Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep

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Description of the actual approach to differential diagnosis and treatment options in central breathing disturbances

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ABSTRACT The complexity of central breathing disturbances during sleep has become increasingly obvious. They present as central sleep apnoeas (CSAs) and hypopnoeas, periodic breathing with apnoeas, or irregular breathing in patients with cardiovascular, other internal or neurological disorders, and can emerge under positive airway pressure treatment or opioid use, or at high altitude. As yet, there is insufficient knowledge on the clinical features, pathophysiological background and consecutive algorithms for stepped-care treatment. Most recently, it has been discussed intensively if CSA in heart failure is a “marker” of disease severity or a “mediator” of disease progression, and if and which type of positive airway pressure therapy is indicated. In addition, disturbances of respiratory drive or the translation of central impulses may result in hypoventilation, associated with cerebral or neuromuscular diseases, or severe diseases of lung or thorax. These statements report the results of an European Respiratory Society Task Force addressing actual diagnostic and therapeutic standards. The statements are based on a systematic review of the literature and a systematic two-step decision process. Although the Task Force does not make recommendations, it describes its current practice of treatment of CSA in heart failure and hypoventilation.
that several issues remain unresolved. These include the following.

1.2. Definitions

The ICSD-3 defines subgroups of central apnoea according to the presence and type of any underlying diseases (table 3). The Task Force complies with the nosological classification of ICSD-3, despite the fact that several issues remain unresolved. These include the following.

**Introduction**

The relevance of sleep disordered breathing (SDB) associated with cardiovascular and metabolic comorbidities, the increasing opioid use, the coincidence with highly prevalent diseases (chronic obstructive pulmonary disease (COPD)) and epidemiological changes (obesity) influence the prevalence and phenotypes of SDB. The use of continuous positive airway pressure (CPAP) in the treatment of obstructive sleep apnoea (OSA), has unveiled treatment-emergent central sleep apnoea (CSA). As yet, there is insufficient knowledge of the clinical features, pathophysiological background and consecutive algorithms for treatment of CSA. While there is ample evidence that moderate-to-severe OSA is associated with worse disease outcomes, it is unclear whether CSA or its treatment is of any prognostic significance with respect to disease progress [1].

**1. General aspects**

**1.1. Methods**

The members of the Task Force performed a literature research using electronic databases (Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO), hand searches of relevant papers and screening of reference lists up from October 1, 2012, to September 30, 2015. The main inclusion and exclusion criteria were: articles published in English; data on human subjects; no reviews, guidelines or case reports; at least three subjects included; and cardiorespiratory monitoring or polysomnography (PSG) available. The search strategies for each chapter are presented in the online supplement. All other tables are available in the online supplementary material (tables e1.3–e3.6). Individual studies were evaluated according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001) [2] (table 1). The present European Respiratory Society statement combines an evidence-based approach with the clinical expertise of the Task Force members, based on a two-step discussion process: first, within subgroups focusing on different sections; second, in the whole group. When assessing the full body of evidence supporting each statement, we used the grades A–D (table 2). The available evidence for several of the topics addressed did not allow definite recommendations. Therefore, we did not produce a formal guideline. This statement aims to provide an overview of the literature and current practice. It does not make recommendations for clinical practice.

The Task Force followed, in general, the order of the International Classification of Sleep Disorders (3rd edition) (ICSD-3) [3]. However, the entities of CSA and hypoventilation syndromes can also be differentiated based on pathophysiological patterns (hypocapnic/normocapnic versus hypercapnic phenotypes). This differentiation has been added, where feasible.

**1.2. Definitions**

The ICSD-3 defines subgroups of central apnoea according to the presence and type of any underlying diseases (table 3). The Task Force complies with the nosological classification of ICSD-3, despite the fact that several issues remain unresolved. These include the following.
1) Central apnoeas, central hypopnoeas, and the increasing and decreasing pattern of flow and effort (periodic breathing) are polysomnographic patterns, which can be associated with a variety of clinical phenomena. However, the ICSD-3 classification connects polysomnographic patterns closely to specific clinical entities, especially (Hunter–)Cheyne–Stokes breathing (CSB). This approach impedes a clear description of the polysomnographic pattern on the one hand and the clinical syndromes on the other.

2) In addition, there is a fundamental problem with the definitions of CSA and hypoventilation disorders. A specific disease may only be diagnosed if other underlying diseases are excluded and symptoms of CSA cannot be better explained by another medical problem. However, in clinical practice, many patients suffer from more than one disorder predisposing and attributing to central SDB.

**Statements**

**Definitions**

The members of the Task Force:

1) describe abnormal breathing patterns of central origin appearing in a periodic fashion as “periodic breathing with or without apnoea”;

2) describe the polysomnographic pattern of waxing and waning of the airflow and effort with or without apnoeas as "periodic breathing", independent of its origin (e.g. cardiovascular disorders, high altitude or opioid intake); and

3) acknowledge that the term CSB has historically been used to describe periodic breathing with apnoeas in the context of heart failure or stroke, but replace the term CSB with “periodic breathing with apnoea in the setting of heart failure (or another underlying disease)”. 

**Clinical entities**

The members of the Task Force:

1) identify and describe, separately and individually, any concurrent underlying disease or risk factor of central SBD in order to avoid simplifying the pathogenesis by preferring one of several similar relevant causes; and

2) initiate treatment based on symptoms, impact on comorbidities and outcome.

**TABLE 1 Evidence levels assigned to each individual study**

<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>1a</td>
<td>Systematic analysis (systematic review) of RCTs with homogenous results</td>
</tr>
<tr>
<td>1b</td>
<td>Particular RCT with limited dispersion</td>
</tr>
<tr>
<td>1c</td>
<td>Therapy; before its introduction, all patients died</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review of cohort studies with homogenous results</td>
</tr>
<tr>
<td>2b</td>
<td>Particular cohort studies or RCT of lower quality</td>
</tr>
<tr>
<td>2c</td>
<td>“Outcomes” research; ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review of case-control studies with homogenous results</td>
</tr>
<tr>
<td>3b</td>
<td>Particular case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case studies and cohort studies or case-control studies of limited quality</td>
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<tr>
<td>5</td>
<td>Expert opinion</td>
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</table>


1) Central apnoeas, central hypopnoeas, and the increasing and decreasing pattern of flow and effort (periodic breathing) are polysomnographic patterns, which can be associated with a variety of clinical phenomena. However, the ICSD-3 classification connects polysomnographic patterns closely to specific clinical entities, especially (Hunter–)Cheyne–Stokes breathing (CSB). This approach impedes a clear description of the polysomnographic pattern on the one hand and the clinical syndromes on the other.

2) In addition, there is a fundamental problem with the definitions of CSA and hypoventilation disorders. A specific disease may only be diagnosed if other underlying diseases are excluded and symptoms of CSA cannot be better explained by another medical problem. However, in clinical practice, many patients suffer from more than one disorder predisposing and attributing to central SDB.

**TABLE 2 Grades used when assessing the full body of evidence contributing to a statement**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Consistent level 1 studies</td>
</tr>
<tr>
<td>B</td>
<td>Consistent level 2 or 3 studies, or extrapolations of level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>Level 4 studies, or extrapolations of level 2 or 3 studies</td>
</tr>
<tr>
<td>D</td>
<td>Level 5 studies or inconsistent studies of other levels</td>
</tr>
</tbody>
</table>

Information from [2].
### 1.3. Measurement techniques

The study of the sleep apnoea–hypopnoea syndrome as well as nocturnal hypoventilation has made considerable advances in the last decade. These are at least partly due to the development and refinement of noninvasive sensors and techniques [4–8]. The detection of obstructive events (apnoeas, hypopnoeas, flow limitation and snoring) requires sensors with a good frequency response (nasal prongs during diagnostic PSG). Information on respiratory effort is mandatory for assessment of central events. The optimal way to assess nocturnal hypoventilation is by monitoring gas exchange (arterial oxygen saturation ($S_{a}O_{2}$) and, especially, that of carbon dioxide) and respiratory effort [4–8]. The various sensors used to analyse central breathing disorders during sleep were reviewed.

