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

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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.

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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.

TABLE 1 Evidence levels assigned to each individual study

1a	Systematic analysis (systematic review) of RCTs with homogenous results
1b	Particular RCT with limited dispersion
1c	Therapy; before its introduction, all patients died
2a	Systematic review of cohort studies with homogenous results
2b	Particular cohort studies or RCT of lower quality
2c	"Outcomes" research; ecological studies
3a	Systematic review of case–control studies with homogenous results
3b	Particular case–control study
4	Case studies and cohort studies or case–control studies of limited quality
5	Expert opinion

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). RCT: randomised controlled trial. Information from [2].

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

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations of level 1 studies
C	Level 4 studies, or extrapolations of level 2 or 3 studies
D	Level 5 studies or inconsistent studies of other levels

Information from [2].

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

CSA with Cheyne–Stokes breathing
Central apnoea due to a medical disorder without Cheyne–Stokes breathing
CSA due to high-altitude periodic breathing
CSA due to a medication or substance
Primary CSA
Primary CSA of infancy
Primary CSA of prematurity
Treatment-emergent CSA
Obesity hypoventilation syndrome
Congenital central alveolar hypoventilation syndrome
Late-onset central hypoventilation with hypothalamic dysfunction
Idiopathic central alveolar hypoventilation
Sleep-related hypoventilation due to a medication or substance
Sleep-related hypoventilation due to a medical disorder
Sleep-related hypoxaemia

CSA: central sleep apnoea.

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_{aO_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_{aCO_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).

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 hypoventilation 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 servoventilation (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 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 ⩾15 events per h sleep) occurs in 21–37% of patients with stable congestive HFrEF [60–63]. Despite increased use of β-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 β-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 ⩾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].

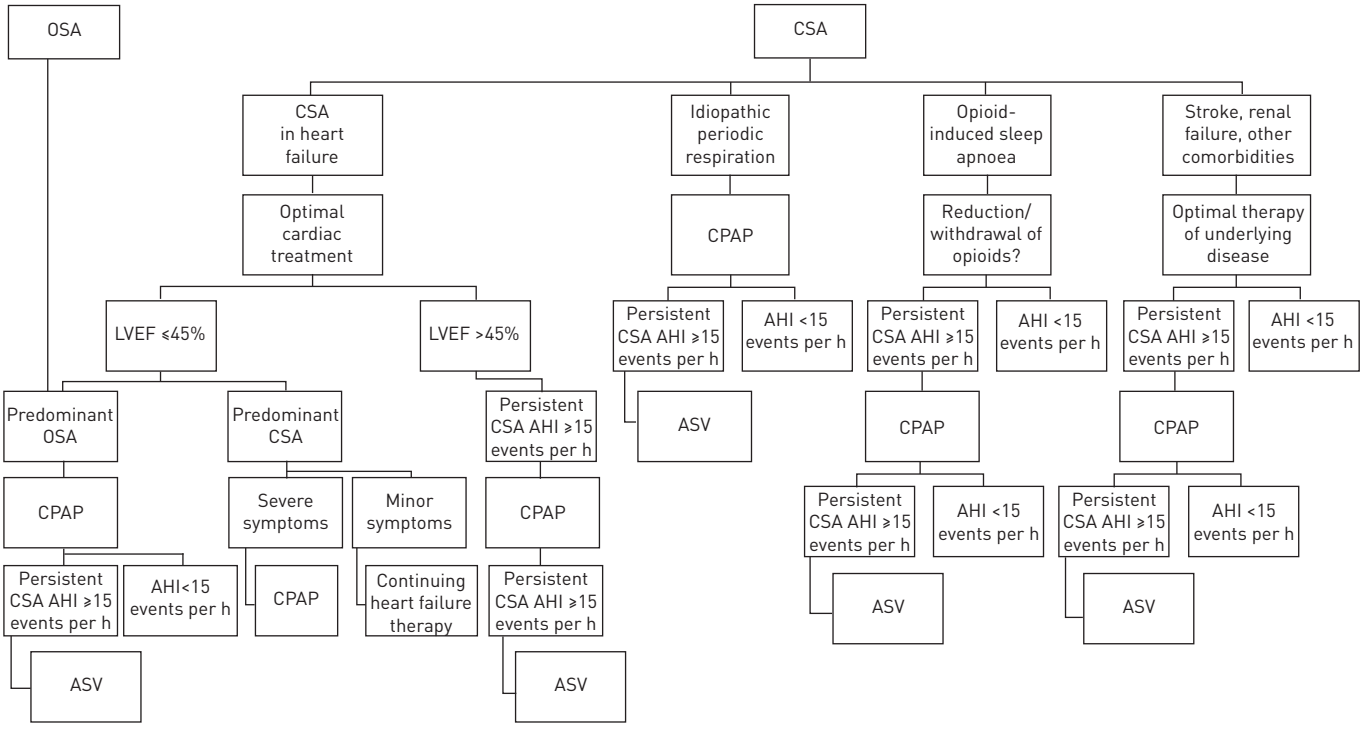

FIGURE 1 Current practice on the treatment of central sleep apnoea (CSA), including periodic breathing. The figure describes the current practice of how the members of the Task Force treat patients with CSA or coexisting obstructive sleep apnoea (OSA) and CSA, and is not intended as a general recommendation. For details, refer to the text. CPAP: continuous positive airway pressure; AHI: apnoea–hypopnoea index; ASV: adaptive servoventilation; LVEF: left ventricular ejection fraction.

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 hypocapnia [103]. The largest and only long-term, 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 $\geqslant$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 P_{CO_2}, BPAP-ST did not change P_{CO_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 P_{CO_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 BIPAP-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 ⩽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 fulfil 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 (⩾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 synergistic 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. Kolilekas *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) ⩾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 ⩾5 events per h and ⩾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 consecutive 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 apnoea. 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, 249–254]. Strategies to increase therapeutic adherence should be encouraged [229, 252, 255, 256]. In some cases, tracheal invasive ventilation is used with an improvement in survival [254, 257], while diaphragm pacing seems to have no benefit [258]. NIV can improve QoL [230, 245, 253, 259, 260], gas exchange [261, 262] and subjective sleep quality [230, 253, 257, 259], which is often impaired in these patients [261–264]. In contrast, NIV has divergent results on objective measures of sleep [261–264] (table e3.3.A).

Duchenne muscular dystrophy

In DMD patients, P_{aCO_2} and vital capacity predict nocturnal hypoventilation [231, 232], while a vital capacity $\leqslant$680 mL predicts daytime 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, 265–269] (table e3.3.B.)

Myotronic 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_{aO_2} and/or P_{aCO_2} also significantly improve [233, 282, 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 $kg \cdot m^{-2}$) 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

TABLE 4 Staging of hypoventilation in obesity

0	At risk	BMI >30 $kg \cdot m^{-2}$	OSA	No hypercapnia
I	Obesity-associated sleep hypoventilation	BMI >30 $kg \cdot m^{-2}$	OSA/hypoventilation during sleep	Intermittent hypercapnia during sleep, full recovery during sleep (P_{aCO_2} or P_{tcCO_2} morning~evening) Serum bicarbonate <27 $mmol \cdot L^{-1}$ during wake
II	Obesity-associated sleep hypoventilation	BMI >30 $kg \cdot m^{-2}$	OSA/hypoventilation during sleep	Intermittent hypercapnia during sleep (P_{aCO_2} or P_{tcCO_2} morning>evening) Serum bicarbonate ⩾27 $mmol \cdot L^{-1}$ during wake Bicarbonate increased during day
III	Obesity hypoventilation	BMI >30 $kg \cdot m^{-2}$	OSA/hypoventilation during sleep	Sustained hypercapnia (P_{CO_2} >45 mmHg) while awake
IV	Obesity hypoventilation syndrome	BMI >30 $kg \cdot m^{-2}$	OSA/hypoventilation during sleep	Sustained hypercapnia while awake, cardiometabolic comorbidities

BMI: body mass index; OSA: obstructive sleep apnoea; P_{aCO_2}: arterial carbon dioxide tension; P_{tcCO_2}: transcutaneous carbon dioxide tension; P_{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 $mmol \cdot L^{-1}$) 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 hypoventilation, 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 cmH_2O, 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).

Statement

Evidence suggests that nocturnal NIV in stable hypercapnic COPD may improve survival and QoL and that inspiratory pressures need to be adjusted to levels high enough to improve ventilation (C).

