and breathing parameters. Sleep-disordered breathing events are well defined according to international guidelines [97]. The frequency of event occurrence during sleep is referred to as the AHI, while the respiratory disturbance index is the sum of the AHI and the respiratory effort related arousal indices (table 1).

Tables 2 and 3 provide the definition of OSAS by the American Academy of Sleep Medicine [98] and the diagnostic criteria listed in the International Classification of Sleep Disorders [1], respectively. Detailed symptoms and signs are summarised in table 4. A proposed diagnostic algorithm is showed in figure 1.

Patient history and questionnaires

A structured interview or specific questionnaires can be helpful in the routine assessment of the clinical features of OSA(S) in patients with arterial hypertension [99, 100]. However, it has been clearly demonstrated that their sensitivity and specificity for the daytime assessment of OSA(S) and excessive daytime sleepiness is insufficiently low [101]. Methods for the objective assessment of daytime sleepiness are available in the online supplementary material.

Technical devices for the classification and quantification of sleep-disordered breathing

The methods for diagnosing OSA include polysomnography (level 1 and 2 devices), polygraphy (level 3 device) and limited channel (level 4) devices (table 5).

Diagnosing hypertension in patients with OSA: assessment of OSA contribution to resistant hypertension

The 2007 ESH/ESC hypertension management guidelines define resistant or refractory hypertension as a condition where a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses has failed to lower systolic and diastolic BP to goal [3]. This definition is in line with that provided by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP [5], which defined resistant hypertension as ''the failure to attain goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic.'' [3–5]. In specialised hypertension clinics the prevalence of resistant hypertension ranges from 5% to 18% of the hypertensive population. Patients with drug-resistant hypertension are at greater risk for stroke, renal insufficiency and comorbid

TABLE 2 American Academy of Sleep Medicine definition of obstructive sleep apnoea syndrome

A combination of at least five obstructive breathing episodes per hour during sleep (apnoea, hypopnoea and respiratory effort related arousals events) and at least one of the following criteria:

A. Excessive daytime sleepiness that is not better explained by other factors

B. Two or more of the following symptoms that are not better explained by other factors:

- Choking or gasping during sleep
- Recurrent awakenings from sleep
- Unrefreshing sleep
- Daytime fatigue
- Impaired concentration

This table was prepared following the criteria developed by the American Academy of Sleep Medicine [98].

cardiovascular events than patients whose BP is well controlled by medical therapy.

Several studies have addressed the potential contribution of OSA to the development and/or persistence of resistant hypertension. Refractory hypertension in patients with OSA is primarily systolic and relatively more pronounced at night [102–104]. Since the night-time systolic BP predicts cardiovascular morbidity and mortality even more accurately than daytime systolic BP, nocturnal increases in systolic BP due to OSA may have particular adverse effects in patients with refractory hypertension.

The evaluation of OSA patients with resistant hypertension should focus on identification of contributing factors and exclusion of other causes of secondary (resistant) hypertension. A diagnosis of OSA should be considered in patients with clinical and biochemical evidence of catecholamine excess in whom a catecholamine-producing tumour cannot be identified. Diagnostic evaluation for other identifiable causes should be tailored for each patient and guided by signs and symptoms.

True resistant hypertension must be distinguished from apparently resistant hypertension, commonly due to a "white coat hypertension" or "isolated office hypertension'' condition (BP elevated in the office environment but normal out of the office). Failure to use appropriate cuffs on large arms of OSA patients might also lead to a serious overestimation of BP values and to a false diagnosis of resistant hypertension. To identify a white coat hypertension phenomenon as well as to investigate the day and night BP profile, ambulatory BP monitoring (ABPM), which improves prediction of cardiovascular risk in hypertensive patients, should be considered in every OSA patient, in particular when resistance to drug treatment is suspected. When using ABPM, the impact of sampling interval in reliably assessing night-time BP has been studied by MARRONE *et al.* [105], with BP measurements set at intervals of 5, 10, 15, 20 and 30 min. A larger number of inaccurate nocturnal mean BP estimates were obtained in OSAS patients than in control subjects. The authors concluded that OSA patients require more frequent BP measurements to obtain a similar accuracy in nocturnal BP evaluation.

In OSA patients, severity of hypertension might not only be overestimated in the case of white coat hypertension, but it might also be underestimated if BP is assessed by office readings only [106], because BP could be normal in the office but frequently elevated outside the doctor's office, in particular during night sleep (a form of the so called "masked hypertension").

