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# Sleep-disordered breathing: clinical features, pathophysiology and diagnosis

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## Summary

In recent decades, the association between sleep-disordered breathing (SDB) and cardio- and cerebrovascular diseases (including hypertension, coronary heart disease and stroke) has been the focus of interest of both clinicians and researchers. A growing concern is the increasing prevalence of SDB in the general population, which can be partly explained by the rise in obesity prevalence and population aging, as well as by the development of enhanced diagnostic tools and approaches. Because of evidence of adverse long-term effects of SDB on cardiovascular morbidity and overall mortality, systematic screening for SDB should be considered for populations at risk. The evidence of a long-term benefit of treatment for SDB, however, is still controversial and the best management approaches are still unclear.

This article summarises available epidemiological data and focuses on the main pathophysiological mechanisms linking SDB to cardio- and cerebrovascular disorders. We will also give a critical overview of the current diagnostic procedures. The available treatment approaches and their prognostic effects on cardio- and cerebrovascular health will be discussed in a second paper.

***Key words:*** *sleep disordered breathing; sleep disorders; sleep apnoea; noninvasive ventilation; cardiovascular events; cerebrovascular events; outcome; cardiovascular morbidity and mortality*

## Introduction

Over the past several decades, the prevalence of sleep-disordered breathing (SDB) has been continuously rising, and SDB, especially obstructive sleep apnoea (OSA), has become a common major health concern in industrialised countries [1–3]. Several factors are likely to have contributed to this increase, including the growing obesity epidemic in our societies, demographic changes with an aging population suffering from more comorbidities, and a raising awareness of SDB as a widespread disease. All forms of SDB may disturb the natural architecture of sleep, leading to excessive daytime sleepiness, fatigue, decreased alertness during the daytime and impaired cognitive functioning. Even more importantly, SDB, especially OSA, is a major risk factor for cerebro- and cardiovascular morbidity and mortality.

This association between SDB and cerebro- and cardiovascular diseases has recently been recognised by both clinicians and researchers. The growing evidence suggesting a causal link between SDB and cerebro- and cardiovascular morbidity has led to recent guidelines pertaining to SDB in the management of acute stroke [4], congestive heart failure [5] and arterial hypertension [6]. However, SDB remains underdiagnosed and undertreated, mainly because the clinical symptoms of SDB are nonspecific

and, in many cases, unrecognised even by the affected patient [7].

We summarise available epidemiological data and focus on the main pathophysiological mechanisms linking SDB to cerebro- and cardiovascular complications. We also provide an overview of current diagnostic approaches.

## Definition of sleep-disordered breathing

Basically, any alteration of respiration during sleep that goes beyond the physiological adaption during the transition from wakefulness to sleep may be considered as sleep disordered breathing [7–10]. Based on the underlying pathophysiological mechanisms, sleep-related breathing disorders are defined and categorised, according to the third edition of the international classification of sleep disorders [8], into four main groups:

1. Obstructive sleep apnoea (OSA)
2. Central sleep apnoea (CSA)
3. Sleep-related hypoventilation disorder
4. Sleep-related hypoxaemia disorder

OSA is characterised by repetitive episodes of complete (apnoea) or partial (hypopnoea) collapse of the upper airways during sleep, with maintained respiratory drive and respiratory effort. It results from various causes of upper airway collapse such as an anatomically narrow upper airway due to obesity, and bony or soft tissue structures. Upper airway resistance or obstruction is generally exacerbated by muscle relaxation during sleep. By definition, OSA may be diagnosed if more than five obstructive respiratory events occur per hour of sleep, even if clinically asymptomatic [8]. Therefore, from a clinical perspective, it is important to distinguish OSA from obstructive sleep apnoea syndrome (OSAS), the latter requiring the presence of clinical daytime and/or sleep-related symptoms, such as excessive sleepiness, in addition to obstructive respiratory events (OSAS = OSA + clinical symptoms). This discrimination has clinical implications because treatment of asymptomatic OSA is usually recommended only if the apnoea-hypopnoea-index (AHI, mean number of apnoeas and hypopnoeas per hour of sleep) is >15/h, or in the presence of relevant cardiovascular comorbidities, whereas in symptomatic patients (OSAS) initiation of therapy should be considered in all cases [8, 11].

In central sleep apnoea (CSA) the upper airway remains patent. CSA is characterised by a reduction or a cessation of the airflow due to absent or reduced respiratory effort related to an impairment of the central respiratory regulation and/or respiratory muscle alteration. According to the third edition of the International Classification of Sleep Disorders (ICSD-3), the polysomnographic diagnostic criteria of CSA include three signs: the number of central apnoeas and/or hypopnoeas is >5/h of sleep, the total number of central events exceeds 50% of the total number of apnoeas/hypopnoeas, and the respiratory pattern shows Cheyne-Stokes respiration [8]. In adults, CSA includes several subgroups of disorders, namely primary CSA, central sleep apnoea with and without Cheyne-Stokes respiration, and CSA due to medication or substances [12]. CSA may also develop at high altitude (CSA due to high altitude periodic breathing), an adaptive reaction associated with high-altitude hypocapnic alkalosis that is completely reversible when the individual returns to sea level. CSA may also occur secondary to neurological disorders such as ischaemic stroke or cerebral haemorrhage where the respiratory centre in the brain stem is affected. Treatment-emergent CSA (formerly known as complex sleep apnoea) is another separate pattern of CSA that may develop in patients treated with positive airway pressure for OSA [8]. Sleep-related hypoventilation disorders are characterised by an abnormal nocturnal increase in the arterial partial pressure of carbon dioxide ($PaCO_2$) due to decreased or impaired ventilation at night, either an increase of at least 10 mm Hg above awake values to 50 mm Hg for at least 10 minutes, or an increase to above 55 mm Hg for at least 10 minutes [8].