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

1 Marin JM, Carrizo SJ, Vicente E, *et al.* Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; 365: 1046–1053.
2 Phillips B, Ball C. Levels of Evidence and Grades of recommendation. Oxford, Oxford Centre for Evidence-Based Medicine, 2001.
3 American Academy of Sleep Medicine. International Classification of Sleep Disorders – Third Edition (ICSD-3). Westchester, American Academy of Sleep Medicine, 2014.
4 Berry RB, Budhiraja R, Gottlieb DJ, *et al.* Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012; 8: 597–619.
5 Redline S, Budhiraja R, Kapur V, *et al.* The scoring of respiratory events in sleep: reliability and validity. *J Clin Sleep Med* 2007; 3: 169–200.
6 Berry RB, Koch GL, Trautz S, *et al.* Comparison of respiratory event detection by a polyvinylidene fluoride film airflow sensor and a pneumotachograph in sleep apnea patients. *Chest* 2005; 128: 1331–1338.
7 Yalamanchali S, Farajian V, Hamilton C, *et al.* Diagnosis of obstructive sleep apnea by peripheral arterial tonometry: meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2013; 139: 1343–1350.
8 Pallin M, O'Hare E, Zaffaroni A, *et al.* Comparison of a novel non-contact biomotion sensor with wrist actigraphy in estimating sleep quality in patients with obstructive sleep apnoea. *J Sleep Res* 2014; 23: 475–484.
9 Randerath WJ, Treml M, Priegnitz C, *et al.* Evaluation of a noninvasive algorithm for differentiation of obstructive and central hypopneas. *Sleep* 2013; 36: 363–368.
10 Dempsey JA, Xie A, Patz DS, *et al.* Physiology in Medicine: Obstructive sleep apnea pathogenesis and treatment--considerations beyond airway anatomy. *J Appl Physiol (1985)* 2014; 116: 3–12.
11 Xie A, Teodorescu M, Pegelow DF, *et al.* Effects of stabilizing or increasing respiratory motor outputs on obstructive sleep apnea. *J Appl Physiol (1985)* 2013; 115: 22–33.
12 Xie A, Bedekar A, Skatrud JB, *et al.* The heterogeneity of obstructive sleep apnea (predominant obstructive *vs* pure obstructive apnea). *Sleep* 2011; 34: 745–750.
13 Malhotra A, Owens RL. What is central sleep apnea? *Respir Care* 2010; 55: 1168–1178.
14 Naughton MT. Loop gain in apnea: gaining control or controlling the gain? *Am J Respir Crit Care Med* 2010; 181: 103–105.

15 Verbraecken JA, De Backer WA. Upper airway mechanics. *Respiration* 2009; 78: 121–133.
16 Whitelaw W. Mechanisms of sleep apnea at altitude. *Adv Exp Med Biol* 2006; 588: 57–63.
17 White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med* 2005; 172: 1363–1370.
18 Younes M, Ostrowski M, Thompson W, *et al.* Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 163: 1181–1190.
19 De Backer WA. Central sleep apnoea, pathogenesis and treatment: an overview and perspective. *Eur Respir J* 1995; 8: 1372–1383.
20 Younes M, Xie A, Skatrud JB, *et al.* Measurement of the CO_2 apneic threshold. *Am J Respir Crit Care Med* 2003; 167: 472.
21 Nakayama H, Smith CA, Rodman JR, *et al.* Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. *Am J Respir Crit Care Med* 2002; 165: 1251–1260.
22 Xi L, Smith CA, Saupe KW, *et al.* Effects of rapid-eye-movement sleep on the apneic threshold in dogs. *J Appl Physiol (1985)* 1993; 75: 1129–1139.
23 Skatrud JB, Henke KG, Dempsey J. A sleep-induced apneic threshold. *Prog Clin Biol Res* 1990; 345: 191–199.
24 Dempsey JA, Skatrud JB. A sleep-induced apneic threshold and its consequences. *Am Rev Respir Dis* 1986; 133: 1163–1170.
25 Skatrud JB, Dempsey JA. Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. *J Appl Physiol* 1983; 55: 813–822.
26 Xie A, Skatrud JB, Dempsey JA. Effect of hypoxia on the hypopnoeic and apnoeic threshold for CO_2 in sleeping humans. *J Physiol* 2001; 535: 269–278.
27 Satoh M, Eastwood PR, Smith CA, *et al.* Nonchemical elimination of inspiratory motor output *via* mechanical ventilation in sleep. *Am J Respir Crit Care Med* 2001; 163: 1356–1364.
28 Dempsey JA, Leevers AM, Wilson CR, *et al.* Apnea prolongation via short-term inhibition. *Sleep* 1996; 19: Suppl., S160–S163.
29 Bernards CM, Knowlton SL, Schmidt DF, *et al.* Respiratory and sleep effects of remifentanil in volunteers with moderate obstructive sleep apnea. *Anesthesiology* 2009; 110: 41–49.
30 Guilleminault C, Cao M, Yue HJ, *et al.* Obstructive sleep apnea and chronic opioid use. *Lung* 2010; 188: 459–468.
31 Walker JM, Farney RJ, Rhondeau SM, *et al.* Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med* 2007; 3: 455–461.
32 Farney RJ, McDonald AM, Boyle KM, *et al.* Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone. *Eur Respir J* 2013; 42: 394–403.
33 Mogri M, Desai H, Webster L, *et al.* Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. *Sleep Breath* 2009; 13: 49–57.
34 Rose AR, Catcheside PG, McEvoy RD, *et al.* Sleep disordered breathing and chronic respiratory failure in patients with chronic pain on long term opioid therapy. *J Clin Sleep Med* 2014; 10: 847–852.
35 Webster LR, Choi Y, Desai H, *et al.* Sleep-disordered breathing and chronic opioid therapy. *Pain Med* 2008; 9: 425–432.
36 Teichtahl H, Wang D, Cunnington D, *et al.* Ventilatory responses to hypoxia and hypercapnia in stable methadone maintenance treatment patients. *Chest* 2005; 128: 1339–1347.
37 Wang D, Teichtahl H, Drummer O, *et al.* Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005; 128: 1348–1356.
38 Sharkey KM, Kurth ME, Anderson BJ, *et al.* Obstructive sleep apnea is more common than central sleep apnea in methadone maintenance patients with subjective sleep complaints. *Drug Alcohol Depend* 2010; 108: 77–83.
39 Jungquist CR, Flannery M, Perlis ML, *et al.* Relationship of chronic pain and opioid use with respiratory disturbance during sleep. *Pain Manag Nurs* 2012; 13: 70–79.
40 Alattar MA, Scharf SM. Opioid-associated central sleep apnea: a case series. *Sleep Breath* 2009; 13: 201–206.
41 Troitino A, Labedi N, Kufel T, *et al.* Positive airway pressure therapy in patients with opioid-related central sleep apnea. *Sleep Breath* 2014; 18: 367–373.
42 Farney RJ, Walker JM, Boyle KM, *et al.* Adaptive servoventilation (ASV) in patients with sleep disordered breathing associated with chronic opioid medications for non-malignant pain. *J Clin Sleep Med* 2008; 4: 311–319.
43 Javaheri S, Malik A, Smith J, *et al.* Adaptive pressure support servoventilation: a novel treatment for sleep apnea associated with use of opioids. *J Clin Sleep Med* 2008; 4: 305–310.
44 Ramar K, Ramar P, Morgenthaler TI. Adaptive servoventilation in patients with central or complex sleep apnea related to chronic opioid use and congestive heart failure. *J Clin Sleep Med* 2012; 8: 569–576.
45 Chowdhuri S, Ghabsha A, Sinha P, *et al.* Treatment of central sleep apnea in U.S. veterans. *J Clin Sleep Med* 2012; 8: 555–563.
46 Charters T, Saxon E. Tourism and Mountains. A practical guide to managing the environmental and social impacts of mountain tours. Paris, United Nations Environment Programme, Division of Technology, Industry and Economics, 2007.
47 Bloch K, Buenzli J, Latshang T, *et al.* Sleep at high altitude: guesses and facts. *J Appl Physiol* 2015; 119: 1466–1480.
48 Latshang TD, Lo Cascio CM, Stowhas AC, *et al.* Are nocturnal breathing, sleep, and cognitive performance impaired at moderate altitude (1,630–2,590m)? *Sleep* 2013; 36: 1969–1976.
49 Bloch KE, Latshang TD, Turk AJ, *et al.* Nocturnal periodic breathing during acclimatization at very high altitude at Mount Muztagh Ata (7,546m). *Am J Respir Crit Care Med* 2010; 182: 562–568.
50 Nussbaumer-Ochsner Y, Ursprung J, Siebenmann C, *et al.* Effect of short-term acclimatization to high altitude on sleep and nocturnal breathing. *Sleep* 2012; 35: 419–423.
51 Fischer R, Lang SM, Leitl M, *et al.* Theophylline and acetazolamide reduce sleep-disordered breathing at high altitude. *Eur Respir J* 2004; 23: 47–52.
52 Nussbaumer-Ochsner Y, Schuepfer N, Ursprung J, *et al.* Sleep and breathing in high altitude pulmonary edema susceptible subjects at 4,559 meters. *Sleep* 2012; 35: 1413–1421.
53 Nussbaumer-Ochsner Y, Schuepfer N, Ulrich S, *et al.* Exacerbation of sleep apnoea by frequent central events in patients with the obstructive sleep apnoea syndrome at altitude: a randomised trial. *Thorax* 2010; 65: 429–435.

54 Nussbaumer-Ochsner Y, Latshang TD, Ulrich S, *et al.* Patients with obstructive sleep apnea syndrome benefit from acetazolamide during an altitude sojourn: a randomized, placebo-controlled, double-blind trial. *Chest* 2012; 141: 131–138.

55 Latshang TD, Nussbaumer-Ochsner Y, Henn RM, *et al.* Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. *JAMA* 2012; 308: 2390–2398.

56 Arzt M, Woehrle H, Oldenburg O, *et al.* Prevalence and predictors of sleep-disordered breathing in patients with stable chronic heart failure: the SchlaHF registry. *JACC Heart Fail* 2016; 4: 116–125.

57 Bitter T, Faber L, Hering D, *et al.* Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. *Eur J Heart Fail* 2009; 11: 602–608.

58 Mansfield DR, Solin P, Roebuck T, *et al.* The effect of successful heart transplant treatment of heart failure on central sleep apnea. *Chest* 2003; 124: 1675–1681.