The occurrence of both white coat and masked hypertension requires out-of-office BP monitoring to be regularly implemented in OSA patients. This could be obtained through the use of 24-h ABPM and, in some cases, home BP monitoring [107]. However, the role of home BP monitoring in quantifying

TABLE 3 International Classification of Sleep Disorders (ICSD) diagnostic criteria for obstructive sleep apnoea

A. At least one of the following applies:

1) The patient complies of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue or insomnia;

2) The patient wakes up with breath holding, gasping or chocking; or

3) The bed partner reports loud snoring, breathing interruptions or both during the patient's sleep.

B. Polysomnographic recording shows the following:

1) Five or more scoreable respiratory events (*i.e.* apnoea, hypopnoea or RERA) per hour of sleep;

2) Evidence of respiratory effort during all or a portion of each sleep event.

OR

C. Polysomnographic recording shows the following:

1) $\geqslant$15 or scoreable respiratory events (*i.e.* apnoea, hypopnoea or RERA) per hour of sleep:

2) Evidence of respiratory effort during all or a portion of each sleep event.

D. The disorder is not explained by another current sleep disorder, medical or neurological disorder, medication use or a substance abuse disorder

For obstructive sleep apnoea diagnosis A, B and D or C and D must be fulfilled. RERA: respiratory effort related arousals. This table was prepared by our group based on ICSD-2 [1].

TABLE 4 Clinical symptoms, characteristics and objective findings suggesting a high probability for obstructive sleep apnoea syndrome

1) OSA related symptoms and clinical signs
Night-time
Witnessed apnoeas
Loud, frequent and intermittent snoring
Dry mouth
Thirsty during the night
Nocturnal diuresis
Choking; dyspnoea
Disturbed sleep
Sweating; nasal congestion (preferably night-time)
Family history of snoring and sleep apnoea
Daytime
Increased daytime sleepiness
Daytime fatigue
Concentration difficulties
Monotony intolerance
Morning pain in the throat
Headache (preferably in the morning hours)
2) Frequent clinical characteristics
Male sex
Post-menopausal females
Overweight, preferably central obesity[#] (linkage between history of obesity and snoring/witnessed apnoeas/sleepiness)
History of cardiovascular disease (ischaemic heart disease, stroke or heart failure, probability of OSA 30% to >50%)
Upper airway anatomic abnormalities (enlarged tonsils and uvula, adenoids and macroglossia, according to Friedman classification stage III)
Retrognathia
3) Objective findings in the cardiovascular/metabolic risk assessment of hypertensive patients
Refractory hypertension (likelihood of OSA 50% to >80%)
Nocturnal non-dipping of 24-h blood pressure
Left ventricular hypertrophy
Generalised atherosclerotic disease
Holter ECG (nocturnal bradycardia/tackycardia, SA and AV blocks during the sleep period, increased occurrence of SVES/VES during sleep period, atrial fibrillation, paroxysmal nocturnal atrial fibrillation)
Metabolic disease like diabetes mellitus

OSA: obstructive sleep apnoea. [#]: *e.g.* body mass index >30 kg·m^{-2} indicates a 50% probability of OSA, and neck circumference >17 inch in males and 16 inches in females.

BP elevation in OSA patients is still under evaluation [107–109]. In general, ABPM should be preferred to home BP monitoring due its ability to provide detailed information on BP during night-time when OSA episodes occur. Although night-time BP can now be obtained with a few recent devices for home BP monitoring, this information is limited by a very low sampling frequency.

Different types of BP measurements in OSA patients

BP changes can be monitored both in a clinical setting and in daily life, using various techniques aimed at measuring BP in a more continuous way and, thus, exploring different BP variability components, including the circadian changes in BP whose alteration is known to occur frequently in OSA patients.

As previously mentioned in this document, the physiological reduction in BP during sleep is frequently blunted in OSA [110]. This occurs both in normotensive and hypertensive OSA subjects. Thus, BP may be increased during the night, resulting in different ratios between evening and morning values when ambulatory or only clinic/home BP measurements are reported. This difference has been found to be related to the severity of sleep apnoea, although limited to males [111]. Systolic BP values, but not pulse pressure, have been found to correlate with AHI when BP elevation is quantified in terms of mean BP, but not in terms of pulse pressure [112].

In addition to ABPM and home BP monitoring, other methods for BP assessment have been used in OSA. Continuous BP measurements can be obtained using beat-to-beat BP recording with photoplethysmographic finger cuff devices (*e.g.* Finapres, Finometer or Portapres; Finapres Medical Systems, Amsterdam, the Netherlands), which allow a more detailed quantification of possible changes in BP variability in patients affected by OSA. Finally, another indirect technique, based on assessment of pulse transit time, has been suggested to reflect BP changes [113], but this technique still needs proper validation according to international protocols [4, 107].