The category of sleep-related hypoxaemia disorder was introduced to distinguish cases with sustained periods of significant hypoxaemia during sleep in the absence of other predefined SDB or hypoventilation.

Different types of SDB can overlap in the same patient. Also, the features of both obstructive and central events can be found within the same respiratory episodes, when initially the respiratory effort is absent with the subsequent resumption. In these cases, mixed SDB is often diagnosed [13, 14].

## Epidemiology of sleep-disordered breathing in cerebro- and cardiovascular diseases

The most comprehensive data on SDB epidemiology are available for OSA. The first large-scale population-based study from the USA, published in 1993, showed that 9% of females and 24% of males in a middle-aged population present with an AHI >5/h, and 2 and 4%, respectively, suffer from symptomatic OSAS [1].

**Table 1:** The prevalence of SDB in various cardiovascular diseases and co-morbidities and adjusted odds/hazard ratios for the presence of these diseases in patients with SDB, mainly OSA.

| Pathology | Prevalence of SDB | Odds/hazard ratio | Ref. |
|---|---|---|---|
| Arterial hypertension | AHI ≥5/h: 58–74%<br>AHI ≥ 15/h: 10–30% | 1.33–1.96 | [2, 26–31] |
| Resistant arterial hypertension | AHI ≥ 5/h: 88%<br>AHI ≥10/h: 60–83%<br>AHI ≥30/h: 26–32% | | [32, 33] |
| Coronary artery disease (including acute myocardial infarction, post-revascularisation patients) | AHI ≥5/h: 83%<br>AHI ≥10/h: 30–64%<br>AHI ≥15/h: 64% | 1.27–3.1* | [15, 16, 34–37] |
| Congestive heart failure | AHI ≥10/h: 72%<br>AHI ≥15/h: 60–64%<br>AHI ≥20/h: 53%<br>AHI ≥30/h: 36% | 1.13–2.38† | [13–16, 38–40] |
| Heart rhythm and conduction disorders | AHI ≥5/h: 60–66%<br>AHI ≥10/h: 59%<br>AHI ≥15/h: 14–47%<br>AHI ≥30/h: 20–27% | | [41–44] |
| Atrial fibrillation | AHI ≥5/h: 70–74%<br>AHI ≥10/h: 49%<br>AHI ≥15/h: 25–43%<br>AHI ≥30/h: 13% | 2.18–3.29‡ | [21, 39, 45–48] |
| Stroke | AHI ≥5/h: 79–86%<br>AHI ≥15/h: 35–40%<br>AHI ≥30/h: 30% | 1.76–1.97 | [7, 15, 34, 49–52] |
| Asymptomatic carotid stenosis | AHI ≥10/h: 69% | | [53] |
| Pulmonary hypertension | AHI ≥10/h: 60%<br>AHI ≥15/h: 42% | | [54–56] |
| Obesity | AHI ≥5/h: 8–78%<br>AHI ≥15/h: 2–35% | | [57, 58] |
| Diabetes mellitus | AHI ≥5/h: 60–63%<br>AHI ≥15/h: 26–37%<br>AHI ≥30/h: 10–12% | 1.43–2.30§ | [2, 22, 59–61] |
| Chronic kidney disease | AHI ≥5/h: 54%<br>AHI ≥15/h: 32–39%<br>AHI ≥30/h: 6% | | [62, 63] |
| Haemodialysis | AHI ≥10/h: 89%<br>AHI ≥15/h: 50% | | [64–67] |

AHI = apnoea/hypopnoea index; OSA = obstructive sleep apnoea; SDB = sleep-disordered breathing
* Dose-dependent, the highest risk was observed in males aged <70 years.
† Dose-dependent; in men, the adjusted hazard ratio of incident heart failure was 1.13 per 10 AHI units increase, 1.58 for AHI ≥30/h vs AHI <5/h, no association in woman
‡ AHI >5/h; in multivariate analysis only the lowest oxygen desaturation was associated with atrial fibrillation (hazard ratio 3.29 per 1% decrease)
§ Adjusted odds ratio for AHI ≥15/h vs <5/h

These data were revised by Peppard et al. in 2013, and a significant increase in SDB prevalence during the previous two decades was established. According to Peppard et al., 26% of the general middle-aged population is affected by OSA and a rise, ranging from 14 to 55% depending on gender and age of the subgroups, was observed [3]. This increase in OSA prevalence has also been reported from European countries. Based on data from a Swiss cohort including 2121 randomly selected subjects (mean age 57, range 40–85 years) from the city of Lausanne, the SDB rates are estimated to be 60% in females and 83% in males (based on the presence of an AHI of ≥5/h), and 23 and 49%, respectively (based on a more stringent definition with an AHI ≥15/h) [2]. As described earlier, elderly vs younger subjects and males vs females showed higher rates. Recently, studies demonstrated that the prevalence of relevant SDB is much higher in individuals with known cerebro- and cardiovascular events [15–18] and reaches values up to 50 to 90% in specific cohorts [7, 19–21]. This was confirmed in pooled populations in later meta-analyses [20]. This might imply a direct association between SDB and cerebro- and cardiovascular morbidity. However, proving that SDB can independently cause cerebro- and cardiovascular diseases remains a difficult issue, because most cerebro- and cardiovascular diseases share common risk factors with SDB, such as obesity, male sex, age, smoking, or metabolic disorders [22–25]. Further, more severe SDB is associated with a higher prevalence of cardiovascular diseases, indicating a dose-dependent association also present after a multivariate adjustment for major cardiovascular risk factors [15]. Interestingly, the type and distribution of SDB may vary in different diseases (table 1) with OSA (AHI ≥10/h) being commonly seen in systemic hypertension [11, 68, 69], coronary artery disease [34, 70], heart rhythm disorders [21, 41], pulmonary hypertension [54] and stroke [7, 15, 20, 49, 71]. In contrast, CSA is predominantly seen in patients with congestive heart failure, especially with left-ventricular systolic dysfunction (in up to 30–50%), typically with CSR that is characterised by cyclic fluctuations in breathing in a waxing-waning (crescendo-decrescendo) mode, and in stroke patients (up to 25–30% in acute stroke) [7, 38, 71–73].