59 Oldenburg O, Bitter T, Fox H, *et al.* Heart failure. *Somnology* 2014; 18: 19–25.

60 Javaheri S. Sleep disorders in systolic heart failure: a prospective study of 100 male patients. The final report. *Int J Cardiol* 2006; 106: 21–28.

61 Sin DD, Fitzgerald F, Parker JD, *et al.* Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med* 1999; 160: 1101–1106.

62 Solin P, Bergin P, Richardson M, *et al.* Influence of pulmonary capillary wedge pressure on central apnea in heart failure. *Circulation* 1999; 99: 1574–1579.

63 Yumino D, Wang H, Floras JS, *et al.* Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. *J Card Fail* 2009; 15: 279–285.

64 Chan J, Sanderson J, Chan W, *et al.* Prevalence of sleep-disordered breathing in diastolic heart failure. *Chest* 1997; 111: 1488–1493.

65 Sekizuka H, Osada N, Miyake F. Sleep disordered breathing in heart failure patients with reduced versus preserved ejection fraction. *Heart Lung Circ* 2013; 22: 104–109.

66 Shah RV, Abbasi SA, Heydari B, *et al.* Obesity and sleep apnea are independently associated with adverse left ventricular remodeling and clinical outcome in patients with atrial fibrillation and preserved ventricular function. *Am Heart J* 2014; 167: 620–626.

67 Wachter R, Luthje L, Klemmstein D, *et al.* Impact of obstructive sleep apnoea on diastolic function. *Eur Respir J* 2013; 41: 376–383.

68 Andreas S, Hagenah G, Moller C, *et al.* Cheyne–Stokes respiration and prognosis in congestive heart failure. *Am J Cardiol* 1996; 78: 1260–1264.

69 Sin DD, Logan AG, Fitzgerald FS, *et al.* Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne–Stokes respiration. *Circulation* 2000; 102: 61–66.

70 Roebuck T, Solin P, Kaye DM, *et al.* Increased long-term mortality in heart failure due to sleep apnoea is not yet proven. *Eur Respir J* 2004; 23: 735–740.

71 Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne–Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med* 1996; 153: 272–276.

72 Lanfranchi PA, Braghiroli A, Bosimini E, *et al.* Prognostic value of nocturnal Cheyne–Stokes respiration in chronic heart failure. *Circulation* 1999; 99: 1435–1440.

73 Corra U, Pistono M, Mezzani A, *et al.* Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation* 2006; 113: 44–50.

74 Jilek C, Krenn M, Sebah D, *et al.* Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study. *Eur J Heart Fail* 2011; 13: 68–75.

75 Damy T, Margarit L, Noroc A, *et al.* Prognostic impact of sleep-disordered breathing and its treatment with nocturnal ventilation for chronic heart failure. *Eur J Heart Fail* 2012; 14: 1009–1019.

76 Javaheri S, Shukla R, Zeigler H, *et al.* Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007; 49: 2028–2034.

77 Yumino D, Bradley TD. Central sleep apnea and Cheyne–Stokes respiration. *Proc Am Thorac Soc* 2008; 5: 226–236.

78 Khayat R, Jarjoura D, Porter K, *et al.* Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J* 2015; 36: 1463–1469.

79 Bitter T, Westerheide N, Prinz C, *et al.* Cheyne–Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. *Eur Heart J* 2011; 32: 61–74.

80 Kreuz J, Skowasch D, Horlbeck F, *et al.* Usefulness of sleep-disordered breathing to predict occurrence of appropriate and inappropriate implantable-cardioverter defibrillator therapy in patients with implantable cardioverter-defibrillator for primary prevention of sudden cardiac death. *Am J Cardiol* 2013; 111: 1319–1323.

81 Sinha AM, Skobel EC, Breithardt OA, *et al.* Cardiac resynchronization therapy improves central sleep apnea and Cheyne–Stokes respiration in patients with chronic heart failure. *J Am Coll Cardiol* 2004; 44: 68–71.

82 Rubin AE, Gottlieb SH, Gold AR, *et al.* Elimination of central sleep apnoea by mitral valvuloplasty: the role of feedback delay in periodic breathing. *Thorax* 2004; 59: 174–176.

83 Vazir A, Hastings PC, Morrell MJ, *et al.* Resolution of central sleep apnoea following implantation of a left ventricular assist device. *Int J Cardiol* 2010; 138: 317–319.

84 Lorenzi-Filho G, Rankin F, Bies I, *et al.* Effects of inhaled carbon dioxide and oxygen on Cheyne–Stokes respiration in patients with heart failure. *Am J Respir Crit Care Med* 1999; 159: 1490–1498.

85 Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. *Am J Respir Crit Care Med* 2006; 173: 234–237.

86 Andreas S, Reiter H, Luthje L, *et al.* Differential effects of theophylline on sympathetic excitation, hemodynamics, and breathing in congestive heart failure. *Circulation* 2004; 110: 2157–2162.

87 Szollosi I, Jones M, Morrell MJ, *et al.* Effect of CO_2 inhalation on central sleep apnea and arousals from sleep. *Respiration* 2004; 71: 493–498.

88 Thomas RJ, Daly RW, Weiss JW. Low-concentration carbon dioxide is an effective adjunct to positive airway pressure in the treatment of refractory mixed central and obstructive sleep-disordered breathing. *Sleep* 2005; 28: 69–77.

89 Javaheri S, Sands SA, Edwards BA. Acetazolamide attenuates hunter-Cheyne–Stokes breathing but augments the hypercapnic ventilatory response in patients with heart failure. *Ann Am Thorac Soc* 2014; 11: 80–86.
90 Javaheri S, Parker TJ, Wexler L, *et al.* Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med* 1996; 335: 562–567.
91 Hanly PJ, Millar TW, Steljes DG, *et al.* The effect of oxygen on respiration and sleep in patients with congestive heart failure. *Ann Intern Med* 1989; 111: 777–782.
92 Krachman SL, D'Alonzo GE, Berger TJ, *et al.* Comparison of oxygen therapy with nasal continuous positive airway pressure on Cheyne–Stokes respiration during sleep in congestive heart failure. *Chest* 1999; 116: 1550–1557.
93 Javaheri S, Ahmed M, Parker TJ, *et al.* Effects of nasal O_2 on sleep-related disordered breathing in ambulatory patients with stable heart failure. *Sleep* 1999; 22: 1101–1106.
94 Andreas S, Clemens C, Sandholzer H, *et al.* Improvement of exercise capacity with treatment of Cheyne–Stokes respiration in patients with congestive heart failure. *J Am Coll Cardiol* 1996; 27: 1486–1490.
95 Staniforth AD, Kinnear WJ, Starling R, *et al.* Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne–Stokes respiration. *Eur Heart J* 1998; 19: 922–928.
96 Teschler H, Dohring J, Wang YM, *et al.* Adaptive pressure support servo-ventilation: a novel treatment for Cheyne–Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001; 164: 614–619.
97 Arzt M, Schulz M, Wensel R, *et al.* Nocturnal continuous positive airway pressure improves ventilatory efficiency during exercise in patients with chronic heart failure. *Chest* 2005; 127: 794–802.
98 Zhang XL, Yin KS, Li XL, *et al.* Efficacy of adaptive servoventilation in patients with congestive heart failure and Cheyne–Stokes respiration. *Chin Med J (Engl)* 2006; 119: 622–627.
99 Iber C, Ancoli-Israel S, Chesson AL, *et al.* The AASM manual for the scoring of sleep and associated events: Rules, Technology and Technical Specifications, 1st Edn. Westchester, American Academy of Sleep Medicine. 2007.
100 Naughton MT, Benard DC, Liu PP, *et al.* Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med* 1995; 152: 473–479.
101 Naughton MT, Liu PP, Bernard DC, *et al.* Treatment of congestive heart failure and Cheyne–Stokes respiration during sleep by continuous positive airway pressure. *Am J Respir Crit Care Med* 1995; 151: 92–97.
102 Tkacova R, Liu PP, Naughton MT, *et al.* Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 1997; 30: 739–745.
103 Naughton MT, Benard DC, Rutherford R, *et al.* Effect of continuous positive airway pressure on central sleep apnea and nocturnal PCO2 in heart failure. *Am J Respir Crit Care Med* 1994; 150: 1598–1604.
104 Bradley TD, Logan AG, Kimoff RJ, *et al.* Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005; 353: 2025–2033.
105 Arzt M, Floras JS, Logan AG, *et al.* Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a *post hoc* analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation* 2007; 115: 3173–3180.
106 Noda A, Izawa H, Asano H, *et al.* Beneficial effect of bilevel positive airway pressure on left ventricular function in ambulatory patients with idiopathic dilated cardiomyopathy and central sleep apnea-hypopnea: a preliminary study. *Chest* 2007; 131: 1694–1701.
107 Kohnlein T, Welte T, Tan LB, *et al.* Assisted ventilation for heart failure patients with Cheyne–Stokes respiration. *Eur Respir J* 2002; 20: 934–941.
108 Kasai T, Narui K, Dohi T, *et al.* Efficacy of nasal bi-level positive airway pressure in congestive heart failure patients with Cheyne–Stokes respiration and central sleep apnea. *Circ J* 2005; 69: 913–921.
109 Dohi T, Kasai T, Narui K, *et al.* Bi-level positive airway pressure ventilation for treating heart failure with central sleep apnea that is unresponsive to continuous positive airway pressure. *Circ J* 2008; 72: 1100–1105.
110 Fietze I, Blau A, Glos M, *et al.* Bi-level positive pressure ventilation and adaptive servo ventilation in patients with heart failure and Cheyne–Stokes respiration. *Sleep Med* 2008; 9: 652–659.
111 Philippe C, Stoica-Herman M, Drouot X, *et al.* Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne–Stokes respiration in heart failure over a six month period. *Heart* 2006; 92: 337–342.
112 Arzt M, Wensel R, Montalvan S, *et al.* Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. *Chest* 2008; 134: 61–66.
113 Kasai T, Usui Y, Yoshioka T, *et al.* Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne–Stokes respiration. *Circ Heart Fail* 2010; 3: 140–148.
114 Campbell AJ, Ferrier K, Neill AM. Effect of oxygen versus adaptive pressure support servo-ventilation in patients with central sleep apnoea-Cheyne Stokes respiration and congestive heart failure. *Intern Med J* 2012; 42: 1130–1136.
115 Randerath WJ, Nothofer G, Priegnitz C, *et al.* Long-term auto servo-ventilation or constant positive pressure in heart failure and co-existing central with obstructive sleep apnea. *Chest* 2012; 142: 440–447.
116 Oldenburg O, Bitter T, Wellmann B, *et al.* Trilevel adaptive servoventilation for the treatment of central and mixed sleep apnea in chronic heart failure patients. *Sleep Med* 2013; 14: 422–427.
117 Aurora RN, Chowdhuri S, Ramar K, *et al.* The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep* 2012; 35: 17–40.
118 Bitter T, Westerheide N, Faber L, *et al.* Adaptive servoventilation in diastolic heart failure and Cheyne–Stokes respiration. *Eur Respir J* 2010; 36: 385–392.
119 Hastings PC, Vazir A, Meadows GE, *et al.* Adaptive servo-ventilation in heart failure patients with sleep apnea: a real world study. *Int J Cardiol* 2010; 139: 17–24.
120 Koyama T, Watanabe H, Kobukai Y, *et al.* Beneficial effects of adaptive servo ventilation in patients with chronic heart failure. *Circ J* 2010; 74: 2118–2124.
121 Haruki N, Takeuchi M, Kaku K, *et al.* Comparison of acute and chronic impact of adaptive servo-ventilation on left chamber geometry and function in patients with chronic heart failure. *Eur J Heart Fail* 2011; 13: 1140–1146.
122 Oldenburg O, Bitter T, Lehmann R, *et al.* Adaptive servoventilation improves cardiac function and respiratory stability. *Clin Res Cardiol* 2011; 100: 107–115.
123 Yoshihisa A, Shimizu T, Owada T, *et al.* Adaptive servo ventilation improves cardiac dysfunction and prognosis in chronic heart failure patients with Cheyne–Stokes respiration. *Int Heart J* 2011; 52: 218–223.