The features of the most common BP measurement techniques used in diagnosing hypertension in OSA are summarised in table 6 and additional information can be found in the online supplementary material. A possible flow chart indicating when to perform ABPM in OSA patients with suspected hypertension is reported in figure 2.

MANAGEMENT OF OSA AND ASSOCIATED HYPERTENSION

Lifestyle changes

Lifestyle changes should be considered as an integral part in the management of all patients with OSAS, including hypertensive OSAS, since obesity and a sedentary lifestyle are very common in such patients. Patients with mild OSAS may be adequately managed by this intervention alone. Patients with mild OSA should be instructed to avoid sleeping in the supine position when polysomnographic recordings demonstrate OSA events to occur in such a posture.

Obesity and weight loss

However, while the link of excess weight and obesity with OSA has long been accepted, it is conversely still debated how much a weight-reduction programme can improve OSA and reduce BP [114]. Surprisingly, there are no large-scale controlled trials on the effects of weight loss in OSA. Only smaller scale studies of dietary [115], surgical [116] or pharmacological [117] weight loss have consistently shown that considerable reduction of various indices of OSA severity is obtained by weight loss. In an observational study, a weight loss of 10% predicted a 26% (95% CI 18–34%) decrease in AHI [114]. However, information on BP changes was provided in only a few of these small-scale observational studies, and even massive weight loss and the related reduction of OSA was found to result in proportionally modest and sometimes nonsignificant reductions of BP [117, 118] .

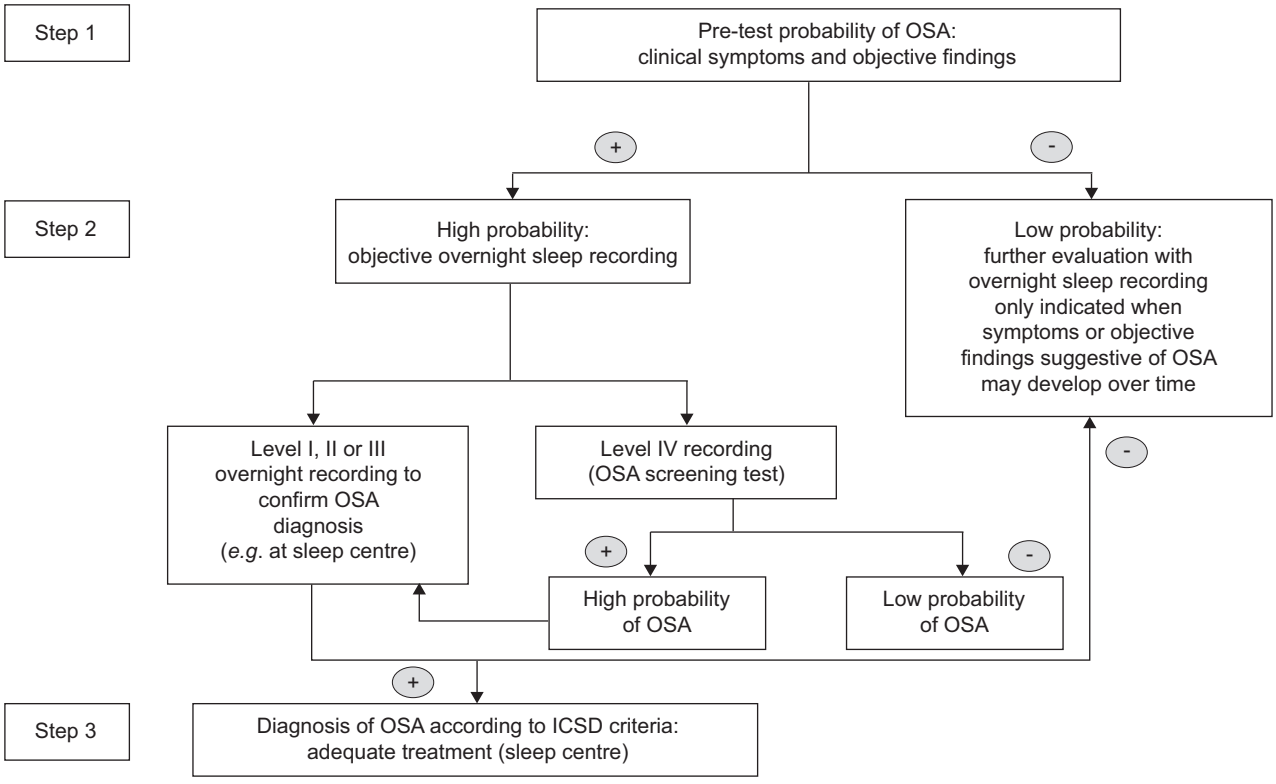

FIGURE 1. Proposed diagnostic algorithm for obstructive sleep apnoea (OSA). ICSD: International Classification of Sleep Disorders.