#### Overview of the evidence

Full PSG with oesophageal pressure measurement is the optimal procedure to diagnose CSA and is considered as the gold standard. In routine practice, different surrogates of respiration and/or respiratory effort are used, including flow, thoracoabdominal movement, pulse transit time (PTT), electromyography (EMG) of the diaphragmatic muscle, suprasternal pressure, jaw movement and forehead venous pressure. The most common surrogates used are the thoracoabdominal bands, especially respiratory inductive plethysmography (RIP). RIP belts have replaced piezoelectric belts in more recent studies and can be used in a calibrated or uncalibrated manner. PTT that reflects changes in pleural pressure and detects autonomic arousals is a useful tool to distinguish central and obstructive events. New developments, combining different simple variables analysed by visual analysis of the PSG [9], artificial intelligence or mathematical procedures, are promising. The pneumotachograph is the gold standard for accurate assessment of breathing flow. Nasal prongs have been proposed as excellent surrogates in the routine assessment of respiratory flow, especially for dynamic obstruction (hypopnoea), and have been validated extensively. For static obstruction (apnoea), thermistor or thermocouples are sufficient. A capnography-based apnoea–hypopnoea index (AHI), calculated from the end-tidal carbon dioxide tension waves, significantly correlates with the AHI as measured by traditional PSG. However, classification of apnoeas and hypopnoeas is not well validated. To assess hypoventilation during routine PSG, most often, transcutaneous carbon dioxide and end-tidal carbon dioxide are used as surrogate markers for arterial carbon dioxide tension ($P_{a}CO_{2}$). In addition, respiratory effort could be evaluated by thoracoabdominal bands, flow limitation, diaphragmatic EMG or PTT.

For a detailed description on measurement techniques, the reader is referred to the online supplement (text and tables e1.3.A–P).

#### Statements

1) Evidence shows that the nasal cannula is the best validated surrogate for hypopnoea detection for its good frequency response, while thermistor, which analyses the oronasal flow, is the recommended sensor for detection of apnoeas (A).

2) Evidence shows that RIP can be reliably used to classify respiratory events in a routine setting. Oesophageal manometry is used in selected research protocols (A).

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**TABLE 3 Subgroups of central apnoea and hypoventilation disorders according to the International Classification of Sleep Disorders (3rd edition) [3]**

<table>
<thead>
<tr>
<th>Subgroups of central apnoea and hypoventilation disorders</th>
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<tbody>
<tr>
<td>CSA with Cheyne–Stokes breathing</td>
</tr>
<tr>
<td>Central apnoea due to a medical disorder without Cheyne–Stokes breathing</td>
</tr>
<tr>
<td>CSA due to high-altitude periodic breathing</td>
</tr>
<tr>
<td>CSA due to a medication or substance</td>
</tr>
<tr>
<td>Primary CSA</td>
</tr>
<tr>
<td>Primary CSA of infancy</td>
</tr>
<tr>
<td>Primary CSA of prematurity</td>
</tr>
<tr>
<td>Treatment-emergent CSA</td>
</tr>
<tr>
<td>Obesity hypoventilation syndrome</td>
</tr>
<tr>
<td>Congenital central alveolar hypoventilation syndrome</td>
</tr>
<tr>
<td>Late-onset central hypoventilation with hypothalamic dysfunction</td>
</tr>
<tr>
<td>Idiopathic central alveolar hypoventilation</td>
</tr>
<tr>
<td>Sleep-related hypoventilation due to a medication or substance</td>
</tr>
<tr>
<td>Sleep-related hypoventilation due to a medical disorder</td>
</tr>
<tr>
<td>Sleep-related hypoxaemia</td>
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CSA: central sleep apnoea.
3) Central hypopnoeas are very difficult to score. They are defined as the proportional diminution in both naso-oral flow and respiratory effort in absence of specific characteristics of an obstructive hypopnoea: inspiratory flow flattening shape, thoracoabdominal paradox and snoring (A). For definite differentiation of central and obstructive hypopnoeas, PSG may be required (detection of sleep–wake transition, and differentiation of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep) (A).

4) There is a need for novel and simple devices and sensors for sleep diagnosis to allow straightforward and cost-effective diagnostic approaches, and thus reach a larger population.

5) The daytime hallmark feature of hypoventilation is diurnal hypercapnia. To find these patients, a series of daytime tests are useful: FVC <50% and venous bicarbonate >27 mmol (A).

6) Evidence suggests that classical PSG sensors together with measurement of \( P_{aCO_2} \) and oesophageal pressure are the optimal way to assess nighttime hypoventilation. Instead of \( P_{aCO_2} \) and intrathoracic pressure, which are invasive techniques, surrogates are used. \( P_{aCO_2} \) can be estimated by transcutaneous carbon dioxide and end-tidal carbon dioxide (A). Oesophageal pressure can be evaluated by thoracoabdominal bands, flow limitation, EMG of the thoracic muscles or PTT (A).

During noninvasive ventilation (NIV) titration, more sensors are required: minute ventilation measurement, pressures, leak sensors and procedures to detect asynchronies (the latter two are the most likely problems to occur during NIV) (A).

2. Central sleep apnoea

2.1. Pathophysiology

CSA is defined by cessation of airflow without respiratory effort, in contrast to OSA, where respiratory effort is ongoing. However, both conditions are very much related to each other. There is growing evidence that central events represent instability of the breathing pattern and that this instability may provoke obstructive events [10–12]. CSA can be related to unstable breathing caused by high loop gain or to a decreased output from the central neurons, as it also occurs in narcotic-induced CSA [13]. In these circumstances, CSA goes along with hypercapnia, but this is rather an exceptional clinical condition. In addition, delays due to haemoglobin binding and prolonged circulation time may play a role. Loop gain refers to the tendency of a patient to develop unstable breathing. Loop gain has two components [14–19]: plant gain and controller gain. Controller gain is related to chemosensitivity (hypoxic and hypercapnic ventilatory responses), while plant gain is related to the modification in carbon dioxide tension (\( P_{CO_2} \)) resulting from a given change in ventilation [10]. High loop gain predisposes to hyperventilation and subsequent lowering of \( P_{CO_2} \) below the apnoeic threshold. The apnoeic threshold is elevated during NREM sleep. When carbon dioxide drops below the apnoeic threshold, an apnoea will occur and last until the carbon dioxide increases above the threshold. Increased carbon dioxide sensitivity below the set-point for ventilation at rest (as occurs in hypoxic conditions) diminishes the difference between the carbon dioxide apnoea threshold value and the \( P_{CO_2} \) at the set point. In these circumstances, patients will rapidly develop central apnoeas [20–26]. However, nonchemical stimuli may also play a role in the elimination of respiratory drive. For example, increased frequency of controlled mechanical ventilation may lead to ventilator-induced central apnoeas [27, 28] (table e2.1.A).

2.2. Drug-induced CSA

Drug-induced CSA is incompletely explored. Drugs like sodium oxybate may promote CSA, while acetazolamide (ACT) and hypnotics like zolpidem and triazolam may attenuate the breathing disorder. The literature in this field is limited but solid data demonstrate that CSA and irregular breathing may be induced and maintained by opioids. Thus, an influence of opioid medication on breathing may be relevant in diagnostic sleep studies and during introduction of pressure-based ventilatory support.

Overview of the evidence

The typical finding after opioid intake is an increased dominance of CSA, while OSA is marginally increased or unchanged [29, 30]. Bizarre or atypical forms of breathing occur [31]. The condition is typically accompanied by nocturnal hypoxaemia [32, 33]. Sleep may be fragmented but marginally affected in published studies. Daytime hyperventilation and hypercapnia may occur [34]. Benzodiazepines may potentiate the effect of opioids on ventilation [35]. The exact mechanism of action behind breathing abnormalities during sleep is unknown but an attenuated central ventilatory chemosensory response provides a likely explanation [36].