124 Pepperell JC, Maskell NA, Jones DR, *et al.* A randomized controlled trial of adaptive ventilation for Cheyne–Stokes breathing in heart failure. *Am J Respir Crit Care Med* 2003; 168: 1109–1114.
125 Sharma BK, Bakker JP, McSharry DG, *et al.* Adaptive servoventilation for treatment of sleep-disordered breathing in heart failure: a systematic review and meta-analysis. *Chest* 2012; 142: 1211–1221.
126 Arzt M, Schroll S, Series F, *et al.* Auto-servoventilation in heart failure with sleep apnoea: a randomised controlled trial. *Eur Respir J* 2013; 42: 1244–1254.
127 Kasai T, Kasagi S, Maeno K, *et al.* Adaptive servo-ventilation in cardiac function and neurohormonal status in patients with heart failure and central sleep apnea nonresponsive to continuous positive airway pressure. *JACC Heart Fail* 2013; 1: 58–63.
128 Takama N, Kurabayashi M. Safety and efficacy of adaptive servo-ventilation in patients with severe systolic heart failure. *J Cardiol* 2014; 63: 302–307.
129 Joho S, Oda Y, Ushijima R, *et al.* Effect of adaptive servoventilation on muscle sympathetic nerve activity in patients with chronic heart failure and central sleep apnea. *J Card Fail* 2012; 18: 769–775.
130 Koyama T, Watanabe H, Tamura Y, *et al.* Adaptive servo-ventilation therapy improves cardiac sympathetic nerve activity in patients with heart failure. *Eur J Heart Fail* 2013; 15: 902–909.
131 Iwaya S, Yoshihisa A, Nodera M, *et al.* Suppressive effects of adaptive servo-ventilation on ventricular premature complexes with attenuation of sympathetic nervous activity in heart failure patients with sleep-disordered breathing. *Heart Vessels* 2014; 29: 470–477.
132 Bitter T, Gutleben KJ, Nolker G, *et al.* Treatment of Cheyne–Stokes respiration reduces arrhythmic events in chronic heart failure. *J Cardiovasc Electrophysiol* 2013; 24: 1132–1140.
133 American Academy of Sleep Medicine. Special safety notice: ASV therapy for central sleep apnea patients with heart failure. www.aasmnet.org/articles.aspx?id=5562 Date last assessed: July 21, 2015. Date last updated: August 2015.
134 Hetland A, Haugaa KH, Olseng M, *et al.* Three-month treatment with adaptive servoventilation improves cardiac function and physical activity in patients with chronic heart failure and Cheyne–Stokes respiration: a prospective randomized controlled trial. *Cardiology* 2013; 126: 81–90.
135 Yoshihisa A, Suzuki S, Yamaki T, *et al.* Impact of adaptive servo-ventilation on cardiovascular function and prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep-disordered breathing. *Eur J Heart Fail* 2013; 15: 543–550.
136 Birner C, Series F, Lewis K, *et al.* Effects of auto-servo ventilation on patients with sleep-disordered breathing, stable systolic heart failure and concomitant diastolic dysfunction: subanalysis of a randomized controlled trial. *Respiration* 2014; 87: 54–62.
137 Brack T, Randerath W, Bloch KE. Cheyne–Stokes respiration in patients with heart failure: prevalence, causes, consequences and treatments. *Respiration* 2012; 83: 165–176.
138 Lipford MC, Park JG, Ramar K. Sleep-disordered breathing and stroke: therapeutic approaches. *Curr Neurol Neurosci Rep* 2014; 14: 431.
139 Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. *J Clin Sleep Med* 2010; 6: 131–137.
140 Siccoli MM, Valko PO, Hermann DM, *et al.* Central periodic breathing during sleep in 74 patients with acute ischemic stroke - neurogenic and cardiogenic factors. *J Neurol* 2008; 255: 1687–1692.
141 Boentert M, Young P. Sleep-related breathing disorders and cerebrovascular diseases. *Somnology* 2014; 18: 13–18.
142 Nachtmann A, Siebler M, Rose G, *et al.* Cheyne–Stokes respiration in ischemic stroke. *Neurology* 1995; 45: 820–821.
143 Perks WH, Horrocks PM, Cooper RA, *et al.* Sleep apnoea in acromegaly. *Br Med J* 1980; 280: 894–897.
144 Grunstein RR, Ho KY, Sullivan CE. Sleep apnea in acromegaly. *Ann Intern Med* 1991; 115: 527–532.
145 Akkoyunlu ME, Ilhan MM, Bayram M, *et al.* Does hormonal control obviate positive airway pressure therapy in acromegaly with sleep-disordered breathing? *Respir Med* 2013; 107: 1803–1809.
146 Roemmler J, Gutt B, Fischer R, *et al.* Elevated incidence of sleep apnoea in acromegaly-correlation to disease activity. *Sleep Breath* 2012; 16: 1247–1253.
147 Grunstein RR, Ho KK, Sullivan CE. Effect of octreotide, a somatostatin analog, on sleep apnea in patients with acromegaly. *Ann Intern Med* 1994; 121: 478–483.
148 Grunstein RR, Ho KY, Berthon-Jones M, *et al.* Central sleep apnea is associated with increased ventilatory response to carbon dioxide and hypersecretion of growth hormone in patients with acromegaly. *Am J Respir Crit Care Med* 1994; 150: 496–502.
149 Pelttari L, Polo O, Rauhala E, *et al.* Nocturnal breathing abnormalities in acromegaly after adenomectomy. *Clin Endocrinol (Oxf)* 1995; 43: 175–182.
150 Mondini S, Guilleminault C. Abnormal breathing patterns during sleep in diabetes. *Ann Neurol* 1985; 17: 391–395.
151 Punjabi NM, Shahar E, Redline S, *et al.* Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *Am J Epidemiol* 2004; 160: 521–530.
152 Kent BD, Grote L, Ryan S, *et al.* Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. *Chest* 2014; 146: 982–990.
153 Kent BD, Grote L, Bonsignore MR, *et al.* Sleep apnoea severity independently predicts glycaemic health in nondiabetic subjects: the ESADA study. *Eur Respir J* 2014; 44: 130–139.
154 Resnick HE, Redline S, Shahar E, *et al.* Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. *Diabetes Care* 2003; 26: 702–709.
155 Bottini P, Dottorini ML, Cristina Cordoni M, *et al.* Sleep-disordered breathing in nonobese diabetic subjects with autonomic neuropathy. *Eur Respir J* 2003; 22: 654–660.
156 Kuzniar TJ, Morgenthaler TI. Treatment of complex sleep apnea syndrome. *Chest* 2012; 142: 1049–1057.
157 Elias RM, Bradley TD, Kasai T, *et al.* Rostral overnight fluid shift in end-stage renal disease: relationship with obstructive sleep apnea. *Nephrol Dial Transplant* 2012; 27: 1569–1573.
158 Elias RM, Chan CT, Paul N, *et al.* Relationship of pharyngeal water content and jugular volume with severity of obstructive sleep apnea in renal failure. *Nephrol Dial Transplant* 2013; 28: 937–944.
159 Beecroft JM, Duffin J, Pierratos A, *et al.* Decreased chemosensitivity and improvement of sleep apnea by nocturnal hemodialysis. *Sleep Med* 2009; 10: 47–54.
160 Tada T, Kusano KF, Ogawa A, *et al.* The predictors of central and obstructive sleep apnoea in haemodialysis patients. *Nephrol Dial Transplant* 2007; 22: 1190–1197.