It remains unclear why hypertension in obese subjects with OSA appears to be proportionally resistant to weight loss in spite of the sometimes pronounced effects on OSA severity. One possibility is that obesity, hypertension and OSA share a common trait that characterises at least a subgroup of patients with sleep-disordered breathing. An additional factor to be considered is the type of BP measurement used. Objective and reproducible BP were employed measurements in only a minority of cases, such as home and ambulatory BP monitoring. Other factors potentially interfering with the BP effects of weight loss and reduction in OSA severity include duration of hypertension and occurrence of target organ damage, because the occurrence of structural cardiovascular changes in patients with long lasting hypertension might make the BP elevation less sensitive to a nonpharmacological treatment.

Ethanol

Ethanol ingestion increases the frequency and duration of apnoeas because of the combined effects of reducing upper airways muscle tone and depressing the arousal response. It is also known that moderate to heavy alcohol consumption may lead to a BP increase, both in normotensive and in hypertensive

TABLE 5 Diagnostic tools for the evaluation of obstructive sleep apnoea syndrome

Levels of sleep monitoring	Type of monitoring device and setting	Parameters measured
Level 1	Attended in-lab polysomnography	Polysomnography including electroencephalogram, electromyogram, electrocardiogram or heart rate, airflow, respiratory effort, and oxygen saturation Additional externally assessed parameters can be included (*e.g.* blood pressure, oesophageal pressure, transcutaneous CO_2 and video surveillance) Investigation performed in the sleep lab under continuous supervision
Level 2	Unattended polysomnography in the hospital/ sleep unit or at home	Polysomnography including electroencephalogram, electromyogram, electrocardiogram or heart rate, airflow, respiratory effort, and oxygen saturation Investigation performed without any supervision
Level 3	Polygraphic limited channel recording, mainly modified portable sleep apnoea monitoring	Minimum of four channels including ventilation or airflow (at least two channels to detect respiratory movements or respiratory effort and airflow, heart rate or electrocardiography, and oxygen saturation)
Level 4	Single or two channel device	One or two channels, typically including oxygen saturation or airflow

TABLE 6 Different types of blood pressure (BP) measurements used in diagnosing hypertension in patients with obstructive sleep apnoea

	Advantages	Limitations
Office BP measurement	Cornerstone in the approach to hypertension diagnosis and management for over a century Easily available Related to outcome in large epidemiological and intervention studies	Intrinsic inaccuracy of the auscultatory technique (mainly for diastolic BP and in specific populations) Observer's bias and digit preference Only isolated measurement allowed Interference by white coat effect Inability to account for physiological BP variability No information on nocturnal BP
Home BP monitoring	A number of measurements during the day and also over several days, weeks or months are possible; assessment of treatment effects at different times of the day and over extended periods No alarm reaction to BP measurement Good reproducibility Good prognostic value Relatively low cost Patient friendliness (in semiautomatic devices) Involvement of patient in hypertension management Possibility of digital storage, printout, PC download or tele-transmission of BP values (in some devices/systems) Improvement of patients' compliance to treatment Improvement of hypertension control rates	Need of patient training (short for automated devices) Possible use of inaccurate devices Measurement errors Limited reliability of BP values reported by patients Induction of anxiety resulting in excessive monitoring Treatment changes made by patients on the basis of casual home measurements without doctor's guidance Normality thresholds and therapeutic targets still debated Lack of night recordings
24-ABPM	No observer bias and digit preference Large number of BP values available over 24 h in daily life particularly in true ambulatory conditions No alerting reaction to BP automated measurements (no white coat effect) Higher reproducibility of 24 h average BP No placebo effect Allows assessment of 24 h, daytime, night-time and hourly BP values Allows assessment of BP variability (although limited with discontinuous BP monitoring) Allows assessment of day to night BP changes (dippers, nondippers and extreme dippers); better if performed over repeated recordings 24 h average BP more closely related to target-organ damage of hypertension Superior prognostic value of 24 h, daytime or night-time average BP Allows assessment of effectiveness and time distribution of BP control by treatment over 24 h, also through mathematical indices (trough/peak ratio and smoothness index)	Possible inaccuracy of automated BP readings Interference with patient's daily activities Quality of sleep affected to a greater or lesser degree Limited reproducibility of hourly BP values Reference ''normal'' ambulatory BP values still under debate Need for more evidence on prognostic value of different ABPM parameters High costs
Beat-by-beat BP monitoring	Possibility to accurately assess beat-by-beat BP variability	Invasive methods: poorly suited to a clinical setting Noninvasive methods: possible inaccuracies due to pulse wave distortion in peripheral arteries, limited availability because of relatively high cost, need of expert operators

ABPM: ambulatory BP monitoring.

subjects. It has been suggested that a reduction in alcohol intake might help in reducing both OSA severity and its BP effects [3–5].