The two main groups of clinical patients exposed to opioids are those on chronic pain treatment and those treated for opiate addiction in methadone programmes.

CSA with mixed apnoea or ataxic breathing was reported in approximately 14–60% of patients in methadone programmes [37, 38]. Similar findings were reported in patients with chronic pain receiving...
opioid analgesics. A study in patients on chronic opiate therapy for pain found significant CSA in 24% [35], while other studies suggested a lower prevalence [39]. A small randomised controlled trial (RCT) of remifentanil reported a dramatic shift from OSA to CSA in patients with moderate OSA [29]. Some [35, 37] but not other [38] studies reported an association between opioid plasma concentration and conventionally assessed respiratory variables, suggesting considerable interindividual differences in pharmacodynamics for this response. In the light of a widespread long-term use of opioid analgesics, their potential negative influence on sleep-related breathing disturbances appears to be incompletely recognised in clinical sleep medicine.

Some studies have investigated how the effectiveness of pressure-based therapy is affected by chronic opioid medication [40, 41]. Residual respiratory events and hypoxaemia were seen after both CPAP and adaptive servventilation (ASV) therapy [42], and ASV was potentially superior to CPAP [43] and effective in almost 60% of patients with complex apnoea related to chronic heart failure (CHF) or chronic opioid use [44]. Other data suggest that a combination of positive airway pressure (PAP) and oxygen may be particularly effective in patients on prescribed opioid therapy [44] (tables e2.2.A–C).

**Statements**
1) Opioids may, in a dose-dependent manner, induce CSA dominated by hypoxaemia during sleep (B).
2) Most data suggest that both ASV and bilevel positive airway therapy are superior to conventional CPAP for elimination of opioid-associated CSA (B).

### 2.3. CSA at high altitude

Altitude-related effects on control of breathing (normo/hypocapnic CSA) and sleep and altitude-related illnesses are increasingly recognised as important health problems worldwide, especially due to growing global tourism [46, 47].

**Overview of the evidence**

CSA at altitude is termed high-altitude periodic breathing (HAPB). The definition is not standardised and methods used to assess ventilation vary among studies. Major limitations of published studies prevent definitive conclusions on certain aspects of HAPB. Nevertheless, available data suggest that HAPB may occur in healthy subjects at altitudes of >1600 m and is associated with sleep disturbances [48]. With increasing altitude, the amount of HAPB and the percentage of affected persons increase. At extreme altitude (6850 m), CSA has been observed in all exposed mountaineers with AHI as high as 140 events per h [49]. Acclimatisation has been associated with persistence or even a further increase in the amount of HAPB [50]. Whether altitude-related illness such as acute mountain sickness or high-altitude pulmonary oedema predisposes to HAPB requires further studies (table e2.3.A).

Few studies suggest that ACT reduces HAPB in healthy subjects at altitude [51]. In subjects susceptible to high-altitude pulmonary oedema, dexamethasone reduced HAPB and improved nocturnal oxygen saturation at 4559 m [52]. Oxygen enrichment of room air or recompression in a hypobaric chamber also reduced the amount of HAPB.

Data on patients with pre-existing respiratory disorders at altitude are scant. RCTs have been performed in patients with obstructive sleep apnoea syndrome (OSAS). Untreated lowlanders with OSA living below 800 m experienced pronounced hypoxaemia and an exacerbation of breathing disorders with predominant CSA during a stay at 1630 and 2590 m [53]. Treatment with ACT improved HAPB partially [54], and combined treatment with acetazolamide and automatic continuous positive airway pressure (autoCPAP) nearly completely prevented emergence of HAPB/CSA in OSA patients at 1630 and 2590 m [54] (table e2.3.A–B).

**Statements**
1) Healthy lowlanders travelling to altitudes >1600 m may experience CSA, which is termed HAPB in this setting. The severity of CSA/HAPB increases with increasing altitude (B).
2) Patients with OSAS living near sea level may show exacerbation of breathing disturbances in the first few days at altitude.
3) The evidence suggests that oxygen-enriched air or ACT reduces CSA/HAPB and improves nocturnal oxygen saturation in healthy lowlanders staying at altitude (B).
4) Combined treatment with ACT and automatic positive airway pressure (APAP) is an appropriate treatment in this setting as it prevents central apnoeas and improves nocturnal oxygen saturation compared to APAP alone (B).
2.4. CSA in cardiovascular diseases

2.4.1. CSA in heart failure

CSA is highly prevalent in patients with stable congestive heart failure with reduced ejection fraction (HFrEF) [56] but also in those with preserved ejection fraction (HFpEF) [57]. It presents as normo/hypocapnic CSA. While it is recognised that heart failure contributes to the development of CSA [58] and that CSA is associated with impaired prognosis in these patients, the role of treatment of CSA in heart failure is of debate. Cardiovascular diseases that contribute to the severity of heart failure, such as hypertension, coronary artery disease and atrial fibrillation, may worsen CSA [59]. Evidence that CSA aggravates hypertension, coronary artery disease or atrial fibrillation is sparse. Therefore, the focus of this chapter is on heart failure [2].

2.4.1.1. Prevalence of CSA in heart failure

CSA (AHI $\geq 15$ events per h sleep) occurs in 21–37% of patients with stable congestive HFrEF [60–63]. Despite increased use of $\beta$-receptor blockers and spironolactone, which should reduce the propensity for CSA, the CSA prevalence did not change [63]. The cohorts studied were predominantly male [60, 62, 63]. Patients with CSA and HFrEF have lower left ventricular ejection fraction (LVEF), and higher New York Heart Association functional class and pulmonary capillary wedge pressure (PCWP) compared to those HFrEF patients with OSA or without sleep-related breathing disorders [60, 62, 63].

The prevalence of CSA in HFpEF is less defined. Estimates vary from 18% to 30% depending on body weight, the cut-off levels used and the different diagnostic criteria of HFpEF [57, 64–66]. Prevalence of CSA increases with increasing impairment of diastolic function [57]. By contrast, CSA is rather uncommon among subjects with at least one risk factor for diastolic dysfunction, but without overt HFpEF [67]. Compared to OSA patients, those with CSA and HFpEF have a worse haemodynamic profile, while those with both OSA and CSA have a higher body mass index (BMI) and are more likely to have hypertension compared to patients without sleep apnoea [57].

Statements
1) CSA is a common comorbidity of HFrEF and HFpEF (A).
2) The severity of CSA is related to the severity of HFrEF and HFpEF (C).

2.4.1.2. Prognostic significance of CSA in patients with HFrEF

Previous studies were limited by their small sample size [68–70], a low number of women [68–75] and noncontemporary heart failure therapy (e.g. low rate of $\beta$-blocker use and device therapy) [68–72, 76]. Nevertheless, the vast majority of these studies found that HFrEF patients with CSA have an increased mortality risk or risk for death/heart transplantation [69, 71–77]. This risk is most evident in moderate-to-severe CSA (AHI $\geq 20$ events per h) and is independent of the severity of heart failure [72–75]. Most recently, data from a large, long-term observational study confirmed increased mortality in hospitalised HFrEF patients with CSA [78]. One possible mechanism is that CSA promotes malignant ventricular arrhythmias [79, 80].

Statements
1) In HFrEF, there is an association between the presence of CSA and an increased risk of ventricular arrhythmias (C).
2) In HFrEF, the presence of CSA is associated with an increased risk of death (B).

2.4.1.3. Treatment of CSA in heart failure

Treatment of CSA in heart failure is summarised in figure 1.

Treatment of heart failure

Treatments of heart failure that reduce PCWP [62] or increase LVEF [58, 81] can alleviate or abolish CSA (e.g. mitral valvuloplasty [82], cardiac resynchronisation therapy or left ventricular assist device [81, 83] and cardiac transplantation [58]). Normalisation of LVEF by cardiac transplantation is associated with a resolution of CSA in 50% of cases [58].