161 Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med* 2001; 344: 102–107.
162 Jean G, Piperno D, Francois B, *et al.* Sleep apnea incidence in maintenance hemodialysis patients: influence of dialysate buffer. *Nephron* 1995; 71: 138–142.
163 Pressman MR, Benz RL, Schleifer CR, *et al.* Sleep disordered breathing in ESRD: acute beneficial effects of treatment with nasal continuous positive airway pressure. *Kidney Int* 1993; 43: 1134–1139.
164 Owada T, Yoshihisa A, Yamauchi H, *et al.* Adaptive servoventilation improves cardiorenal function and prognosis in heart failure patients with chronic kidney disease and sleep-disordered breathing. *J Card Fail* 2013; 19: 225–232.
165 Kolilekas L, Manali E, Vlami KA, *et al.* Sleep oxygen desaturation predicts survival in idiopathic pulmonary fibrosis. *J Clin Sleep Med* 2013; 9: 593–601.
166 Bye PT, Issa F, Berthon-Jones M, *et al.* Studies of oxygenation during sleep in patients with interstitial lung disease. *Am Rev Respir Dis* 1984; 129: 27–32.
167 Hira HS, Sharma RK. Study of oxygen saturation, breathing pattern and arrhythmias in patients of interstitial lung disease during sleep. *Indian J Chest Dis Allied Sci* 1997; 39: 157–162.
168 Mermigkis C, Stagaki E, Amfilochiou A, *et al.* Sleep quality and associated daytime consequences in patients with idiopathic pulmonary fibrosis. *Med Princ Pract* 2009; 18: 10–15.
169 Perez-Padilla R, West P, Lertzman M, *et al.* Breathing during sleep in patients with interstitial lung disease. *Am Rev Respir Dis* 1985; 132: 224–229.
170 McNicholas WT, Coffey M, Fitzgerald MX. Ventilation and gas exchange during sleep in patients with interstitial lung disease. *Thorax* 1986; 41: 777–782.
171 Lancaster LH, Mason WR, Parnell JA, *et al.* Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest* 2009; 136: 772–778.
172 Pihtili A, Bingol Z, Kiyan E, *et al.* Obstructive sleep apnea is common in patients with interstitial lung disease. *Sleep Breath* 2013; 17: 1281–1288.
173 Reid T, Vennelle M, McKinley M, *et al.* Sleep-disordered breathing and idiopathic pulmonary fibrosis – is there an association? *Sleep Breath* 2015; 19: 719–721.
174 Mermigkis C, Stagaki E, Tryfon S, *et al.* How common is sleep-disordered breathing in patients with idiopathic pulmonary fibrosis? *Sleep Breath* 2010; 14: 387–390.
175 Lee RN, Kelly E, Nolan G, *et al.* Disordered breathing during sleep and exercise in idiopathic pulmonary fibrosis and the role of biomarkers. *QJM* 2015; 108: 315–323.
176 Corte TJ, Wort SJ, Talbot S, *et al.* Elevated nocturnal desaturation index predicts mortality in interstitial lung disease. *Sarcoidosis Vasc Diffuse Lung Dis* 2012; 29: 41–50.
177 Clark M, Cooper B, Singh S, *et al.* A survey of nocturnal hypoxaemia and health related quality of life in patients with cryptogenic fibrosing alveolitis. *Thorax* 2001; 56: 482–486.
178 Midgren B, Hansson L, Eriksson L, *et al.* Oxygen desaturation during sleep and exercise in patients with interstitial lung disease. *Thorax* 1987; 42: 353–356.
179 Tatsumi K, Kimura H, Kunitomo F, *et al.* Arterial oxygen desaturation during sleep in interstitial pulmonary disease. Correlation with chemical control of breathing during wakefulness. *Chest* 1989; 95: 962–967.
180 Shea SA, Winning AJ, McKenzie E, *et al.* Does the abnormal pattern of breathing in patients with interstitial lung disease persist in deep, non-rapid eye movement sleep? *Am Rev Respir Dis* 1989; 139: 653–658.
181 Vazquez JC, Perez-Padilla R. Effect of oxygen on sleep and breathing in patients with interstitial lung disease at moderate altitude. *Respiration* 2001; 68: 584–589.
182 Schulz R. Precapillary pulmonary hypertension. *Somnology* 2014; 18: 31–33.
183 Minic M, Granton JT, Ryan CM. Sleep disordered breathing in group 1 pulmonary arterial hypertension. *J Clin Sleep Med* 2014; 10: 277–283.
184 Schulz R, Baseler G, Ghofrani HA, *et al.* Nocturnal periodic breathing in primary pulmonary hypertension. *Eur Respir J* 2002; 19: 658–663.
185 Ulrich S, Fischler M, Speich R, *et al.* Sleep-related breathing disorders in patients with pulmonary hypertension. *Chest* 2008; 133: 1375–1380.
186 Ulrich S, Keusch S, Hildenbrand FF, *et al.* Effect of nocturnal oxygen and acetazolamide on exercise performance in patients with pre-capillary pulmonary hypertension and sleep-disturbed breathing: randomized, double-blind, cross-over trial. *Eur Heart J* 2015; 36: 615–623.
187 Morgenthaler TI, Kagramanov V, Hanak V, *et al.* Complex sleep apnea syndrome: is it a unique clinical syndrome? *Sleep* 2006; 29: 1203–1209.
188 Javaheri S, Smith J, Chung E. The prevalence and natural history of complex sleep apnea. *J Clin Sleep Med* 2009; 5: 205–211.
189 Cassel W, Canisius S, Becker HF, *et al.* A prospective polysomnographic study on the evolution of complex sleep apnoea. *Eur Respir J* 2011; 38: 329–337.
190 Dernaika T, Tawk M, Nazir S, *et al.* The significance and outcome of continuous positive airway pressure-related central sleep apnea during split-night sleep studies. *Chest* 2007; 132: 81–87.
191 Lehman S, Antic NA, Thompson C, *et al.* Central sleep apnea on commencement of continuous positive airway pressure in patients with a primary diagnosis of obstructive sleep apnea-hypopnea. *J Clin Sleep Med* 2007; 3: 462–466.
192 Kuzniar TJ, Kasibowska-Kuzniar K, Ray DW, *et al.* Clinical heterogeneity of patients with complex sleep apnea syndrome. *Sleep Breath* 2013; 17: 1209–1214.
193 Eckert DJ, Jordan AS, Merchia P, *et al.* Central sleep apnea: pathophysiology and treatment. *Chest* 2007; 131: 595–607.
194 Tkacova R, Niroumand M, Lorenzi-Filho G, *et al.* Overnight shift from obstructive to central apneas in patients with heart failure: role of P_{CO_2} and circulatory delay. *Circulation* 2001; 103: 238–243.
195 Randerath WJ. New ventilator support in complex phenotypes: coexisting CSA and OSA. *In:* Barbé F, Pépin J-L. Obstructive Sleep Apnoea (ERS Monograph). Sheffield, European Respiratory Society, 2015; pp. 266–279.
196 Kuzniar TJ. The complexities of complex sleep apnea. *J Clin Sleep Med* 2013; 9: 1193–1194.
197 Skatrud JB, Dempsey JA, Badr S, *et al.* Effect of airway impedance on CO_2 retention and respiratory muscle activity during NREM sleep. *J Appl Physiol (1985)* 1988; 65: 1676–1685.
198 Salloum A, Rowley JA, Mateika JH, *et al.* Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2010; 181: 189–193.