Exercise

While there are strong theoretical reasons to believe that a formal exercise programme may benefit OSA, there are remarkably few objective data on this subject. Indirect evidence on the relationship between exercise and OSA comes from the Wisconsin sleep cohort study, which showed that lack of exercise was associated with increased severity of sleep-disordered breathing even after adjustment for BMI [119]. GIEBELHAUS *et al*. [120] evaluated the impact of a 6-month structured exercise programme on OSA severity in a small group of OSA patients who were being treated concurrently

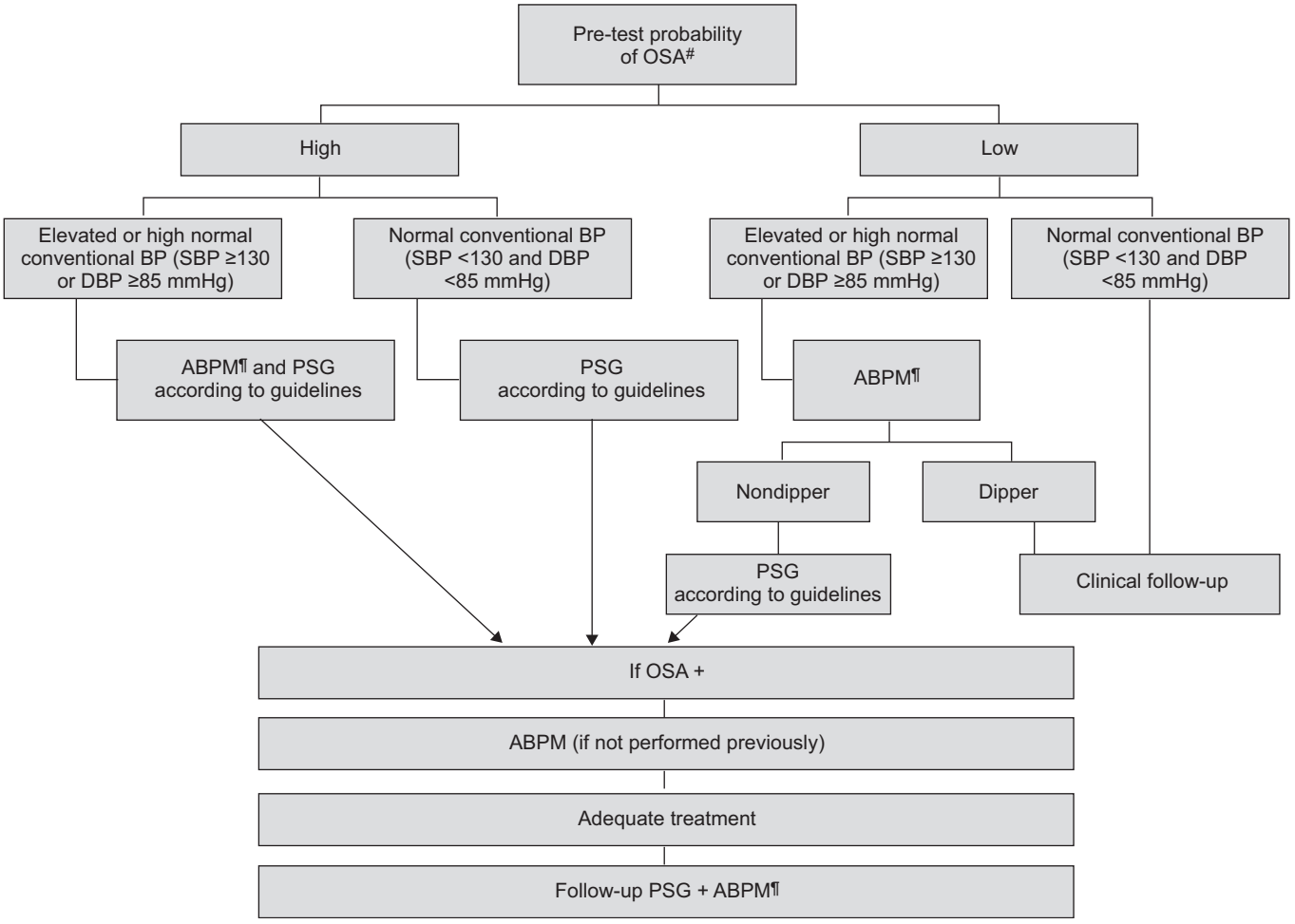

FIGURE 2. Proposed algorithm for the diagnostic management of patients with hypertension associated with obstructive sleep apnoea (OSA). BP: blood pressure; SBP: systolic BP; DBP: diastolic BP; ABPM: ambulatory BP monitoring; PSG: polysomnography. #: according to clinical evaluation and questionnaires, *e.g.* Epworth and Berlin; ¶: hypertension guidelines recommend use of home BP monitoring in most hypertensive patients.