Respiratory stimulants

Respiratory stimulants, such as theophylline, ACT and carbon dioxide, augment ventilation in HFrEF with normocapnic or hypocapnic CSA [84–88]. These agents can alter respiratory control instability, decrease the likelihood of crossing the apnoea threshold, and diminish the propensity for central apnoeas and hypopnoeas [84, 85, 89, 90].
Oxygen
It has been consistently shown that supplemental oxygen reduces the AHI by 37–85% in stable HFrEF with CSA [84, 91–98]. Normalisation of $S_aO_2$ in hypocapnic HFrEF patients is accompanied by rises in $P_{CO_2}$ and persistence of periodic breathing [84]. In the absence of oxygen desaturations, such respiratory events are not scored as hypopnoeas [99]. Although nocturnal oxygen therapy may reduce CSA, hypoxia and LVEF in heart failure, the available evidence at this time may not support its use in the long term [94, 97, 98]. However, other end-points such as exercise capacity [94] or catecholamines [95] were positively affected.

Continuous positive airway pressure
Based on findings from short-term single-centre trials, CPAP can alleviate CSA, improve LVEF and quality of life (QoL), and reduce sympathetic activity, mitral regurgitation and biomarkers of heart failure (e.g. atrial natriuretic peptide) [69, 100–102]. Minute ventilation during sleep fell and $P_{aCO_2}$ levels rose to normal values with CPAP in HFrEF patients with hypopnoea [103]. The largest and longest-only, multicentre RCT of CPAP in HFrEF and CSA was the CanPAP (Canadian Positive Airway Pressure for Heart Failure and Central Sleep Apnoea) trial [104]. CPAP reduced the AHI by 53% with residual CSA (AHI ≥15 events per h) persisting in 43% of the 258 patients. LVEF and exercise capacity increased modestly while sympathetic activity, fell consistent with previous studies. CPAP did not improve transplant-free survival. A post hoc analysis [105] indicated that patients whose AHI was suppressed below 15 events per h had a significantly greater improvement in LVEF and transplant-free survival, suggesting that suppression of respiratory disturbances may contribute to improved cardiovascular outcome. HFrEF with CSA that persists on CPAP treatment has increased mortality rates [104, 105].

Bilevel positive airway pressure
Bilevel positive airway pressure (BPAP) involves expiratory and inspiratory PAP support (EPAP and IPAP, respectively). The EPAP is set to the lowest level maintaining upper airway patency, thus suppressing obstructive disturbances. BPAP can be applied without (spontaneous (S) mode) or with a back-up rate (spontaneous-timed (ST) mode).
Spontaneous BPAP

In HFrEF with severe CSA, BPAP-S significantly reduces the AHI [106, 107]. However, BPAP-S seems no more effective than CPAP [107]. In one small RCT, use of BPAP-S was associated with an absolute increase of LVEF of 20.3±8.2%. Whether this effect was independent from medical intervention is uncertain [106].

Spontaneous-timed BPAP

There is consistent evidence that, in patients with HFrEF with severe CSA, BPAP-ST reduces the AHI [96, 108–110]. In one RCT, in HFrEF patients with severe CSA, BPAP-ST was more effective than CPAP [96]. While in HFrEF patients with hypocapnic CSA, CPAP and ASV led to an increase in $PCO_2$, BPAP-ST did not change $PCO_2$, indicating that hyperventilation is maintained with this treatment.

Three trials reported that BPAP-ST improves LVEF [108, 109]. In the only RCT, the increase of LVEF in the BPAP-ST group (26–31%, p<0.01) was not significantly different from the control intervention ASV (25–27%) [110].

Adaptive servoventilation

ASV was designed to stabilise ventilation in patients with CSA and CSB. Algorithms of the ASV devices vary. Common to all devices is that EPAP is applied to facilitate upper airway patency. In order to counterbalance excessive ventilatory responses and central hypopnoea or apnoea, a variable inspiratory pressure support and a back-up rate are applied. The devices attempt to maintain a target minute ventilation/flow, which is just below the long-term average ventilation of the patient.

ASV suppresses central apnoea and hypopnoea more efficiently than oxygen, CPAP or BPAP-ST [96, 111–116]. A meta-analysis indicated that the AHI is reduced by 31 events per h (95% CI −25−−36 events per h) over baseline and by 12–23 events per h compared with CPAP [117]. In addition, ASV normalises $PCO_2$ in HFrEF patients with hypocapnic CSA during sleep [78, 96].

With respect to cardiac function, a meta-analysis of six nonrandomised [118–123] and four RCTs [110, 113, 115, 124, 125] examined the effects of ASV on LVEF compared to control interventions. ASV improved LVEF and the 6-min walk distance [125]. However, the majority of the RCTs did not support that ASV improves LVEF more than control interventions (standard medical therapy, CPAP or BPAP-ST) [110, 115, 124, 126]. RCTs in HFrEF with CSA consistently demonstrate that ASV reduces brain natriuretic peptide (BNP) (N-terminal pro-BNP) [113, 115, 124, 126–128], indicating improvement of cardiac loading conditions and function. In addition, ASV in HFrEF and CSA reduces muscle and cardiac sympathetic nerve activity [129–131].

In observational studies, PAP treatment targeted to suppress CSA (CPAP or ASV) in patients with HFrEF with severe CSA is associated with significant improvement in survival [74, 75] and a reduction in ventricular arrhythmias [132]. The intention-to-treat analysis of the large-scale RCT SERVE-HF in patients with HFrEF (LVEF ≤45%) did not show a difference in the primary combined end-point. However, it showed a significantly higher all-cause and cardiovascular mortality in the ASV group compared to the control group [74]. To date, publication of important SERVE-HF explorative subanalyses and results from another larger scale trial (ADVENT-HF) are pending [133].

Few data are available on treatment of CSA in HFpEF or HFrEF with concomitant diastolic dysfunction and these mainly refer to ASV [134–136]. In an observational, uncontrolled study [118], ASV was effective in reducing CSA and improving cardiac function. Only one study addressed the potential prognostic impact of SDB in HFpEF. In a RCT including 36 patients, ASV significantly improved the central as well as the obstructive apnoea index, with an 18-month higher event-free rate [135]. However, this study is difficult to interpret in our context, since obstructive apnoeas were common (table e2.4.1.A).

Statements

1) Evidence shows that optimal cardiac treatment of HFrEF may improve CSA (C).

2) Evidence suggests that HFrEF patients with CSA can be treated with CPAP, if CPAP suppresses CSA and improves symptoms (C).

3) In heart failure and symptomatic CSA, the members of the Task Force perform a trial of CPAP (C). However, if CPAP does not suppress CSA, they do not continue it for prolonged periods.

4) ASV normalises the AHI in patients with CHF and CSA more effectively compared to CPAP therapy and nocturnal oxygen (A).

5) Based upon the available information at this time, members of the Task Force stop prescribing ASV to treat CSA in patients with stable HFrEF with LVEF ≤45% (B).
6) Before starting a patient with CSA on ASV, the members of the Task Force assess for the presence of HFrEF with an LVEF $\leq 45\%$ to see if they are in the higher risk group (C).

7) The members of the Task Force use BPAP-ST, ACT and theophylline only in normo/hypocapnic CSA related to HFrEF, if adequate trials of indicated therapies fail (C).

### 2.4.2. CSA in stroke patients

CSB is regarded as a characteristic sequel of an extensive cerebrovascular accident and regularly found immediately after the stroke, while it declines markedly 3 and 6 months into recovery [137, 138]. The prevalence varies widely (3–72%) [139–142], the pathophysiology is poorly understood, the influence of CSB on the recovery of stroke patients remains unclear and CPAP therapy is only tolerated by a minority of patients (table e2.4.2.A).

**Statement**

Evidence shows that CSA is often present in patients after stroke but the prognostic significance of CSA in these patients is still uncertain (C).

### 2.5. CSA in other internal or neurological diseases, other than cardiovascular diseases

#### 2.5.1. CSA in other internal diseases

Certain endocrine diseases have been reported to be associated with CSA. No systematic screening efforts are performed today with the exception of screening procedures for OSA in acromegaly patients.