199 Galetke W, Anduleit N, Kenter M, *et al.* Evaluation of a new algorithm for patients with Cheyne–Stokes breathing and obstructive sleep apnea. *Am J Respir Crit Care Med* 2008; 177: A480.
200 Arzt M, Schroll S, Series F, *et al.* Auto-servo ventilation in heart failure with sleep apnea – a randomized controlled trial. *Eur Respir J* 2013; 42: 1244–1254.
201 Galetke W, Ghassemi BM, Priegnitz C, *et al.* Anticyclic modulated ventilation versus continuous positive airway pressure in patients with coexisting obstructive sleep apnea and Cheyne–Stokes respiration: a randomized crossover trial. *Sleep Med* 2014; 15: 874–879.
202 Morgenthaler TI, Kuzniar TJ, Wolfe LF, *et al.* The complex sleep apnea resolution study: a prospective randomized controlled trial of continuous positive airway pressure versus adaptive servoventilation therapy. *Sleep* 2014; 37: 927–934.
203 Dellweg D, Kerl J, Hoehn E, *et al.* Randomized controlled trial of noninvasive positive pressure ventilation (NPPV) *versus* servoventilation in patients with CPAP-induced central sleep apnea (complex sleep apnea). *Sleep* 2013; 36: 1163–1171.
204 Xie A, Wong B, Phillipson EA, *et al.* Interaction of hyperventilation and arousal in the pathogenesis of idiopathic central sleep apnea. *Am J Respir Crit Care Med* 1994; 150: 489–495.
205 Xie A, Rankin F, Rutherford R, *et al.* Effects of inhaled CO_2 and added dead space on idiopathic central sleep apnea. *J Appl Physiol* 1997; 82: 918–926.
206 Banno K, Okamura K, Kryger MH. Adaptive servo-ventilation in patients with idiopathic Cheyne–Stokes breathing. *J Clin Sleep Med* 2006; 2: 181–186.
207 DeBacker WA, Verbraecken J, Willemen M, *et al.* Central apnea index decreases after prolonged treatment with acetazolamide. *Am J Respir Crit Care Med* 1995; 151: 87–91.
208 Quadri S, Drake C, Hudgel DW. Improvement of idiopathic central sleep apnea with zolpidem. *J Clin Sleep Med* 2009; 5: 122–129.
209 Verbraecken J, Willemen M, Wittesaele W, *et al.* Short-term CPAP does not influence the increased CO_2 drive in idiopathic central sleep apnea. *Monaldi Arch Chest Dis* 2002; 57: 10–18.
210 Benditt JO, Boitano LJ. Pulmonary issues in patients with chronic neuromuscular disease. *Am J Respir Crit Care Med* 2013; 187: 1046–1055.
211 Donath J, Miller A. Restrictive chest wall disorders. *Semin Respir Crit Care Med* 2009; 30: 275–292.
212 Steier J, Jolley CJ, Seymour J, *et al.* Neural respiratory drive in obesity. *Thorax* 2009; 64: 719–725.
213 Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. *Am J Respir Crit Care Med* 2011; 183: 292–298.
214 McNicholas WT. Impact of sleep in respiratory failure. *Eur Respir J* 1997; 10: 920–933.
215 Deegan PC, McNicholas WT. Pathophysiology of obstructive sleep apnoea. *Eur Respir J* 1995; 8: 1161–1178.
216 Parameswaran K, Todd DC, Soth M. Altered respiratory physiology in obesity. *Can Respir J* 2006; 13: 203–210.
217 Lin CK, Lin CC. Work of breathing and respiratory drive in obesity. *Respirology* 2012; 17: 402–411.
218 Ladosky W, Botelho MA, Albuquerque JP Jr. Chest mechanics in morbidly obese non-hypoventilated patients. *Respir Med* 2001; 95: 281–286.
219 DeLorey DS, Wyrick BL, Babb TG. Mild-to-moderate obesity: implications for respiratory mechanics at rest and during exercise in young men. *Int J Obes (Lond)* 2005; 29: 1039–1047.
220 Rubinstein I, Zamel N, DuBarry L, *et al.* Airflow limitation in morbidly obese, nonsmoking men. *Ann Intern Med* 1990; 112: 828–832.
221 Pankow W, Podszus T, Gutheil T, *et al.* Expiratory flow limitation and intrinsic positive end-expiratory pressure in obesity. *J Appl Physiol* 1998; 85: 1236–1243.
222 Lin CC, Wu KM, Chou CS, *et al.* Oral airway resistance during wakefulness in eucapnic and hypercapnic sleep apnea syndrome. *Respir Physiol Neurobiol* 2004; 139: 215–224.
223 Phipps PR, Starritt E, Caterson I, *et al.* Association of serum leptin with hypoventilation in human obesity. *Thorax* 2002; 57: 75–76.
224 Shimura R, Tatsumi K, Nakamura A, *et al.* Fat accumulation, leptin, and hypercapnia in obstructive sleep apnea-hypopnea syndrome. *Chest* 2005; 127: 543–549.
225 Berger KI, Goldring RM, Rapoport DM. Obesity hypoventilation syndrome. *Semin Respir Crit Care Med* 2009; 30: 253–261.
226 Ayappa I, Berger KI, Norman RG, *et al.* Hypercapnia and ventilatory periodicity in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2002; 166: 1112–1115.
227 Perez IA, Keens TG. Peripheral chemoreceptors in congenital central hypoventilation syndrome. *Respir Physiol Neurobiol* 2013; 185: 186–193.
228 Doherty LS, Kiely JL, Deegan PC, *et al.* Late-onset central hypoventilation syndrome: a family genetic study. *Eur Respir J* 2007; 29: 312–316.
229 Carratu P, Spicuzza L, Cassano A, *et al.* Early treatment with noninvasive positive pressure ventilation prolongs survival in Amyotrophic Lateral Sclerosis patients with nocturnal respiratory insufficiency. *Orphanet J Rare Dis* 2009; 4: 10.
230 Bourke SC, Tomlinson M, Williams TL, *et al.* Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol* 2006; 5: 140–147.
231 Hukins CA, Hillman DR. Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. *Am J Respir Crit Care Med* 2000; 161: 166–170.
232 Toussaint M, Steens M, Soudon P. Lung function accurately predicts hypercapnia in patients with Duchenne muscular dystrophy. *Chest* 2007; 131: 368–375.
233 Leger P, Bedicam JM, Cornette A, *et al.* Nasal intermittent positive pressure ventilation. Long-term follow-up in patients with severe chronic respiratory insufficiency. *Chest* 1994; 105: 100–105.
234 Simonds AK, Muntoni F, Heather S, *et al.* Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* 1998; 53: 949–952.
235 Toussaint M, Steens M, Wasteels G, *et al.* Diurnal ventilation *via* mouthpiece: survival in end-stage Duchenne patients. *Eur Respir J* 2006; 28: 549–555.
236 Soudon P, Steens M, Toussaint M. A comparison of invasive versus noninvasive full-time mechanical ventilation in Duchenne muscular dystrophy. *Chron Respir Dis* 2008; 5: 87–93.

237 McKim DA, Griller N, LeBlanc C, *et al.* Twenty-four hour noninvasive ventilation in Duchenne muscular dystrophy: a safe alternative to tracheostomy. *Can Respir J* 2013; 20: e5–e9.
238 Begin P, Mathieu J, Almirall J, *et al.* Relationship between chronic hypercapnia and inspiratory-muscle weakness in myotonic dystrophy. *Am J Respir Crit Care Med* 1997; 156: 133–139.
239 Pincherle A, Patruno V, Raimondi P, *et al.* Sleep breathing disorders in 40 Italian patients with myotonic dystrophy type 1. *Neuromuscul Disord* 2012; 22: 219–224.
240 Poussel M, Thil C, Kaminsky P, *et al.* Lack of correlation between the ventilatory response to CO_2 and lung function impairment in myotonic dystrophy patients: evidence for a dysregulation at central level. *Neuromuscul Disord* 2015; 25: 403–408.
241 Nugent AM, Smith IE, Shneerson JM. Domiciliary-assisted ventilation in patients with myotonic dystrophy. *Chest* 2002; 121: 459–464.
242 Mellies U, Stehling F, Dohna-Schwake C, *et al.* Respiratory failure in Pompe disease: treatment with noninvasive ventilation. *Neurology* 2005; 64: 1465–1467.
243 Smith BK, Collins SW, Conlon TJ, *et al.* Phase I/II trial of adeno-associated virus-mediated alpha-glucosidase gene therapy to the diaphragm for chronic respiratory failure in Pompe disease: initial safety and ventilatory outcomes. *Hum Gene Ther* 2013; 24: 630–640.
244 Sancho J, Servera E, Banuls P, *et al.* Predictors of need for noninvasive ventilation during respiratory tract infections in medically stable, non-ventilated subjects with amyotrophic lateral sclerosis. *Respir Care* 2015; 60: 492–497.
245 Lyall RA, Donaldson N, Fleming T, *et al.* A prospective study of quality of life in ALS patients treated with noninvasive ventilation. *Neurology* 2001; 57: 153–156.
246 Mendoza M, Gelinas DF, Moore DH, *et al.* A comparison of maximal inspiratory pressure and forced vital capacity as potential criteria for initiating non-invasive ventilation in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2007; 8: 106–111.
247 Jackson CE, Rosenfeld J, Moore DH, *et al.* A preliminary evaluation of a prospective study of pulmonary function studies and symptoms of hypoventilation in ALS/MND patients. *J Neurol Sci* 2001; 191: 75–78.
248 Bourke SC, Tomlinson M, Williams TL, *et al.* Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurology* 2006; 5: 140–147.
249 Gonzalez-Bermejo J, Morelot-Panzini C, Arnol N, *et al.* Prognostic value of efficiently correcting nocturnal desaturations after one month of non-invasive ventilation in amyotrophic lateral sclerosis: a retrospective monocentre observational cohort study. *Amyotroph Lateral Scler Frontotemporal Degener* 2013; 14: 373–379.
250 Lechtzin N, Scott Y, Busse AM, *et al.* Early use of non-invasive ventilation prolongs survival in subjects with ALS. *Amyotroph Lateral Scler* 2007; 8: 185–188.
251 Pinto AC, Evangelista T, Carvalho M, *et al.* Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. *J Neurol Sci* 1995; 129: Suppl., 19–26.
252 Kleopa KA, Sherman M, Neal B, *et al.* Bipap improves survival and rate of pulmonary function decline in patients with ALS. *J Neurol Sci* 1999; 164: 82–88.
253 Bourke SC, Bullock RE, Williams TL, *et al.* Noninvasive ventilation in ALS: indications and effect on quality of life. *Neurology* 2003; 61: 171–177.
254 Dreyer P, Lorenzen CK, Schou L, *et al.* Survival in ALS with home mechanical ventilation non-invasively and invasively: a 15-year cohort study in west Denmark. *Amyotroph Lateral Scler Frontotemporal Degener* 2014; 15: 62–67.
255 Gruis KL, Brown DL, Schoennemann A, *et al.* Predictors of noninvasive ventilation tolerance in patients with amyotrophic lateral sclerosis. *Muscle Nerve* 2005; 32: 808–811.
256 Lo Coco D, Marchese S, Pesco MC, *et al.* Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. *Neurology* 2006; 67: 761–765.
257 Spataro R, Bono V, Marchese S, *et al.* Tracheostomy mechanical ventilation in patients with amyotrophic lateral sclerosis: clinical features and survival analysis. *J Neurol Sci* 2012; 323: 66–70.
258 Mahajan KR, Bach JR, Saporito L, *et al.* Diaphragm pacing and noninvasive respiratory management of amyotrophic lateral sclerosis/motor neuron disease. *Muscle Nerve* 2012; 46: 851–855.
259 Butz M, Wollinsky KH, Wiedemuth-Catrinescu U, *et al.* Longitudinal effects of noninvasive positive-pressure ventilation in patients with amyotrophic lateral sclerosis. *Am J Phys Med Rehabil* 2003; 82: 597–604.
260 Bach JR, Rajaraman R, Ballanger F, *et al.* Neuromuscular ventilatory insufficiency: effect of home mechanical ventilator use v oxygen therapy on pneumonia and hospitalization rates. *Am J Phys Med Rehabil* 1998; 77: 8–19.
261 Vrijsen B, Buyse B, Belge C, *et al.* Noninvasive ventilation improves sleep in amyotrophic lateral sclerosis: a prospective polysomnographic study. *J Clin Sleep Med* 2015; 11: 559–566.
262 de Carvalho M, Costa J, Pinto S, *et al.* Percutaneous nocturnal oximetry in amyotrophic lateral sclerosis: periodic desaturation. *Amyotroph Lateral Scler* 2009; 10: 154–161.
263 Ferguson KA, Strong MJ, Ahmad D, *et al.* Sleep-disordered breathing in amyotrophic lateral sclerosis. *Chest* 1996; 110: 664–669.
264 Boentert M, Brenscheidt I, Glatz C, *et al.* Effects of non-invasive ventilation on objective sleep and nocturnal respiration in patients with amyotrophic lateral sclerosis. *J Neurol* 2015; 262: 2073–2082.
265 Smith PE, Edwards RH, Calverley PM. Ventilation and breathing pattern during sleep in Duchenne muscular dystrophy. *Chest* 1989; 96: 1346–1351.
266 Raphael JC, Chevret S, Chastang C, *et al.* Randomised trial of preventive nasal ventilation in Duchenne muscular dystrophy. French Multicentre Cooperative Group on Home Mechanical Ventilation Assistance in Duchenne de Boulogne Muscular Dystrophy. *Lancet* 1994; 343: 1600–1604.
267 Biggar WD, Harris VA, Eliasoph L, *et al.* Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. *Neuromuscul Disord* 2006; 16: 249–255.
268 Eagle M, Bourke J, Bullock R, *et al.* Managing Duchenne muscular dystrophy – the additive effect of spinal surgery and home nocturnal ventilation in improving survival. *Neuromuscul Disord* 2007; 17: 470–475.
269 Buyse GM, Voit T, Schara U, *et al.* Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial. *Lancet* 2015; 385: 1748–1757.