with CPAP and demonstrated a reduction in AHI off CPAP compared to pre-therapy.

The possibility of specific exercise programmes targeting the upper airways dilating muscles has been considered, but there are no objective data to support the efficacy of such an approach. Nonetheless, regular aerobic exercise training has been reported to be associated with a BP reduction in hypertension [3–5].

Choice of antihypertensive drugs in hypertensive patients with OSA

The choice of antihypertensive medications in hypertensive patients with concomitant OSA may have specific implications for their optimal clinical management. The effects of antihypertensive agents on OSA activity are not uniform. Only a few studies compared different agents through parallel group or cross-over designs. Unfortunately, statistical power was usually poor due to low patient numbers. Although a decline in OSA severity may be associated with BP reduction, such reduction may also be possibly related to a direct effect of the drug itself [121]. Finally, effects of long-term treatment with certain antihypertensive agents on OSA severity have never been systematically addressed during clinical trials. In general, there is no obvious antihypertensive drug class which has repetitively demonstrated superior antihypertensive efficacy in OSA patients [43]. In summary, additional clinical research is needed in order to identify preferred compounds for an adequate BP control in this group of high-risk patients.

CPAP treatment in OSA patients with hypertension

Many studies have assessed the impact of active therapy of OSA on BP levels both in normotensive and hypertensive patients with variable results (table S1).

The various reports have employed widely different methodologies, ranging from short-term placebo-controlled protocols to long-term observational studies. Despite the widely differing methodologies, the overall findings of these reports is that CPAP therapy in OSAS results in a lowering of BP levels, which is most pronounced when assessed by ABPM and in patients with severe OSA that regularly use CPAP every night for at least 5 h per night and who have pre-existing hypertension. The benefit affects both systolic and diastolic BP, and is evident both during wakefulness and sleep.

Identification of daytime sleepiness as a factor associated with OSA and hypertension is not a new finding [42, 122]. While it has been debated whether CPAP therapy improves BP control in non-sleepy patients, a recent report by BARBÈ *et al*. [123] indicates a significant benefit of long-term CPAP therapy in OSA patients on BP levels, even among non-sleepy patients [124].

Four meta-analyses of studies of CPAP therapy in OSA have been published in recent years. BAZZANO *et al*. [125] included 16 randomised clinical trials published between 1980 and 2006 in their meta-analysis with a total of 818 participants, which compared CPAP to control, had a minimum treatment duration of 2 weeks and reported BP changes during the intervention or control period. Mean net change in systolic BP for those treated with CPAP compared with control was -2.46 mmHg, mean net change in diastolic BP was -1.83 mmHg and mean net change in mean arterial pressure was -2.22 mmHg. ALAJMI *et al*. [126] performed a comprehensive literature search up to July 2006 to identify 10 randomised controlled trials that included an appropriate control group and reported systolic and diastolic BP before and after CPAP or control. The analysis included data from 587 subjects. CPAP compared with control reduced systolic BP by 1.38 mmHg and diastolic BP by 1.53 mmHg. MO and HE [127] included randomised controlled trials published between 2000 to 2006 in both English and Chinese. Study inclusion criteria included treatment duration of at least 4 weeks and measurement of 24-h ABPM before and after CPAP or control (non-CPAP) periods. Seven studies with 471 participants were included. Overall, CPAP reduced 24-h systolic BP by 0.95 mmHg, 24-h diastolic BP by 1.78 mmHg, and 24-h mean BP by 1.25 mmHg. In the analysis by HAENTJENS *et al*. [128], only studies that had used 24-h ABPM assessments were included with 572 patients from 12 randomised placebo-controlled trials. CPAP treatment compared with placebo reduced 24-h systolic BP by 1.64 mmHg and 24-h diastolic BP by 1.48 mmHg. In a pre-specified meta-regression analysis, greater CPAP treatment-related reduction in 24-h mean BP was observed in subjects with more severe OSA and in those most adherent to the use of CPAP.