## Sleep-disordered breathing and arterial hypertension

A causal association between OSA and arterial hypertension was first suggested over 30 years ago, making it one of the most investigated and well-recognised relationships between OSA and a vascular comorbidity [74]. OSA is observed in up to 30 to 50% of all hypertensive individuals and in more than 80% of all patients suffering from drug-resistant arterial hypertension [11, 75]. The most commonly observed blood pressure features in OSA patients include elevated diastolic blood pressure, nocturnal hypertension and a non-dipping circadian blood pressure profile. Moreover, OSA (AHI ≥15/h) is recognised as one of the most prevalent causes of treatment-resistant hypertension; in a high-risk cohort, severe OSA was associated with a four-fold increase in the prevalence of resistant elevated blood pressure despite intensive antihypertensive treatment, even after adjustment for the major cardiovascular risk factors [68]. However, despite the growing evidence supporting this association, there are still some unanswered questions. The trials addressing the antihypertensive effects of continuous positive airway pressure (CPAP) used as sleep apnoea treatment are controversial. An antihypertensive effect of CPAP therapy for OSA has been demonstrated in a recent meta-analysis, but it was rather modest reaching only -2 to -3 mm Hg and was more profound for systolic and nocturnal blood pressure values [76, 77]. In a prospective observational study of 1889 participants followed for more than 11 years, Marin et al. demonstrated that CPAP prevents new-onset hypertension in treatment-compliant patients (hazard ratio 0.71, 95% confidence interval [CI ] 0.53–0.94]) compared with control subjects with AHI <5/h, and the protective effect was observed despite an increase in body mass index (BMI) [26]. However, this protective effect is not observed in asymptomatic (e.g., non-sleepy) OSA patients [78].

## Sleep-disordered breathing and stroke / cerebrovascular disease

Current data demonstrate a strong association between SDB and ischaemic stroke, although the exact underlying mechanisms are still not completely elucidated. The prevalence of SDB (AHI ≥5/h) in stroke survivors significantly exceeds that in the general population and reaches 50 to 86% (AHI ≥30/h: 30%). Stroke localisation and lesion volume

are discussed as potential influencing factors. However, no convincing evidence has until now been provided, and the influence of particular cerebral topographies are controversial [7, 49, 50, 79–81]. CSA with or without Cheyne-Stokes respiration is found in patients with lesions in the central autonomic network (e.g., medulla oblongata), suggesting a link to cardiorespiratory central control [7].

Some studies showed an association between SDB and nocturnal onset of cerebrovascular events, including the wake-up stroke that comprises up to 25 to 30% of all acute cerebrovascular events. Thus, wake-up stroke patients show more severe sleep apnoea than those with daytime stroke onset, and the frequency of moderate-to-severe SDB (AHI >15/h) is higher in wake-up stroke patients [82–84]. However, in the recently published SLEEP-TIGHT study, the frequencies of SDB in wake-up stroke and non-wake-up stroke patients were similar [84], and the causal relationship is still uncertain.

SDB tends to improve from the acute to the subacute phase of stroke, and this may be more the case for CSA than OSA [79, 85–87]. Various reasons for the improvement of SDB are discussed, including the amelioration of neurological deficits, a higher level of physical activity and less time spent in the supine position during sleep.

As mentioned above, comorbid cardiovascular diseases and metabolic dysregulations frequently seen in OSA patients may all promote stroke. However, OSA and CSA with or without Cheyne-Stokes respiration are frequently encountered in acute and chronic stroke patients (with OSA being the predominant type), even in the absence of other classical cardiovascular or metabolic risk factors [7, 49, 88]. Therefore, SDB itself may increase the risk of stroke independently of these factors. Some studies provided evidence of the dominant role of hypoxaemia (in particular when its duration exceeds 10% of sleep) in incident stroke in subjects with SDB [89]. The risk of stroke in SDB was confirmed to be three- to four-fold higher after adjustment for the major cardiovascular risk factors [90, 91]. Interestingly, some studies noted gender-specific differences, with a significantly higher impact of OSA on stroke incidence in men, but not in women.

There is growing evidence that SDB adversely affects early stroke outcome and is associated with a worse functional outcome in the acute and subacute phases [7, 80]. Presence of SDB is also an independent predictor of higher mortality rates after stroke, and mortality increases in proportion to the AHI values [51, 92]. A recently published systematic review focused on the effects of SDB after cerebrovascular events, and demonstrated that OSA is a risk factor for vascular event recurrence and all-cause mortality in post-stroke patients [93]. However, the effects of positive airway pressure (PAP) treatment on post-stroke outcomes are controversial [94–96]. At the same time, the prognostic cut-offs of SDB severity, and therefore the indication for treatment initiation after stroke, are not established and further investigations are required. An international multicentre study (SAS-CARE) addressing these issues recently completed patient recruitment, and first results will be published in 2017 [97]. A second prospective interventional randomised trial (eSATIS), evaluating early adaptive servoventilation treatment in acute stroke patients with severe SDB, was started in 2015 (ClinicalTrials.gov Identifier: NCT02554487) [98].