270 Boentert M, Karabul N, Wenninger S, *et al.* Sleep-related symptoms and sleep-disordered breathing in adult Pompe disease. *Eur J Neurol* 2015; 22: 369–376, e327.
271 Mellies U, Ragette R, Schwake C, *et al.* Sleep-disordered breathing and respiratory failure in acid maltase deficiency. *Neurology* 2001; 57: 1290–1295.
272 Kishnani PS, Corzo D, Nicolino M, *et al.* Recombinant human acid α-glucosidase: major clinical benefits in infantile-onset Pompe disease. *Neurology* 2007; 68: 99–109.
273 Nicolino M, Byrne B, Wraith JE, *et al.* Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. *Genet Med* 2009; 11: 210–219.
274 Kansagra S, Austin S, DeArmey S, *et al.* Longitudinal polysomnographic findings in infantile Pompe disease. *Am J Med Genet A* 2015; 167A: 858–861.
275 Barbe F, Quera-Salva MA, de Lattre J, *et al.* Long-term effects of nasal intermittent positive-pressure ventilation on pulmonary function and sleep architecture in patients with neuromuscular diseases. *Chest* 1996; 110: 1179–1183.
276 Meyer TJ, Pressman MR, Benditt J, *et al.* Air leaking through the mouth during nocturnal nasal ventilation: effect on sleep quality. *Sleep* 1997; 20: 561–569.
277 Ward S, Chatwin M, Heather S, *et al.* Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. *Thorax* 2005; 60: 1019–1024.
278 Chatwin M, Nickol AH, Morrell MJ, *et al.* Randomised trial of inpatient *versus* outpatient initiation of home mechanical ventilation in patients with nocturnal hypoventilation. *Respir Med* 2008; 102: 1528–1535.
279 Crescimanno G, Marrone O, Vianello A. Efficacy and comfort of volume-guaranteed pressure support in patients with chronic ventilatory failure of neuromuscular origin. *Respirology* 2011; 16: 672–679.
280 Crescimanno G, Canino M, Marrone O. Asynchronies and sleep disruption in neuromuscular patients under home noninvasive ventilation. *Respir Med* 2012; 106: 1478–1485.
281 Crescimanno G, Misuraca A, Purrazzella G, *et al.* Subjective sleep quality in stable neuromuscular patients under non-invasive ventilation. *Sleep Med* 2014; 15: 1259–1263.
282 Ferris G, Servera-Pieras E, Vergara P, *et al.* Kyphoscoliosis ventilatory insufficiency: noninvasive management outcomes. *Am J Phys Med Rehabil* 2000; 79: 24–29.
283 Mezon BL, West P, Israels J, *et al.* Sleep breathing abnormalities in kyphoscoliosis. *Am Rev Respir Dis* 1980; 122: 617–621.
284 Guilleminault C, Kurland G, Winkle R, *et al.* Severe kyphoscoliosis, breathing, and sleep: the "Quasimodo" syndrome during sleep. *Chest* 1981; 79: 626–630.
285 Sawicka EH, Branthwaite MA. Respiration during sleep in kyphoscoliosis. *Thorax* 1987; 42: 801–808.
286 Cirignotta F, Gerardi R, Mondini S, *et al.* Breathing disorders during sleep in chest wall diseases. *Monaldi Arch Chest Dis* 1993; 48: 315–317.
287 Bach JR, Robert D, Leger P, *et al.* Sleep fragmentation in kyphoscoliotic individuals with alveolar hypoventilation treated by NIPPV. *Chest* 1995; 107: 1552–1558.
288 Nauffal D, Domenech R, Martinez Garcia MA, *et al.* Noninvasive positive pressure home ventilation in restrictive disorders: outcome and impact on health-related quality of life. *Respir Med* 2002; 96: 777–783.
289 Brooks D, De Rosie J, Mousseau M, *et al.* Long term follow-up of ventilated patients with thoracic restrictive or neuromuscular disease. *Can Respir J* 2002; 9: 99–106.
290 Piper AJ, Sullivan CE. Effects of long-term nocturnal nasal ventilation on spontaneous breathing during sleep in neuromuscular and chest wall disorders. *Eur Respir J* 1996; 9: 1515–1522.
291 Ellis ER, Grunstein RR, Chan S, *et al.* Noninvasive ventilatory support during sleep improves respiratory failure in kyphoscoliosis. *Chest* 1988; 94: 811–815.
292 Gonzalez C, Ferris G, Diaz J, *et al.* Kyphoscoliotic ventilatory insufficiency: effects of long-term intermittent positive-pressure ventilation. *Chest* 2003; 124: 857–862.
293 Zaccaria S, Zaccaria E, Zanaboni S, *et al.* Home mechanical ventilation in kyphoscoliosis. *Monaldi Arch Chest Dis* 1993; 48: 161–164.
294 Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation? *Eur Respir J* 2003; 22: 525–528.
295 Duiverman ML, Bladder G, Meinesz AF, *et al.* Home mechanical ventilatory support in patients with restrictive ventilatory disorders: a 48-year experience. *Respir Med* 2006; 100: 56–65.
296 Janssens JP, Derivaz S, Breitenstein E, *et al.* Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. *Chest* 2003; 123: 67–79.
297 Simonds AK, Elliott MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. *Thorax* 1995; 50: 604–609.
298 Hollier CA, Maxwell LJ, Harmer AR, *et al.* Validity of arterialised-venous $P\,CO_2$, pH and bicarbonate in obesity hypoventilation syndrome. *Respir Physiol Neurobiol* 2013; 188: 165–171.
299 Borel JC, Tamisier R, Gonzalez-Bermejo J, *et al.* Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. *Chest* 2012; 141: 692–702.
300 Murphy PB, Davidson C, Hind MD, *et al.* Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. *Thorax* 2012; 67: 727–734.
301 Wijesinghe M, Williams M, Perrin K, *et al.* The effect of supplemental oxygen on hypercapnia in subjects with obesity-associated hypoventilation: a randomized, crossover, clinical study. *Chest* 2011; 139: 1018–1024.
302 Ambrogio C, Lowman X, Kuo M, *et al.* Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency. *Intensive Care Med* 2009; 35: 306–313.
303 Piper AJ, Wang D, Yee BJ, *et al.* Randomised trial of CPAP *vs* bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. *Thorax* 2008; 63: 395–401.
304 Resta O, Foschino-Barbaro MP, Bonfitto P, *et al.* Prevalence and mechanisms of diurnal hypercapnia in a sample of morbidly obese subjects with obstructive sleep apnoea. *J Appl Physiol* 2000; 94: 240–246.
305 Masa JF, Celli BR, Riesco JA, *et al.* The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. *Chest* 2001; 119: 1102–1107.
306 Banerjee D, Yee BJ, Piper AJ, *et al.* Obesity hypoventilation syndrome: hypoxemia during continuous positive airway pressure. *Chest* 2007; 131: 1678–1684.