**Acromegaly**

SDB is frequent in patients with acromegaly and the majority of these patients present with OSA. A number of studies has reported an increased prevalence of CSA [143] of up to 32% [144], but more recent studies could not confirm those findings [145, 146]. In total, close to 10% of patients with acromegaly fulfill the criteria for CSA, which may be considered as mild CSA. The central apnoea index (CAI) was associated with serum levels of growth hormone, and increased ventilatory responses were associated with growth hormone and insulin-like growth factor-1 levels, suggesting specific pathogenic mechanisms explaining the occurrence of CSA in acromegaly [147, 148]. In addition, patients with CSA also have concomitant cardiac diseases [143, 149]. Surgical or medical treatment of acromegaly may reduce OSA. However, there are no controlled studies addressing treatment effects on CSA (table e2.5.A.).

**Diabetes mellitus**

An early report described a high prevalence of both CSA and OSA in a small group of type 1 diabetes mellitus patients [150]. Subsequent studies found that OSA is the dominant type of SDB in diabetes mellitus and the association is strongly linked to concomitant obesity in type 2 diabetes [151–153]. The occurrence of CSA in diabetes mellitus has been addressed only in a limited number of studies. The Sleep Heart Health Study reported a small but nonsignificant elevation of CSA [154]. In addition, a specific analysis of periodic breathing pattern showed a significant increase in patients with manifest diabetes mellitus. Pharyngeal neuropathy might contribute but no specific pathogenic mechanisms have been clearly identified for an increased likelihood of CSA in diabetes. No association between CSA and autonomic dysfunction could be established [155]. Consequently, the effect of CPAP on CSA in diabetics has not been specifically addressed. In the same line of evidence, patients with diabetes are not overrepresented in the group of OSA patients with treatment-emergent CSA [156] (table e2.5.B).

**End-stage renal disease**

OSA is frequent in end-stage renal disease (ESRD). TADA et al. [157] reported on 30 patients with sleep apnoea in a group of 78 patients on haemodialysis. However, the mean CAI was 4.1 events per h and central apnoea constituted 8% of all SDB events. Eight out of 30 patients showed an elevated CAI ($\geqslant 5$ events per h) and were subsequently classified as patients with CSA.

Fluid retention and centralisation have been shown to be underlying mechanisms for the elevated occurrence of OSA in ESRD [158, 159]. Increased ventilatory sensitivity and destabilised control of breathing also contribute to the increased prevalence of SDB in ESRD [160]. Risk factors for CSA in ESRD include atrial fibrillation and comorbid cardiac dysfunction [157], indicating synergic effects on the occurrence of CSA.

The number of interventional studies for the elimination of CSA is limited and data are uncontrolled. Nocturnal haemodialysis has been proven superior in reducing CSA over conventional haemodialysis during daytime [161]. The results have been supported by subsequent studies. Another approach investigated the effect of different buffers during haemodialysis on CSA [162]. Bicarbonate was associated
with significantly less CSA when compared with acetate buffer, despite similar blood gases. One study showed a high efficacy of CPAP on the reduction of central/mixed apnoeas in ESRD on haemodialysis [163]. A recent observational study reported beneficial effects of ASV on renal function and cardiovascular outcome in 36 patients with CHF and chronic kidney disease, when compared to a control group of 44 patients who did not accept or tolerate ASV [164]. Importantly, patients with ESRD or on haemodialysis at study start were excluded from this study. Finally, nasal oxygen therapy during sleep significantly reduced sleep apnoea in ESRD patients (table e2.5.C).

**Statements**

1) The prevalence of CSA is low in patients with acromegaly and related to disease activity. In diabetes mellitus, OSA is the dominant type of SDB. In ESRD, CSA prevalence is dependent on dialysis procedures and fluid shift during the night (B).

2) The members of the Task Force treat clinically significant CSA in acromegaly, diabetes mellitus and ESRD with CPAP or ASV (C).

### 2.5.2. CSA and hypoventilation in interstitial lung disease

In interstitial lung disease (ILD), nocturnal cough, adverse medication effects, periodic limb movements, breathing difficulties, hypoxaemia, obstructive apnoeas, depression and fatigue may lead to sleep disturbances. The results of recent studies suggest that sleep apnoea may contribute to a worse prognosis in idiopathic pulmonary fibrosis (IPF) [165]. The role of CSA is not well studied in ILD. Nocturnal hypoxia is frequent, whereas the factors leading to nocturnal oxygen desaturations still need to be clearly characterised.

**Overview of the evidence**

Impairments in gas exchange and restrictive lung function abnormalities increase respiratory effort. During sleep, some investigators have found no change of the respiratory rate [166–169]. One study described a decreased respiratory rate with an increased tidal volume and maintained minute ventilation during sleep [170]. There is limited but increasing evidence that ILDs may be associated with the occurrence of SDB. Data are predominantly generated from patients with IPF, sarcoidosis and scleroderma-associated ILD. Analysing the prevalence of SDB in ILD, most trials have focused on OSA and found an incidence between 22% and 90%, whereas the clinical relevance remains unclear [165, 171–175]. However, recent data indicate that the prevalence of clinically significant OSA in IPF is relatively low [175].

Most hypoxic ILD patients show a compensatory hyperventilation. In some cases, the $P_{CO_2}$ may fall below the apnoeic threshold. Overall, there are very little data on hypoventilation and/or central apnoea syndrome in ILD. **KOLLEKAS et al.** [165] analysed the sleep characteristics of 31 consecutive IPF patients and found a low CAI. Nocturnal hypoxia is a common phenomenon in ILD and recent studies identified nocturnal oxygen desaturation as an independent predictor of poorer prognosis [165, 176]. **PEREZ-PADILLA et al.** [169] did not detect OSA in their ILD subjects but found transient oxygen desaturations in ∼50% of total sleep time (transcutaneous oxygen saturation <90%). It is unclear whether oxygen desaturations in non-OSA patients are caused by central apnoeas or hypoventilation but the finding of significant elevation in transcutaneous carbon dioxide levels during sleep in patients with IPF supports hypoventilation as a significant factor [175]. Whereas daytime hypoxaemia is a predictor of nocturnal oxygen desaturation, severity of lung restriction and degree of oxygen desaturation with exercise does not correlate with nocturnal hypoxaemia [177–179]. Oxygen desaturation is more pronounced during sleep than during exercise in patients with IPF [175]. **TATSUMI et al.** [179] analysed the respiratory drive in ILD patients, measuring the change in ventilation in response to changes in $P_{CO_2}$. In their study, daytime respiratory drive showed a negative correlation with the degree of oxygen desaturation in REM and NREM sleep. These data suggest that chemoresponsiveness to elevated $P_{CO_2}$ may play a role in the susceptibility to hypoxia.

There is very little evidence on the effect and no data on the prognostic benefit of oxygen supplementation in ILD patients. **SHEA et al.** [180] were able to show that in ILD patients, the elevated respiratory rate and minute ventilation volume could be reduced by nocturnal supplementation of oxygen. In another study in hypoxic ILD patients, heart rate and respiratory rate could be reduced and oxygenation improved by low-flow oxygen supplementation [181].

**Statements**

1) There is very little evidence on the prevalence and prognostic relevance of CSA and hypoventilation syndromes in ILD patients (D).
2) There is only little evidence on the beneficial effects of oxygen supplementation in case of nocturnal hypoxaemia. Elevated respiratory rate, respiratory minute volume and heart rate are reduced by oxygen supplementation (C).

2.5.3. CSA and pulmonary hypertension
Pulmonary hypertension is a haemodynamic and pathophysiological state consequential to multiple clinical conditions or diseases. While CSB and CSA are common in congestive heart failure, there are only few data on precapillary pulmonary hypertension. Between 0% and 45% of pulmonary hypertension patients have central breathing disturbances when compared with the prevalence of 0–56% for OSA [174–178, 182]. OSA was predominant in chronic thromboembolic and COPD-associated pulmonary hypertension and CSA was mainly seen in idiopathic or chronic thromboembolic pulmonary hypertension.