SDB has increasingly been recognised as a risk factor for cognitive impairment and dementia. Assumed mechanisms underlying this association include cerebral hypoperfusion, endothelial dysfunction, impaired cerebral vasomotor reactivity and neuroinflammation resulting in cerebral small vessel disease and subsequent white matter lesions, grey matter loss and neurodegenerative processes [99].

Because of the relationship between sleep disorders and stroke, as well as the need for multidisciplinary approaches in this field, a taskforce on “Sleep and Stroke” was initiated by four European societies (European Respiratory Society, European Stroke Organisation, European Academy of Neurology and European Sleep Research Society) in 2016. The taskforce is chaired by Professor C.L. Bassetti, Professor W. Randerath, and Dr V. Papavasileiou, and aims at developing position statements based on reviewed evidence.

## Sleep-disordered breathing and coronary artery disease

As for other cerebro- and cardiovascular diseases, in patients with coronary artery disease the prevalence of OSA is higher than in the normal population [35, 70]. In 1999, Peker et al. reported a prevalence of OSA (defined as a respiratory disturbance index of >10/h) of 30% in patients admitted with an acute coronary syndrome, and identified an independent association between OSA and coronary artery disease in a multivariate model (odds ratio 3.1, 95% CI 1.2–8.3) [35]. Recent studies reported a wide range of SDB prevalence in patients with coronary artery disease, from 26 to 69% depending on the investi-

gated population and the criteria to establish the diagnosis of OSA, such as values of AHI, scoring criteria [70, 100].

The interaction between SDB and coronary artery disease also manifests in higher mortality rates if both entities are concomitantly present in a patient. A decade ago, Gami et al. (2005) had already shown that SDB patients are more likely to die suddenly during the classical sleeping hours (from 10 p.m. to 6 a.m.), in contrast to the general population and subjects without sleep apnoea [45]. Almost 10 years later, the same group retrospectively evaluated a sample of US residents consisting of 10 701 adults, and demonstrated that OSA was a strong predictor of sudden cardiac death at night. Moreover, the magnitude of the risk was associated with several parameters characterising OSA severity, including AHI (≥20/h), mean nocturnal oxygen saturation (<93%) and lowest nocturnal oxygen saturation (<78%) [101]. Similarly, the risk of myocardial infarction at night (between midnight and 6 a.m.) is significantly higher in OSA patients than in non-OSA subjects, indirectly indicating a possible interrelation [102]. Supporting the deleterious link, large-scale prospective studies based on general population cohorts demonstrated higher all-cause mortality in untreated SDB patients, particularly in the most severe cases [103–105]. However, a more recent analysis of the Sleep Heart Health Study, with longitudinal data after an 8.7-year follow-up, did not demonstrate an association of OSA with incident coronary artery disease after adjusting for other risk factors. The risk of coronary artery disease was slightly increased in OSA patients younger than 70 years and in patients with severe OSA (AHI >30/h) [16]. The lack of a general association between SDB and coronary artery disease in the Sleep Heart Health Study may be explained in part by the cohort's characteristics: predominantly elderly patients with a mean age of 62 years in whom risk factors other than OSA may play a more important role in an unfavourable prognosis, female prevalence, high frequency of asymptomatic forms (which may be disputable), etc.

Nevertheless, the body of literature addressing the role of OSA as an independent risk factor for coronary artery disease is constantly growing [106]. One supporting clue is the fact that OSA is independently associated with subclinical coronary atherosclerosis, measured as coronary calcification in computed tomography [107], and there is also a higher prevalence of noncalcified occlusive atherosclerotic plaques in OSA patients. In addition, data on the effects of PAP therapy are promising; it appears to reduce the risk of recurrent ischaemic events and the necessity of revascularisation procedures [108, 109].

## Sleep-disordered breathing and heart rhythm disorders

Bradyarrhythmias, including sinus and atrioventricular block of different degrees, are found in 10 to 50% of OSA patients, depending on the population and diagnostic criteria applied [110]. On the other hand, the rate of SDB in patients with implanted pacemakers is up to 50% [111]. Moreover, CPAP therapy has a protective effect against bradyarrhythmias, as demonstrated in prospective studies [112, 113]. Therefore, sleep apnoea is currently considered to be one of the reversible causes of bradyarrhythmias, and a sleep study is recommended before pacemaker implantation [114, 115].

OSA prevalence was two-fold higher in patients with atrial fibrillation than in a general cohort of patients referred to the cardiology clinic (after adjustment for the main risk factors) [21]. In addition, OSA was associated with a higher risk of recurrent atrial fibrillation after radiofrequency ablation procedures [116], as well as atrial fibrillation onset in the postoperative period after coronary artery bypass grafting (odds ratio 1.89, 95% CI 1.24–2.80; p = 0.003) [117]. Although the available data suggest a strong relationship between atrial fibrillation and OSA, further studies are required to make definitive conclusions.

## Pathological mechanisms linking sleep-disordered breathing and cerebro- and cardiovascular diseases – a bidirectional interaction

A variety of underlying SDB-specific pathophysiological mechanisms linking SDB with cerebro- and cardiovascular morbidity have been identified (fig. 1).