Effects of other specific OSA treatments besides CPAP

Limited evidence is available on the effects on BP of OSA treatment through surgical procedures or through use of oral appliances; an issue which deserves to be addressed in future studies [129–131]. Very preliminary data are available on the effects of renal sympathetic denervation through catheter ablation technique in OSA patients, suggesting a reduction of elevated BP of OSA severity and on glycaemic control in patients with resistant hypertension [75].

Treatment of OSA in patients with cardiovascular disease

Congestive heart failure

Only limited evidence is available on whether treatment of OSA improves mortality in congestive heart failure patients, but evidence has reported increased mortality in patients with untreated OSA and congestive heart failure. All evidence is in agreement that OSA treatment decreases mortality, albeit suspicion of OSA in congestive heart failure patients and its treatment are rare [132].

There is no consensus regarding treatment for CSA. Outcome studies focusing on cardiovascular end-points are still necessary to define management strategies for patients with congestive heart failure and either OSA or CSA [133–136].

Stroke

Several publications suggest that CPAP treatment could have favourable effects in stroke patients with OSA [137–141]. Despite this, CPAP acceptance represents a major problem in treating this type of patient. Previous studies have documented that only ~50% (45–70%) of patients can be put under CPAP treatment after stroke, and that only 15% remain under treatment during a 6-yr follow-up [88].

Very few data exist about CPAP treatment during acute stroke [142], but CPAP treatment can be taken into account individually, mainly in patients with mild-to-moderate neurological deficits, moderate-to-severe obstructive sleep apnoea (AHI >30 events·h^{-1}), and high cardiovascular risk profile.

In patients presenting predominantly with central apnoeas or central periodic breathing, oxygen may be beneficial. The benefit of a CPAP treatment in stroke patients with central apnoeas or central periodic breathing has not yet been proven. A novel method of ventilator support called ''adaptive servoventilation'' was shown to prevent central apnoeas in stroke patients with heart failure more efficiently than CPAP or oxygen [143].

PROBLEMS AND PERSPECTIVES

This article intends to provide a guide to the management of patients with both OSA and arterial hypertension, by gathering the information provided by available studies without a formal grading of the strength of the evidence provided. This is partly because the link between OSA and hypertension and OSA and cardiovascular risk represents an issue still under evaluation. In particular, more evidence from longitudinal trials is needed on the impact of OSA on cardiovascular risk in females, on the causal link between OSAS and arterial hypertension or diabetes mellitus and on the effects of OSA treatment with CPAP or other interventions on the reduction of BP level and, in general, on the reduction of patients' cardiovascular risk.

Additional issues to be investigated include patients' compliance with CPAP treatment, and the relationship between OSA and hypertension explored by the use of home and ambulatory BP monitoring. Probably because of the scanty use of these more correct BP measuring methodologies, the existence of a causal link between OSA and hypertension is still a matter of debate. Finally, as far as treatment of OSA is concerned, the number of randomised controlled trials has been too small, and we need more and larger prospective randomised trials to test the efficacy of CPAP and other therapeutic interventions in lowering BP. No trial has been of a sufficiently large size yet to investigate the really important issue as to whether OSA treatment has any beneficial effects on cardiovascular outcomes.

Nonetheless, while there are no doubts that the complex link between OSA, hypertension and cardiovascular risk deserves further studies, the available evidence is certainly sufficient to recommend greater attention both to the identification and to treatment of the BP increase associated with OSA, as well as to the detection of sleep-related breathing disorders in patients with a diagnosis of hypertension. Failure to do so is likely to limit the effectiveness of interventions aimed at reducing the

risk of cardiovascular events in patients followed-up either in sleep or in hypertension centres.

STATEMENT OF INTEREST

Statements of interest for J. Hedner and L. Grote can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

ACKNOWLEDGEMENTS

This report was endorsed by both the European Respiratory Society and the European Society of Hypertension. It is also published by the European Society of Hypertension: Parati G, Lombardi C, Hedner J, *et al*. Position paper on the management of patients with obstructive sleep apnea and hypertension: joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (Cooperation in Scientific and Technological research) ACTION B26 on Obstructive Sleep Apnea. *J Hypertens* 2012; 30: 633–646.