Possible pathophysiological explanations for CSA in pulmonary hypertension include: 1) a fluid shift at night from the legs to the thorax; 2) an impaired cardiac output with a prolongation of circulation time and ventilation–perfusion mismatching, which all promote hyperventilation and hypocapnia, thereby predisposing CSA [183]; and 3) changes in chemosensitivity with a decreased hypoxic drive may prolong apnoeas by delaying the onset of hyperventilatory phases [184].

It is unclear whether central disturbances are of any clinical significance in pulmonary hypertension. From a pathophysiological point of view, it might lead to a disturbed sleep structure and also worsen pulmonary hypertension, as the apnoea-induced hypoxia could induce further pulmonary artery vasoconstriction. In most studies, CSA was not associated with excessive sleepiness. In one study, patients with central SDB had impaired QoL in the physical domains [185].

Nasal oxygen improved periodic breathing in one observational study [184]. We identified only one randomised placebo-controlled trial [186] in patients with precapillary pulmonary hypertension demonstrating that both nocturnal supplemental oxygen and ACT improved nocturnal oxygenation, periodic breathing and exercise performance (table e2.5.D).

**Statements**
1) There is limited evidence suggesting that the prevalence of central apnoeas and periodic breathing is increased in pulmonary hypertension (B).
2) The Task Force members usually screen patients with pulmonary hypertension by cardiorespiratory sleep studies (B).
3) The pathophysiological effect of SDB and the impact of treatment are unclear in these patients (B).
4) Preliminary evidence suggests that both nocturnal supplemental oxygen and ACT may improve nocturnal oxygenation and periodic breathing in precapillary pulmonary hypertension (B).

2.5.4. CSA in neurological diseases other than stroke
The prevalence of SDB is high in patients with several neurological diseases other than stroke. Only few studies analysed specifically CSA and no RCTs have been performed so far that address effects on central SDB.

**Neurodegenerative disease**

**Parkinson’s disease**
The prevalence of sleep apnoea in Parkinson’s disease varied between 20.9% and 66.6% and the majority of studies included a limited number of patients (15–100). OSA is the dominant type of SDB and only few cases are reported to have CSA. In summary, central apnoeas appear not to be elevated in patients with Parkinson’s disease (table e2.5.E).

**Alzheimer’s disease**
Several studies report on the prevalence of OSA in patients with dementia, in particular in patients with Alzheimer’s disease. There are no consistent data on an increased prevalence of central apnoeas in Alzheimer’s disease (table e2.5.F).

2.6. Treatment-emergent central sleep apnoea
The term complex sleep apnoea has been introduced for central apnoeas developing under treatment with CPAP for OSA [187]. The ICSD-3 defines treatment-emergent CSA by: 1) \( \geq 5 \) event per h of predominantly obstructive respiratory events in the diagnostic PSG; 2) significant resolution of obstructive events and emergence or persistence of central events during PAP treatment with a central AHI \( \geq 5 \) events per h and \( \geq 50\% \) central events; and 3) the phenomenon must not be better explained by another CSA disorder.
Overview of the evidence

CSA under therapy can be differentiated according to the response to continued PAP therapy without a back-up respiratory rate [188]. 1) Treatment-emergent CSA is only rare CSA on the baseline evaluation; CSA under CPAP disappears with continued CPAP use. 2) In treatment-persistent CSA, CSA emerges and remains under continuous CPAP use. These phenotypes should be separated from CSA that exists prior to treatment and is not induced by CPAP (treatment-resistant CSA) [188]. The majority of patients with treatment-emergent CSA lost the phenomenon in a prospective follow-up study in 675 OSA patients [189]. The substantial differences in prevalence may be due to different definitions and patient populations [3, 190, 191]. In order to prevent misdiagnosis of treatment-persistent CSA, it is crucially important to identify and treat any underlying diseases [192]. Sleep insufficiency, insomnia and arousals can contribute to the transient emergence of CSA [190, 191]. Excessive titration, post-hyperventilation or post-arousal apnoea, and excessive mouth leakage, misclassification of central hypopnoeas [9, 77, 84, 193], split-night error [194, 195], and adaptation of the loop gain after resolution of upper airway obstruction [196–198] have to be excluded, and do not fulfil the diagnosis of treatment-persistent CSA.

Most studies included primarily patients with almost pure CSB/CSA, while some cohort studies and RCTs focused on co-existing OSA and CSA [115, 199–201]. However, these populations should be differentiated from treatment-persistent CSA. MORGENTHALER et al. [202] performed a multicentre RCT comparing optimised CPAP with ASV over 90 days. Due to a variety of underlying diseases, the definition of treatment-persistent CSA is unclear in the population. The efficacy of CPAP improved substantially over time. However, ASV was superior in terms of respiratory disturbances [195].

Another RCT compared ASV and BPAP-ST in CPAP-persistent CSA. BPAP-ST and ASV significantly and substantially reduced the AHI during the first night. In contrast to BPAP-ST the effect of ASV was stable over time [203] (table e2.6.A).

Statements

1) The members of the Task Force use the term treatment-persistent CSA for patients with CSA newly developing under treatment with CPAP or BPAP and persisting under continuous use (A).

2) They describe the combination of OSA with any phenotype of central disturbances or hypoventilation as ”co-existing OSA and CSA (or CSB or hypoventilation)” (D).

3) They do not use the diagnosis of treatment-emergent CSA for CSA in patients with underlying cardiovascular, endocrine, renal or neurological diseases, or for pre-existing CSA prior to initiation of PAP and transient CSA (A).

4) Evidence suggests that avoidable causes of CSA under PAP may include excessive titration, post-hyperventilation apnoea, post-arousal apnoea, overestimation due to split-night error and misclassification of central hypopnoeas (C).

5) ASV has been shown to more effectively improve treatment-persistent CSA compared to oxygen, CPAP, BPAP-ST and NIV (B).

2.7. Idiopathic CSA

Idiopathic central sleep apnoea (ICSA) is a rare disease of unknown prevalence and origin. It typically presents as hypocapnic CSA. The events are often associated with arousals and consequent hyperventilation leading to a fall of the carbon dioxide level below the apnoea threshold [204]. The relevance of these findings in the pathophysiology of ICSA is in agreement with the therapeutic efficacy of the elevation of carbon dioxide via inhalation or added dead space [205]. There are very limited data on the treatment with zolpidem, ACT or PAP [206–209]. The reduction of arousals by zolpidem was associated with a significant reduction of central apnoeas. Similarly, ACT improved arousals and central apnoeas in a short-term case series. There are no systematic studies but only small case series on the application of PAP in ICSA (table e2.7.A)

Statements

1) Evidence on the epidemiology, pathophysiology and outcome of ICSA is limited (D).

2) The members of the Task Force perform treatment trials with zolpidem or ACT only in symptomatic patients under close supervision (D).

3) CPAP or ASV may be considered in individual symptomatic cases (D).
3. Hypoventilation or hypoxaemic syndromes

3.1. Pathophysiology

Hypoventilation implies a level of alveolar ventilation inadequate to maintain normal gas exchange, typically resulting in hypoxaemia and hypercapnia. Pathophysiological situations include neuromuscular disorders (NMDs) [209, 210], thoracic cage disorders and other mechanical factors [211, 212]. Obesity represents the most common context for hypoventilation to the extent that the combination of obesity and hypoventilation is referred to as the obesity hypoventilation syndrome (OHS) [213].

While single mechanisms may predominate in disorders such as congenital central hypoventilation or thoracic cage deformity, in most cases, increased mechanical load to breathing and decreased ventilatory drive/response combine to produce the overall result. Hypoventilation must be distinguished from sleep apnoea, although both may co-exist since pathophysiological factors are frequently shared [214]. CSA is particularly likely in patients with underlying central neurological disorders, whereas OSA is most likely in patients with obesity [215]. In most patients with hypoventilation, the associated hypercapnia can be reversed by voluntary hyperventilation, which can be objectively evaluated by blood gas measurements before and after a period of hyperventilation.