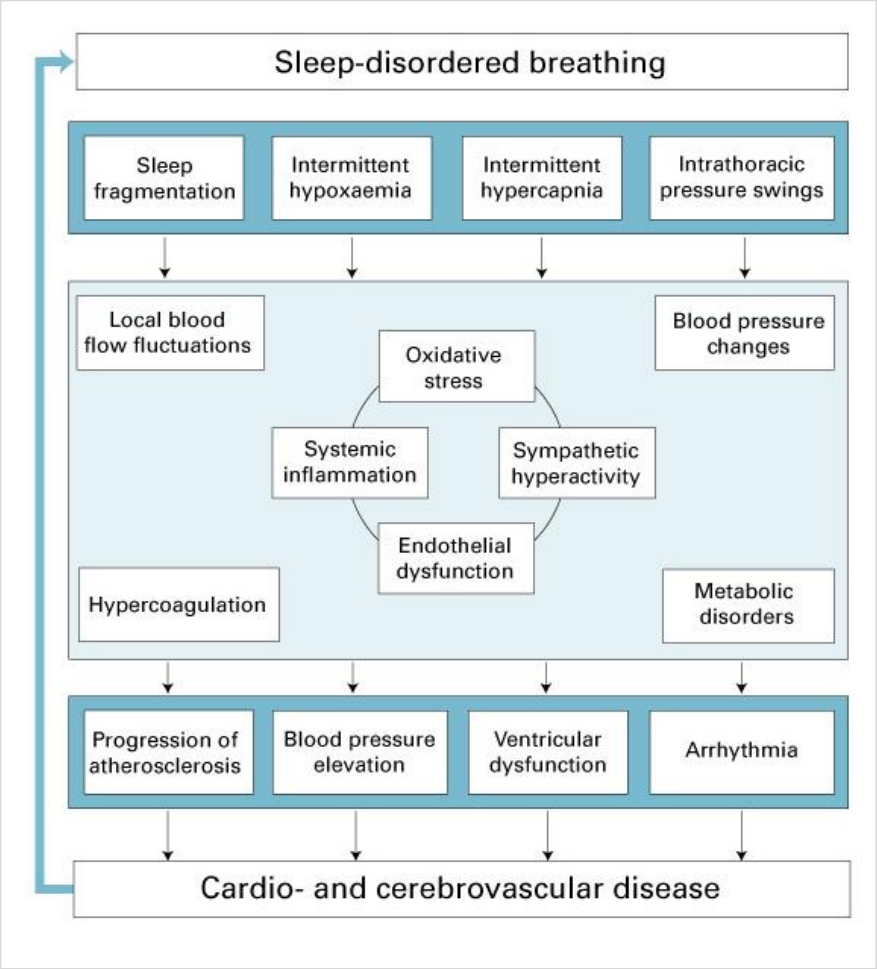


**Figure 1:** Overview of SDB-specific pathophysiological mechanisms linking SDB with cerebro- and cardiovascular morbidity – a bidirectional crosstalk.

Common key features in all types of SDB may contribute to future cerebro- and cardiovascular diseases: intermittent hypoxaemia, intermittent increases in carbon dioxide partial pressure and recurrent arousals. Moreover, unsuccessful respiratory efforts against obstructed upper airways in OSA also cause intrathoracic pressure swings, potentially affecting intrathoracic organs and blood flow towards the heart and the brain. These phenomena can initiate physiological and pathophysiological reactions that promote the development of cerebro- and cardiovascular sequelae.

1. Intermittent hypoxaemia is one of the major pathophysiological features that can occur whenever respiration is impaired. It leads to chemoreflex activation and oxidative stress. Additionally, intermittent hypoxaemia is associated with increased arrhythmogenesis, a potential cause of sudden cardiac death; severity of hypoxemia has been shown to predict sudden cardiac death in OSA patients [101]. Moreover, blood pressure and heart rate surges during apnoeas (see below) can increase myocardial oxygen demand that, against the background of hypoxaemia, can cause relative myocardial ischaemia and potentially threatening heart rhythm disorders. Furthermore, intermittent hypoxaemia with oxidative stress triggers systemic inflammation, which can promote the genesis of atherosclerotic plaques, and potentially contributes to the development of plaque vulnerability and rupture. Severe hypoxaemia, with impaired chemosensitivity and local changes in the cerebral circulation, can also cause cerebral ischaemia, increasing the risk of stroke / transient ischaemic attack and their sequelae [50, 118–120].
2. Recurrent arousals primarily result in activation of the sympathetic nerve system. This acutely leads to intermittent heart rate and blood pressure surges and to a secondary activation of the renin-angiotensin-aldosterone system, a known pathophysiological mechanism in arterial hypertension. Another consequence of recurrent arousals are baroreflex impairment and autonomic dysfunction, namely fluctuations with abrupt rises in

parasympathetic activity (during apnoeas) changing into sympathetic overactivity (at the end of apnoeas) during sleep, and sustained sympathetic hyperactivity during wakefulness [121, 122]. This manifests as a reduced heart rate variability that, in turn, is a known independent predictor of cardiovascular morbidity and mortality. Metabolic changes, including hyperlipidaemia and insulin resistance caused by oxidative stress and sympathetic overactivity, can further contribute to the cardiovascular consequences [24].