307 Pasquina P, Adler D, Farr P, *et al.* What does built-in software of home ventilators tell us? An observational study of 150 patients on home ventilation. *Respiration* 2012; 83: 293–299.
308 Gursel G, Aydogdu M, Gulbas G, *et al.* The influence of severe obesity on non-invasive ventilation (NIV) strategies and responses in patients with acute hypercapnic respiratory failure attacks in the ICU. *Minerva Anestesiol* 2011; 77: 17–25.
309 Lumachi F, Marzano B, Fanti G, *et al.* Hypoxemia and hypoventilation syndrome improvement after laparoscopic bariatric surgery in patients with morbid obesity. *In Vivo* 2010; 24: 329–331.
310 Priou P, Hamel JF, Person C, *et al.* Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. *Chest* 2010; 138: 84–90.
311 Perez de Llano LA, Golpe R, Piquer MO, *et al.* Clinical heterogeneity among patients with obesity hypoventilation syndrome: therapeutic implications. *Respiration* 2008; 75: 34–39.
312 Helling TS. Operative experience and follow-up in a cohort of patients with a BMI > or =70 kg/m^2. *Obes Surg* 2005; 15: 482–485.
313 Davila-Cervantes A, Dominguez-Cherit G, Borunda D, *et al.* Impact of surgically-induced weight loss on respiratory function: a prospective analysis. *Obes Surg* 2004; 14: 1389–1392.
314 Resta O, Guido P, Picca V, *et al.* Prescription of nCPAP and nBIPAP in obstructive sleep apnoea syndrome: Italian experience in 105 subjects. A prospective two centre study. *Respir Med* 1998; 92: 820–827.
315 Pankow W, Nabe B, Lies A, *et al.* Influence of sleep apnea on 24-hour blood pressure. *Chest* 1997; 112: 1253–1258.
316 Lin CC. Effect of nasal CPAP on ventilatory drive in normocapnic and hypercapnic patients with obstructive sleep apnoea syndrome. *Eur Respir J* 1994; 7: 2005–2010.
317 Sugerman HJ, Fairman RP, Baron PL, *et al.* Gastric surgery for respiratory insufficiency of obesity. *Chest* 1986; 90: 81–86.
318 Borel AL, Monneret D, Tamisier R, *et al.* The severity of nocturnal hypoxia but not abdominal adiposity is associated with insulin resistance in non-obese men with sleep apnea. *PLoS One* 2013; 8: e71000.
319 Chau EH, Lam D, Wong J, *et al.* Obesity hypoventilation syndrome: a review of epidemiology, pathophysiology, and perioperative considerations. *Anesthesiology* 2012; 117: 188–205.
320 Kessler R, Chaouat A, Schinkewitch P, *et al.* The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest* 2001; 120: 369–376.
321 Akashiba T, Akahoshi T, Kawahara S, *et al.* Clinical characteristics of obesity-hypoventilation syndrome in Japan: a multi-center study. *Intern Med* 2006; 45: 1121–1125.
322 Mokhlesi B, Tulaimat A, Faibussowitsch I, *et al.* Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. *Sleep Breath* 2007; 11: 117–124.
323 Chouri-Pontarollo N, Borel JC, Tamisier R, *et al.* Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of noninvasive ventilation. *Chest* 2007; 131: 148–155.
324 Mokhlesi B, Kryger MH, Grunstein RR. Assessment and management of patients with obesity hypoventilation syndrome. *Proc Am Thorac Soc* 2008; 5: 218–225.
325 Berg G, Delaive K, Manfreda J, *et al.* The use of health-care resources in obesity-hypoventilation syndrome. *Chest* 2001; 120: 377–383.
326 Borel JC, Roux-Lombard P, Tamisier R, *et al.* Endothelial dysfunction and specific inflammation in obesity hypoventilation syndrome. *PLoS One* 2009; 4: e6733.
327 Jennum P, Kjellberg J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. *Thorax* 2011; 66: 560–566.
328 Borel JC, Tamisier R, Dias-Domingos S, *et al.* Type of mask may impact on continuous positive airway pressure adherence in apneic patients. *PLoS One* 2013; 8: e64382.
329 Nowbar S, Burkart KM, Gonzales R, *et al.* Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med* 2004; 116: 1–7.
330 Perez de Llano LA, Golpe R, Ortiz Piquer M, *et al.* Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. *Chest* 2005; 128: 587–594.
331 Pepin V, Saey D, Whittom F, *et al.* Walking *versus* cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 1517–1522.
332 Castro-Anon O, Perez de Llano LA, De la Fuente Sanchez S, *et al.* Obesity-hypoventilation syndrome: increased risk of death over sleep apnea syndrome. *PLoS One* 2015; 10: e0117808.
333 Javaheri S, Simbartl LA. Respiratory determinants of diurnal hypercapnia in obesity hypoventilation syndrome: what does weight have to do with it? *Ann Am Thorac Soc* 2014; 11: 945–950.
334 Zwillich CW, Sutton FD, Pierson DJ, *et al.* Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. *Am J Med* 1975; 59: 343–348.
335 Lopata M, Onal E. Mass loading, sleep apnea, and the pathogenesis of obesity hypoventilation. *Am Rev Respir Dis* 1982; 126: 640–645.
336 Sampson MG, Grassino K. Neuromechanical properties in obese patients during carbon dioxide rebreathing. *Am J Med* 1983; 75: 81–90.
337 Mokhlesi B. Positive airway pressure titration in obesity hypoventilation syndrome: continuous positive airway pressure or bilevel positive airway pressure. *Chest* 2007; 131: 1624–1626.
338 Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. *Respir Care* 2010; 55: 1347–1362.
339 Macavei VM, Spurling KJ, Loft J, *et al.* Diagnostic predictors of obesity-hypoventilation syndrome in patients suspected of having sleep disordered breathing. *J Clin Sleep Med* 2013; 9: 879–884.
340 Randerath WJ, Stieglitz S, Galetke W, *et al.* Evaluation of a system for transcutaneous long-term capnometry. *Respiration* 2010; 80: 139–145.
341 Bernet-Buettiker V, Ugarte MJ, Frey B, *et al.* Evaluation of a new combined transcutaneous measurement of P_{CO_2}/pulse oximetry oxygen saturation ear sensor in newborn patients. *Pediatrics* 2005; 115: e64–e68.
342 Masa JF, Corral J, Alonso ML, *et al.* Efficacy of different treatment alternatives for obesity hypoventilation syndrome. Pickwick Study. *Am J Respir Crit Care Med* 2015; 192: 86–95.
343 Borel JC, Borel AL, Monneret D, *et al.* Obesity hypoventilation syndrome: from sleep-disordered breathing to systemic comorbidities and the need to offer combined treatment strategies. *Respirology* 2012; 17: 601–610.
344 Windisch W. Impact of home mechanical ventilation on health-related quality of life. *Eur Respir J* 2008; 32: 1328–1336.

345 Windisch W, Freidel K, Schucher B, *et al.* The Severe Respiratory Insufficiency (SRI) Questionnaire: a specific measure of health-related quality of life in patients receiving home mechanical ventilation. *J Clin Epidemiol* 2003; 56: 752–759.

346 Sugerman HJ, Baron PL, Fairman RP, *et al.* Hemodynamic dysfunction in obesity hypoventilation syndrome and the effects of treatment with surgically induced weight loss. *Ann Surg* 1988; 207: 604–613.

347 Lumachi F, Marzano B, Fanti G, *et al.* Relationship between body mass index, age and hypoxemia in patients with extremely severe obesity undergoing bariatric surgery. *In Vivo* 2010; 24: 775–777.

348 O'Donoghue FJ, Catcheside PG, Ellis EE, *et al.* Sleep hypoventilation in hypercapnic chronic obstructive pulmonary disease: prevalence and associated factors. *Eur Respir J* 2003; 21: 977–984.

349 Struik FM, Lacasse Y, Goldstein R, *et al.* Nocturnal non-invasive positive pressure ventilation for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2013; 6: CD002878.

350 Struik FM, Lacasse Y, Goldstein RS, *et al.* Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. *Respir Med* 2014; 108: 329–337.

351 Kohnlein T, Windisch W, Kohler D, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014; 2: 698–705.

352 McEvoy RD, Pierce RJ, Hillman D, *et al.* Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. *Thorax* 2009; 64: 561–566.

353 Clini E, Sturani C, Rossi A, *et al.* The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; 20: 529–538.

354 Chu CM, Chan VL, Lin AW, *et al.* Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax* 2004; 59: 1020–1025.

355 Cheung AP, Chan VL, Liong JT, *et al.* A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis* 2010; 14: 642–649.

356 Funk GC, Breyer MK, Burghuber OC, *et al.* Long-term non-invasive ventilation in COPD after acute-on-chronic respiratory failure. *Respir Med* 2011; 105: 427–434.

357 Struik FM, Sprooten RT, Kerstjens HA, *et al.* Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax* 2014; 69: 826–834.