3.1.1. Pathophysiology of obesity-associated hypoventilation

Obese subjects have an increased demand for ventilation and elevated work of breathing, in addition to slight respiratory muscle weakness and diminished respiratory compliance [216]. Thus, obese individuals have an increased central respiratory drive compared with normal weight patients to compensate for the increased ventilatory requirements [212, 217].

Truncal obesity imposes a significant mechanical load on the respiratory system [218] with evidence of reduced chest wall compliance. Reduced functional residual capacity and peripheral airway obstruction contributes to an increased work of breathing [219]. Expiratory flow limitation [220] promotes dynamic pulmonary hyperinflation and intrinsic positive end-expiratory pressure (PEEPi) [221]. CPAP results in reduced diaphragm electromyogram and inspiratory pressure swings, in addition to removal of PEEPi in obese subjects when supine [212]. Hypercapnic obese patients demonstrate increased upper airway resistance (UAR) both in the upright and supine position, whereas similarly obese normocapnic patients have increased UAR only in the supine position [222]. These factors could result in fatigue and relative weakness of the respiratory muscles.

There is evidence that leptin resistance may contribute reduction in central drive and central hypoventilation in obese patients [223], since serum leptin levels are higher in hypercapnic obese patients after controlling for other confounding variables and levels fall after PAP therapy [224]. Furthermore, OHS patients demonstrate impaired compensatory responses to nocturnal hypercapnia in the setting of nocturnal hypoventilation and/or co-existing sleep apnoea [225]. Such compensatory mechanisms include renal bicarbonate retention and hyperventilation in between periods of apnoea or hypopnoea [226], both of which may be deficient in OHS.

3.1.2. Other mechanisms of hypoventilation

The purest form of hypoventilation relates to inadequate central respiratory drive (Ondine’s curse). This rare form of hypoventilation with impaired chemoreceptor responses is usually congenital and has been demonstrated to be associated with a mutation in the PHOX2B gene with an autosomal-dominant mode of inheritance [227, 228].

A wide range of NMDs may also result in hypoventilation as a consequence of respiratory muscle insufficiency and/or dysfunction [210]. These disorders adversely affect the transmission of respiratory stimulant signals from the brainstem respiratory centre to the respiratory muscles, resulting in insufficiency of contraction in the case of neurological disorders or dysfunction. Hypoventilation is most pronounced during sleep as a consequence of sleep-related physiological adaptations [214] and there may also be associated sleep apnoea.

Statements

Evidence shows that:

1) hypoventilation is typically the result of increased mechanical load to breathing and decreased ventilatory drive/response, which frequently interact (A);

2) obesity is the most prevalent factor contributing to hypoventilation by means of increased mechanical load (A);

3) hypoventilation may co-exist with sleep apnoea, since pathophysiological factors such as obesity and central respiratory insufficiency are frequently shared (A);
4) central hypoventilation is a rare form of hypoventilation, which may be congenital as a result of deficiency of the PHOX2B gene (A); and
5) NMDs may result in hypoventilation as a consequence of respiratory muscle insufficiency and/or dysfunction (A).

3.2. Congenital hypoventilation syndrome
Although rare, the problem of congenital hypoventilation is more often detected, and not limited to children, if genetic assessment is performed. Patients have a better life expectancy when treated with NIV. For further description, the reader is referred to the online supplement (text and tables e3.2 A.-C).

3.3. Hypoventilation/hypoxic diseases secondary to internal or neurological disorders
During disease progression, alveolar hypoventilation (hypercapnic response) develops in several NMDs, such as amyotrophic lateral sclerosis (ALS) [229, 230], Duchenne muscular dystrophy (DMD) [231–237], myotonic dystrophy [238–241] and acid maltase deficiency (AMD) [242, 243].

Amyotrophic lateral sclerosis
Various pulmonary function tests, especially inspiratory muscle strength tests, are used to evaluate alveolar hypoventilation [229, 244–249]. Besides treatment with riluzole, NIV is the only treatment option to increase survival in ALS [229, 230, 240–249]. Strategies to increase therapeutic adherence should be encouraged [229, 230, 240–249]. In some cases, tracheal invasive ventilation is used with an improvement in survival [240–249], while diaphragm pacing seems to have no benefit [250]. NIV can improve QoL [230, 244–249], gas exchange [241, 242] and subjective sleep quality [230, 241, 242, 243], which is often impaired in these patients [242–249]. In contrast, NIV has divergent results on objective measures of sleep [242–249] (table e3.3.A).

Duchenne muscular dystrophy
In DMD patients, PaCO2 and vital capacity predict nocturnal hypoventilation [231, 232], while a vital capacity ≤680 mL predicts hypercapnic failure. Daytime minute ventilation, symptoms, forced expiratory volume in 1 s and base excess have less predictive value. PSG has an additional benefit in DMD patients showing symptoms of OSA. NIV can improve survival, gas exchange and the rate of hospitalisation. Other medical and surgical treatments can also improve respiratory outcomes. Diurnal NIV has shown its benefit in prolonging survival, while tracheal invasive ventilation is an option in selected cases [231–236, 240–243, 244–247] (table e3.3.B.).

Myotonic dystrophy
Age, sex, vital capacity, muscular disability and respiratory muscle strength, but not myotonia itself, appear to be related to hypercapnia. Recently, a study suggested the presence of a central cause of carbon dioxide insensitivity [240]. NIV can improve gas exchange in myotonic dystrophy patients. Prolonged ventilation in congenital myotonic dystrophy patients is related to greater morbidity and developmental delay [238, 240, 241] (table e3.3.C).

Acid maltase deficiency
Hypoventilation in patients with AMD can be predicted from daytime lung function measurements. NIV improves gas exchange. Enzyme replacement therapy has a positive impact on ventilatory failure and survival [242, 243, 270–274] (table e3.3.D).

Mixed NMDs
Studies in heterogeneous NMD populations indicate pulmonary function tests predict SDB. Improvements in gas exchange and symptoms have been observed with NIV. The effects on sleep are divergent [275, 276]. Leaks and patient–ventilator asynchrony seem to affect sleep structure [275, 277–281] (table e3.3.E).

Statements
1) Alveolar hypoventilation is frequently present in several NMDs, including ALS, DMD, myotonic dystrophy and AMD (A).
2) NIV improves survival in ALS (B) and DMD (C).
3) NIV can improve gas exchange and symptoms in NMD (B).
4) NIV improves QoL in ALS and DMD (B).
5) 24 h NIV is a treatment option in NMD when diurnal hypoventilation develops (B).
3.4. Kyphoscoliosis

SDB is highly prevalent in kyphoscoliosis and is often treated using NIV. However, there are no large-scale studies examining the effects of SDB treatment during sleep in kyphoscoliosis.

Sleep (breathing)

Studies examining sleep architecture [282, 283] revealed decreased sleep efficiency with increased stage 1 and reduced slow-wave sleep. The finding that SDB was most common during REM sleep was consistent throughout all studies. Although apnoea and hypopnoea can be present, hypoventilation (hypercapnic response) is the predominant form of SDB in kyphoscoliosis [282–291] (table e3.4.A).

Impact of nocturnal NIV

Sleep hypoventilation improves with nocturnal NIV. However, no amelioration in sleep architecture could be demonstrated [282, 289], and sleep fragmentation associated with transient oxygen desaturations and massive leakage was observed [287]. In contrast, daytime improvements in symptoms related to sleep hypoventilation including subjective sleep quality have been reported.

Daytime $P_{\text{a}O_2}$ and/or $P_{\text{a}CO_2}$ also significantly improve [233, 287–295] and this amelioration is sustained over years [233, 288, 289, 292, 295]. Data on the impact of NIV on inspiratory muscle force or vital capacity are conflicting (no effect versus amelioration), while studies on respiratory drive are scarce [282, 292]. Improvement in dyspnoea sensation and exercise capacity was found in some but not all studies. All studies observed a significant reduction in hospitalisation rate. The survival of kyphoscoliotic patients on NIV is significantly higher than NIV-treated patients suffering from bronchiectasis or COPD. Moreover, in kyphoscoliosis, survival is more favourable when using NIV with or without long-term oxygen therapy (LTOT) than LTOT alone [233, 282, 287–297] (tables e3.4.B–E).