3. Intrathoracic pressure fluctuations intensify chemo- and baroreflex activation. They also lead to increased venous return and changes in heart preload and afterload resulting in myocardial remodelling. Both right and left heart ventricular remodelling, right and left ventricular hypertrophy, myocardial fibrosis, and left and right ventricular diastolic dysfunction are associated with higher arrhythmogenesis and cardiovascular risk. Intrathoracic pressure swings are also transmitted to the vasculature and may cause endovascular sheer stress and endothelial dysfunction. Endothelial dysfunction, together with intermittent hypoxaemia, triggers more rapid atherosclerosis development and arterial remodelling. In the multicentre HeartBEAT study, moderate-to-severe hypoxaemia, defined as an oxygen desaturation index >24.6/h, was associated with a more profound decline in endothelial function assessed by flow mediated vasodilation [123]. The relationship with oxygen desaturation index was more robust than the one with AHI. In post-stroke patients, AHI and severity of nocturnal hypoxemia independently increase the risk for arterial stiffness (odds ratio 5.98, 95% CI 1.11–41.72), even after controlling for age, sex, BMI, hypertension, and diabetes mellitus [124].
4. All three SDB features may enhance the hypercoagulatory state found in sleep apnoea patients, which possibly augments the risk of acute vascular complications (acute coronary syndrome, ischaemic cerebrovascular events) [125–127]. In particular, activation of the prothrombotic system, and alterations of fibrinolysis were found in patients with OSA (an increase in fibrinogen levels [125], increase in plasminogen activator inhibitor-1, tissue-type plasminogen activator [50, 125, 128, 129], etc.).

Despite the afore summarised evidence of a causal relationship between SDB and cerebro- and cardiovascular events and comorbidities, one may assume that the higher cerebro- and cardiovascular risk in OSA patients is just a cumulative effect of shared risk factors, such as obesity, male gender, hypertension, hyperlipidaemia, etc. Intriguingly, however, the relationship between SDB and cerebro- and cardiovascular morbidities seems to be more complex and bidirectional. Specifically, cerebro- and cardiovascular diseases themselves might contribute to the development or aggravation of SDB. In stroke patients, there is a significant reduction in SDB prevalence and severity from the acute to the subacute stroke phase, indicating a direct impact of acute brain damage (and its complications) on SDB [7].

In recent years, a novel concept elucidating the development of SDB in congestive heart failure and other states that are associated with fluid retention (renal disease, hypoproteinaemia, treatment resistant hypertension, and others) has been introduced [130, 131]. In fact, this hypothesis adds some new insights to the traditional understanding and helps to put some pieces of the puzzle together. According to this theory, the recumbent position and the associated changes in gravity in patients with congestive heart failure (at night / during sleep) is associated with a fluid shift from the legs to the upper body, including lungs, neck and upper airway. This was confirmed in a series of high-level experiments with the application of lower body positive pressure in both healthy individuals and congestive heart failure patients. This intervention led to a rapid increase in neck circumference and increased collapsibility of the upper airways (precisely confirmed with magnetic resonance imaging and plethysmographic measurements), thus increasing the risk of OSA development. On the other hand, fluid shifts from the legs leads to an increase in venous return to the heart, thus increasing pulmonary capillary wedge pressure and pulmonary congestion. This stimulates pulmonary irritant receptors, and as a consequence, causes hyperventilation and a reduction in $CO_2$ partial pressure below the apnoea threshold. The latter is crucial for ventilatory control during sleep. Against the background of impaired chemosensitivity that is commonly observed in congestive heart failure patients, even slight changes can cause significant fluctuations in ventilation. Changes in the severity of fluid retention and peripheral oedema can lead to the modulation of the degree of CSA and be responsible for the predominance of either OSA or CSA in patients with congestive heart failure. A bidirectional interaction between sleep apnoea and congestive heart failure is also suggested by the beneficial effects of cardiac resynchronisation therapy and heart transplantation on SDB, particularly with respect to central sleep apnoea [132–134].

## Diagnostic approach – always consider sleep-disordered breathing in cerebro- and cardiovascular patients

Because of the higher prevalence of SDB in populations with cerebro- and cardiovascular diseases and their potential detrimental impacts, it is crucial to consider SDB as a potentially modifiable cardiovascular risk factor, especially given the availability of treatment options [11]. The recognition of a potential role of SDB and its association with cardio/cerebrovascular diseases is reflected in current guidelines for the management of specific diseases such as stroke, arterial hypertension and heart failure [4–6]. However, despite these guidelines and the growing evidence of a strong bidirectional relation between sleep apnoea and cerebro/cardiovascular diseases, the majority of cases still remain undiagnosed [1, 16, 70, 102]. Therefore, the routine implementation of diagnostic approaches and application of reliable and valid screening tools is important, although the results and further treatment strategies should be treated with caution since a general cardiovascular benefit has not yet been confirmed for all comorbidities in recent trials.

Exploration of the patient's history for clinical signs and symptoms of SDB and typical physical risk factors such as obesity and relevant retrognathia should always be the first step (fig. 2). A more comprehensive SDB evaluation should follow in patients at risk. Patients should be asked more detailed questions regarding typical sleep-related and daytime signs and symptoms. These include snoring, witnessed apnoeas, dyspnoea/choking during sleep, repetitive awakenings, dry mouth and nocturnal sweating. Daytime manifestations include excessive daytime sleepiness, fatigue, morning (or nocturnal) headache, cognitive impairment and irritability, etc. The clinical manifestations of CSA may be less evident and are usually dominated by the underlying disease (e.g., heart failure). Fatigue, nonrestorative sleep, hyperventilation and disrupted sleep are frequently found [135].