The author affiliations are as follows. G. Parati: Dept of Clinical Medicine and Prevention, University of Milano-Bicocca, and Dept of Cardiology, S. Luca Hospital, Istituto Auxologico Italiano IRCCS, Milan, Italy; C. Lombardi: Dept of Cardiology, S. Luca Hospital, Istituto Auxologico Italiano IRCCS, Milan, Italy; J. Hedner: Sleep Disorders Centre Sahlgrenska University Hospital, Gothenburg, Sweden; M.R. Bonsignore: Dept of Medicine, Pneumology, Physiology and Nutrition (DIMPEFINU), University of Palermo, Palermo, Italy; L. Grote: Sleep Disorders Centre Sahlgrenska University Hospital, Gothenburg, Sweden; R. Tkacova: Dept of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P J Safarik University L. Pasteur Teaching Hospital, Kosice, Slovakia; P. Lévy: Grenoble University Hospital, CHU Michallon, Grenoble, France; R. Riha: Dept of Sleep Medicine, Royal Infirmary Edinburgh, Edinburgh, UK; C. Bassetti: Dept of Neurology, University Hospital Zurich, Zurich, Switzerland; K. Narkiewicz: Dept of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland; G. Mancia: Dept of Clinical Medicine and Prevention, University of Milano-Bicocca, Milan, Italy; W.T. McNicholas: Respiratory Sleep Disorders Unit, St Vincent's University Hospital, Conway Research Insitute, University College, Dublin, Ireland.

The committee members of the COST Action B26 are as follows. W.T. McNicholas (Chairman; St Vincent's University Hospital, Dublin, Ireland); A. Alonderis (Institute of Psychophysiology and Rehabilitation, Palanga, Lithuania); F. Barbé Illa (Hospital Arnau de Vilanova, Lleida, Spain); M.R. Bonsignore (University of Palmero, Palermo, Italy); P. Calverley (Univeristy Hospital Aintree, Liverpool, UK); W. De Backer (University Hospital Antwerp, Edegem, Belgium); K. Diefenbach (Interdisciplinary Center of Sleep Medicine, Charite Universitaetsmedizin, Berlin, Germany); V. Donic (Faculty Of Medicine, Safarik University, Kosice, Slovakia); I. Fietze (Center of Sleep Medicine, Charite Universitaetsmedizin, Berlin, Germany); K. Franklin (Dept of Surgery, Umea University, Umea, Sweden); T. Gislason (University of Iceland, Medical Faculity, Reykjavik, Iceland); L. Grote (Sleep Disorders Centre Sahlgrenska University Hospital, Gothenburg Sweden); J. Hedner (Sleep Disorders Centre Sahlgrenska University Hospital, Gothenburg Sweden); P. Jennum (Danish Center for Sleep MedicineGlostrup University Hospital, Glostrup, Denmark); P. Lavie (Diagnostic Sleep Laboratory, Faculty of Medicine, Haifa, Israel); P. Levy (Grenoble University Hospital, Grenoble, France); W. Mallin (LKH Enzenbach, Vienna, Austria); J. Montserrat (Hospital Clinico Respiratorio, Barcelona, Spain); E. Papathanasiou (The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus); G. Parati (Dept of Cardiology, S. Luca Hospital, Istituto Auxologico Italiano IRCCS, Milan, Italy); T. Penzel (Center of Sleep Medicine, Charite Universitatsmedizin, Berlin, Germany); P. Pinto (Faculdade de Ciencias Medicas/Universidade Nova de Lisboa, Lisbon, Portugal); M. Pretl (Dept of Neurology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic); R. Riha (Dept of Sleep Medicine, Royal Infirmary Edinburgh, Edinburgh, UK); D. Rodenstein (Cliniques Universitaires Saint-LucFaculte de Medecine, Universite Catholique de Louvain, Brussels, Belgium); T. Saaresranta (University of Turku, Sleep Research Unit, Medical Faculty, University of Turku Dentalia, Turku, Finland); J. Saponjic (Institute for Biological Research-Sinisa Stankovic, University of Belgrade, Belgrade, Serbia); R. Schulz (University of Giessen Lung Center, Giessen, Germany); P. Sliwinski (National Research Institute of Tuberculosis and Lung Diseases, Warsaw, Poland); Z. Tomori (University of P.J. Safarik, Kosice, Slovakia); P. Tonnesen (Hospital Copenhagen, Hellerup, Denmark); G. Varoneckas (Institute of Psychophysiology and Rehabilitation, Palanga, Lithuania); J. Verbraecken (University Hospital Antwerp, Antwerp, Belgium); J. Vesely (Pathological Physiology Medical Faculty, Palacky University, Olomouc, Czech Republic); A. Vitols (Institute of Cardiology, University of Latvia, Riga, Latvia); J.Z. Zielinski (National Research Institute of Tuberculosis and Lung Diseases, Warsaw, Poland).

The authors acknowledge the contribution by V. Somers (Division of Cardiovascular Diseases, Dept of Internal Medicine, Mayo Clinic and Foundation, Rochester, MN, USA) and by M. Siccoli (Dept of Neurology, University Hospital Zurich, Zurich, Switzerland).

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