Statements

In kyphoscoliotic patients, the evidence shows that:
1) hypoventilation is the major SDB event (A); and
2) NIV with or without LTOT is the first treatment option (B).

3.5. Obesity hypoventilation syndrome

OHS is defined by diurnal hypercapnia in obese patients (BMI $>30$ kg·m$^{-2}$) when other causes of hypoventilation are excluded (ICSD-3) [298–318]. The most common presentations are either an acute-on-chronic exacerbation of hypercapnic respiratory failure, leading to admission to an intensive care unit (ICU) [310, 318] or a sleep specialist referral for suspected OSA [319]. OHS patients are morbidly obese and demonstrate severe OSA in $>80\%$ of cases. Differences to OSA are more quantitative than qualitative, i.e. higher BMI, higher AHI, lower lung volumes, more hospitalisations and ICU admissions, and higher burden of comorbidities. Daytime sleepiness correlates with severity of REM sleep hypoventilation, another classical feature of OHS [320–325].

OHS is associated with chronic systemic low-grade inflammation and inflammation of the adipose tissue [326]. OHS exhibited higher insulin resistance and more endothelial dysfunction, which supports

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<th>TABLE 4: Staging of hypoventilation in obesity</th>
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BMI: body mass index; OSA: obstructive sleep apnoea; $P_{\text{a}CO_2}$: arterial carbon dioxide tension; $P_{\text{tc}CO_2}$: transcutaneous carbon dioxide tension; $P_{\text{CO}_2}$: carbon dioxide tension.
observational cohort data, demonstrating a higher prevalence of cardiovascular and metabolic diseases [325, 327, 328]. Mortality in OHS is elevated compared with eucapnic obese individuals, even after adjustment for main confounders [310, 329, 330]. In observational cohorts, NIV reduced mortality [331], but long-term mortality is suspected to remain higher than in eucapnic obese patients [332].

Hypercapnia during the day is preceded by hypoventilation during sleep, so diurnal hypercapnia already represents an advanced OHS (table 4). OHS patients showed an increased carbon dioxide production and reduced ventilatory responses to carbon dioxide, which could be part of the diagnostic work-up [333–336]. Increased daytime bicarbonate (cut-off level >27 mmol·L−1) despite normal pH documents chronic hypercapnia during sleep [337–339]. Nocturnal hypercapnia can be monitored by long term transcutaneous capnometry. However, the absolute figures have to be interpreted with caution, while relative changes are mostly reliable [340, 341].

CPAP improves AHI, oxygen saturation, hypercapnia, and ventilatory response to oxygen and carbon dioxide in a majority of OHS patients [316]. The largest RCT compared lifestyle modification alone to additional therapy with CPAP or NIV [342]. NIV improved QoL, spirometry, and 6-min walk distance significantly more than CPAP. NIV was superior to CPAP and lifestyle counselling in most studies [221, 300, 302, 305, 307, 308, 310, 343–345]. Two RCTs addressed inhalation of 100% oxygen versus room air in an acute setting or in stable OHS [234], showing that oxygen reduced minute ventilation [301]. Bariatric surgery in OHS leads to a substantial reduction of body weight and improvement of physiological parameters [313, 317, 346, 347] (table e3.5.A).

**Statements**

1) Most Task Force members screen obese patients for OHS by sampling of blood gases (B), nocturnal transcutaneous \( P_{CO_2} \) and/or determination of serum bicarbonate during wakefulness (C).

2) Increases in \( P_{aCO_2} \) or capillary \( P_{CO_2} \), or marked elevations of transcutaneous \( P_{CO_2} \) (as compared to baseline) during REM sleep indicate OHS (B).

3) CPAP failure is higher in OHS as compared to OSAS (B).

4) NIV during sleep improves hypventilation, sleep, QoL and survival. NIV is superior to lifestyle counselling (B).

5) OHS is associated with impaired ventilatory responses to hypercapnia and hypoxia, and increased cardiometabolic morbidity, which can be improved under NIV (B).

6) NIV with pressure support and target volume ventilation are both effective. Comparative studies do not show superiority of one mode (B).

7) Adherence of >4 h per day to NIV is crucial for improving hypercapnia (B).

8) Monotherapy with oxygen reduces ventilation and increases hypercapnia. Oxygen should only be applied as an adjunct to NIV (B).

9) Bariatric surgery reduces body weight, improves lung function and normalises blood gases (C).

**3.6. Chronic NIV in chronic hypercapnic COPD**

COPD is a chronic disorder associated with high morbidity and mortality worldwide. Only a minority of patients with severe COPD will develop hypercapnia (hypercapnic response). An Australian study showed that the severity of sleep hypoventilation is related to daytime \( P_{aCO_2} \), BMI and REM-AHI [348]. Once patients develop chronic hypercapnic respiratory failure, ventilatory support is necessary (table e3.6.A).

**Stable chronic hypercapnic respiratory failure**

NIV in COPD with stable chronic respiratory failure does not improve lung function, gas exchange, sleep efficiency or 6-min walking-distance [349]. However, inspiratory pressures above 18 cmH₂O, a better compliance to the therapy and a higher baseline \( P_{aCO_2} \) were associated with significantly more reduction in \( P_{aCO_2} \) with therapy [350]. A recent RCT showed a survival benefit, next to benefits in gas exchange, QoL and lung function [351]. This was also shown in the study by McEvoy et al. [352] using lower inspiratory pressures, but at the cost of a decrease in QoL.

A multicentre RCT showed [353] a decrease of the total hospital admissions (45%) and ICU admissions (75%) under NIV as compared to an increase (27% and 50%, respectively) in the control group, compared to the period before the start of the study (table e3.6.B).
Prolonged hypercapnia after acute respiratory failure

NIV has become an established treatment in acute hypercapnic respiratory failure (AHRF) for patients with COPD exacerbation. However, next to a high in-hospital mortality, after discharge, 60–80% of the patients were re-admitted within 1 year and 30–49% died within the first year after hospital admission for AHRF [354]. Therefore, the question arose whether providing nocturnal NIV for long-term use to patients who recover from an exacerbation but remain hypercapnic, might improve outcome.

Only three RCTs compared NIV with a control group not receiving home NIV after an acute exacerbation with AHRF [355–357]. The largest multicentre RCT [357] could not demonstrate an improvement in time to readmission or death under home NIV for 1 year in patients with prolonged hypercapnia after an episode of NIV for AHRF, despite the use of higher inspiratory pressures and inherently more improvement in gas exchange with NIV (table e3.6.C).

Statement

There is currently insufficient evidence to support the use of home nocturnal NIV in patients with prolonged hypercapnia after a COPD exacerbation with AHRF (B).

Summary and future perspectives

Research in recent decades has improved our understanding of the various pathophysiological components underlying the different phenotypes of central breathing disturbances during sleep. They differ in terms of increased or dampened respiratory drive but also in comorbidities and underlying diseases. Proceedings of medical therapy have led to new clinical phenomena, such as opioid-induced CSA or treatment-emergent CSA. It has become obvious that a precise description of the polysomnographic pattern on the one hand and the clinical situation on the other hand is crucial. However, due to a lack of sufficient evidence, several questions on the impact of central breathing disturbances during sleep and optimal treatment remain open, including:

1) prognostic relevance of CSA;
2) indication for treatment of CSA;
3) differential therapy based on pathophysiological components; and
4) long-term efficacy of PAP therapies and long-term outcome of untreated patients with different phenotypes.

References

14 Naughton MT. Loop gain in apnea: gaining control or controlling the gain? *Am J Respir Crit Care Med* 2010; 181: 103–105.


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