Questionnaires evaluating the likelihood of clinically relevant SDB can be helpful, combined with a physical examination looking for features abetting SDB. For primary screening, there are various questionnaires that can be easily incorporated into routine clinical visits, such as the commonly used Berlin Sleep Apnea questionnaire, STOP-BANG questionnaire (and its modifications), and the recently introduced NoSAS-Score for OSA screening and Epworth sleepiness scale for daytime sleepiness assessment [136, 137]. However, recently published data have raised new issues regarding appropriate questionnaire screening tools in specific cohorts. For example, stroke patients usually demonstrate lower or normal values on the Epworth Sleepiness Scale and Berlin questionnaire as compared with non-stroke patients with SDB [7, 138]. The same is true for patients with atrial fibrillation or congestive heart failure [139, 140]. Such "masked" manifestation can lead to a significant underestimation of SDB burden in special conditions and potentially prevent timely treatment. For example, the HypnoLaus study has shown that the conventional clinical symptoms/signs are less predictive for the presence of SDB than the NoSAS score (a quantitative predictive scale for SDB probability evaluation that includes the following parameters: obesity, neck circumference, age, snoring and gender) [2, 136]. Thus, although disputed by some authors [137, 141], the common screening questionnaires seem to be inappropriate in some cohorts, and more differentiated diagnostic algorithms and individualised approaches are required [64].

Manifestations of SDB are heterogeneous in populations with differing comorbidities. Recently, a concept of different clinical phenotypes or "different clinical faces" of SDB/OSA has been suggested [142]. A collaborative Icelandic-American group identified three main clusters by grouping them according to the complaints/symptoms and comorbidities as follows: "disturbed sleep group", "minimally symptomatic group" and the most prevalent "excessive daytime sleepiness group" consisting of 32.7%, 24.7%, and 42.6%, respectively, of the Icelandic cohort studied [142]. The probability of comorbid cardiovascular diseases differed between the subtypes, being lowest in the third cluster – the sleepiest one. Intriguingly, the probability of cerebro- and cardiovascular pathology was highest in the second group, which has minimal symptoms, and thus, according to current practice, is the last to be referred to sleep centres for specific SDB therapy [142, 143]. The heterogeneity of clinical manifestations might also be associated with different responses to therapy and/or adherence to treatment, potentially serving as a tool to choose treatment.

Therefore, objective diagnostic approaches should be applied at a low threshold for specific subgroups of patients, such as those with high estimated cerebro- or cardiovascular risks. In these cases, specialised instrumental examination may be considered the first step regardless of the presence of the clinical manifestations.

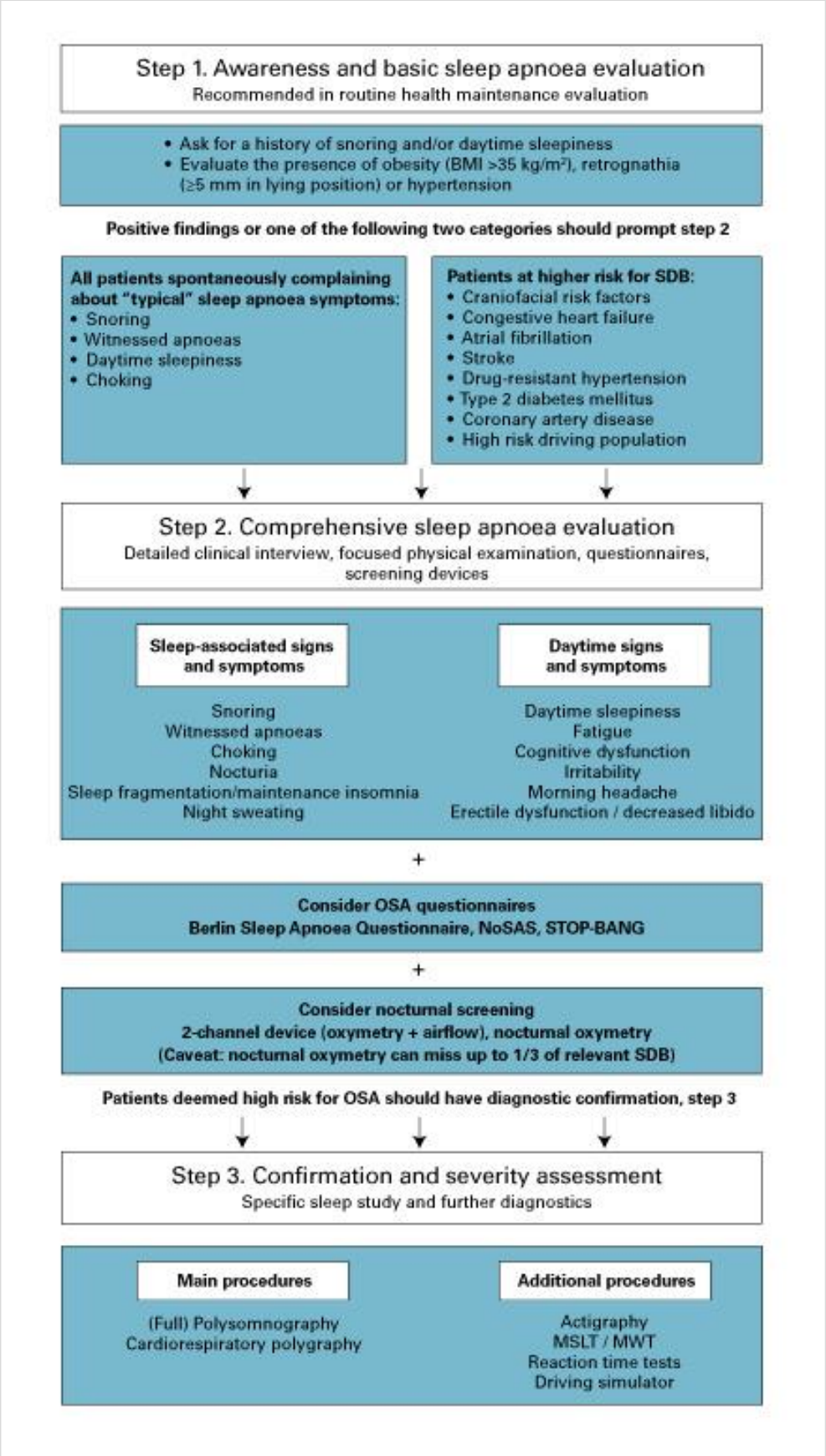


**Figure 2:** Suggestion for a simple three-step algorithm for the evaluation of sleep-disordered breathing (SDB).

BMI = body mass index; MSLT = multiple sleep latency test; MWT = maintenance of wakefulness text; OSA = obstructive sleep apnoea

Based on American Academy of Sleep Medicine (AASM) criteria, four categories of diagnostic devices are distinguished (table 2), with attended observed video polysomnography as the "gold standard". However, simple two-channel devices, including nocturnal oximetry and recording of the airflow, may be sufficient for screening and should be preferred to nocturnal oximetry only, which may miss at least one third of all relevant SDB. Cardiorespiratory polygraphy is usually referred to as a screening test, but it may be sufficient to establish the diagnosis in individuals with high clinical suspicion of SDB, as shown in recent studies reporting acceptable results for SDB identification by portable polygraphy in patients with cardiovascular comorbidities [144].

**Table 2:** Types of diagnostic tool (according to the American Academy of Sleep Medicine classification).

| Monitor | Type of the diagnostic tool | Parameters recorded | Benefits | Disadvantages |
|---|---|---|---|---|
| **Type I** | Attended, in-lab standard full (video) polysomnography | ≥7 channels<br>including EEG, chin EMG, ECG, airflow, (chest, abdominal) respiratory efforts, oximetry, leg movements, position | – "Gold standard"<br>– Sleep structure assessment<br>– Opportunity to perform interventions | – Costly<br>– Labour-intensive<br>– Discomfort for the patient<br>– Experienced and trained personnel (technician)<br>– In-lab |
| **Type II** | Unattended full (video) polysomnography | ≥7 channels<br>including EEG, chin EMG, heart rate or ECG, airflow, (chest, abdominal) respiratory efforts, oximetry, leg movements, position | – Sleep structure assessment<br>– Both in the lab and at home | – Costly<br>– Labour-intensive<br>– Discomfort for the patient<br>– No opportunity to perform interventions<br>– Experienced and trained personnel (technician) |
| **Type III** | Polygraphy, limited channel devices (portable) | ≥4 channels including ventilation or airflow (at least 2 channels of respiratory movements, or airflow and respiratory movements), oximetry, heart rate or ECG, position, leg movements (optional) | – Inexpensive<br>– Easy to perform<br>– More comfortable<br>– Portable (home) monitoring | – Higher risk of false-positive and false-negative results |
| **Type IV** | Limited channel devices (screening) | 1 or 2 channels, usually oximetry and heart rate or airflow | – Inexpensive<br>– Easy to perform (screening)<br>– More comfortable<br>– Portable, home monitoring | – Higher risk of false-positive and false-negative results |

ECG = electrocardiogram; EEG = electroencephalogram; EMG = electromyogram

One of the most relevant controversial issues is the choice of scoring criteria for sleep-associated respiratory events, independent of the diagnostic device used, since different recommended rules have been implemented in clinical practice and research during the last two decades. This may cause significant differences in the number of recorded respiratory events and, thus, the prevalence and severity of SDB. In a cohort of heart failure patients, a difference of 4.6 events per hour was established in AHI

scoring according to AASM "recommended" and "alternative" rules, leading to a significant change in the detected SDB prevalence (29% vs 46%, p<0.001, based on an AHI ≥15/h) [145].

Currently, various alternative diagnostic tools are being developed, including portable, one-channel, non-contact devices (based on acoustic or bioradiolocation signals, etc.) [146, 147]. However, their utility in comorbid states has not yet been verified, although they appear to be promising screening devices and tools for long-term and repeated monitoring.

## Conclusion

SDB is associated with cerebro- and cardiovascular diseases. Accumulating data provide new insights into the underlying mechanisms and need for novel management approaches. Undoubtedly, a wider implementation of screening tools is required, in particular in patients at high risk for cerebro- and/or cardiovascular diseases, as well as better application of preventive and therapeutic approaches. At present, some issues remain controversial, including the choice of diagnostic criteria and tools, the benefits of PAP therapy in some populations, the paradoxical effects of sleep apnoea in certain cohorts (e.g., preconditioning effects of sleep apnoea-associated intermittent hypoxaemia), etc.. These questions can be answered in multicentre trials and in large multidisciplinary collaborative research projects (e.g., the International Collaboration of Sleep Apnea Cardiovascular Trialists, INCOSACT, SAS-CARE, eSATIS [97, 98, 148] that could facilitate the promotion of research ideas, standardise procedures and regulations while advancing our scientific understanding on the role of SDB in cardiovascular morbidity and mortality.

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**Authors' contribution**
Sebastian R. Ott and Lyudmila Korostovtseva contributed equally to the manscript

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