

# Chronic hypoventilation syndromes and sleep-related hypoventilation

Sebastian Böing<sup>1\*</sup>, Winfried J. Randerath<sup>1,2\*</sup>

<sup>1</sup>Institute of Pneumology, Clinic for Pneumology and Allergology, Centre of Sleep Medicine and Respiratory Care, Bethanien Hospital, Solingen, Germany; <sup>2</sup>University of Cologne, Solingen, Germany

\*These authors contributed equally to this work.

**Contributions:** (I) Conception and design: All authors; (II) Administrative support: C Miltz; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors.; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Winfried J. Randerath, MD, FCCP, Professor of Medicine. Institute of Pneumology, Clinic for Pneumology and Allergology, Centre of Sleep Medicine and Respiratory Care, Bethanien Hospital, University of Cologne, Aufderhöherstraße 169-175, 42699 Solingen, Germany. Email: randerath@klinik-bethanien.de.

**Abstract:** Chronic hypoventilation affects patients with disorders on any level of the respiratory system. The generation of respiratory impulses can be impaired in congenital disorders, such as central congenital alveolar hypoventilation, in alterations of the brain stem or complex diseases like obesity hypoventilation. The translation of the impulses via spinal cord and nerves to the respiratory muscles can be impaired in neurological diseases. Thoraco-skeletal or muscular diseases may inhibit the execution of the impulses. All hypoventilation disorders are characterized by a reduction of the minute ventilation with an increase of daytime hypercapnia. As sleep reduces minute ventilation substantially in healthy persons and much more pronounced in patients with underlying thoraco-pulmonary diseases, hypoventilation manifests firstly during sleep. Therefore, sleep related hypoventilation may be an early stage of chronic hypoventilation disorders. After treatment of any prevailing underlying disease, symptomatic therapy with non-invasive ventilation (NIV) is required. The adaptation of the treatment should be performed under close medical supervision. Pressure support algorithms have become most frequently used. The most recent devices automatically apply pressure support and vary inspiratory and expiratory pressures and breathing frequency in order to stabilize upper airways, normalize ventilation, achieve best synchronicity between patient and device and aim at optimizing patients' adherence.

**Keywords:** Chronic hypoventilation syndromes; sleep related hypoventilation; hypercapnic respiratory failure; pathophysiology; obesity hypoventilation syndrome (OHS)

Submitted Jan 02, 2015. Accepted for publication Jun 05, 2015.

doi: 10.3978/j.issn.2072-1439.2015.06.10

**View this article at:** <http://dx.doi.org/10.3978/j.issn.2072-1439.2015.06.10>

## Introduction

Under physiological conditions, alveolar ventilation is closely adapted to metabolism. The minute ventilation is regulated according to the prevailing carbon dioxide production so that the arterial carbon dioxide partial pressure (PaCO<sub>2</sub>) is adjusted to values between 35–45 mmHg. Increases (hyperventilation) or decreases (hypoventilation) of the minute ventilation lead to excess elimination or accumulation of carbon dioxide,

respectively, and destabilize the acid-base balance. However, consecutive increases of the pH value (respiratory alkalosis) or decreases (respiratory acidosis) are only measured during acute changes of ventilation. In contrast, if hyper- or hypoventilation continues for hours, the pH level is stabilized by variations of the renal bicarbonate (HCO<sub>3</sub><sup>-</sup>) excretion (1). Therefore, chronic hypoventilation syndromes are characterized by:

- Diminishment of the minute ventilation, i.e.,

reductions of the tidal volume or breathing frequency;

- Elevation of the  $\text{PaCO}_2 > 45$  mmHg;
- pH level in a normal range and an increase of  $\text{HCO}_3^-$  (metabolic compensation).

Chronic hypoventilation is also called hypercapnic respiratory failure or type II respiratory failure. The diminution of minute ventilation can generate from all levels of the respiratory system including insufficient respiratory drive (brain stem), impaired transmission of the breathing impulses (spinal cord, peripheral nerve), and morphological or functional abnormalities of the musculo-skeletal system of the thorax. Failure of the respiratory regulation on the one hand or execution of the impulses on the other hand represent different facets of the pathophysiology which can be described as “won’t breathe” and “can’t breathe” (2). Congenital central alveolar hypoventilation and opioid use represent examples of central disturbances, while amyotrophic lateral sclerosis (ALS), phrenic nerve palsy, muscle dystrophies, idiopathic sclerosis are examples of insufficient execution of ventilation. However, the obesity hypoventilation syndrome (OHS) combines components of both pathomechanisms. Chronic hypoventilation with daytime hypercapnia and sleep-related hypoventilation (SRH) do not differ substantially. Actually, SRH seems to represent an early stage of chronic hypoventilation. Nevertheless, this hypothesis has to be confirmed and the number of patients with advancing severity has to be evaluated in future research.

The most recent edition of the International Classification of Sleep Disorders (3) describes six subtypes of hypoventilation disorders in the chapter of sleep related breathing disorders:

- OHS;
- Congenital central alveolar hypoventilation syndrome (CCHS);
- 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.

The term CCHS replaces the name “Ondine’s curse”. CCHS requires evidence of a mutation of the PHOX2B-gene leading to a diffuse imbalance of the autonomic system. Differences in the mutation discriminate congenital from *de novo* development (4). Despite its congenital character, the disease may manifest in adulthood in some cases (3,5). Late-onset phenotypes may present with respiratory

failure after general anesthesia, severe respiratory illness or respiratory depressants (6). However, in most cases hypoventilation begins during childhood and is more pronounced during sleep. The failure of central respiratory drive may be associated with respiratory rest during sleep. CCHS may be accompanied with other phenomena like Hirschsprung’s disease, cardiac arrhythmia, and tumors (6,7).

Idiopathic central alveolar hypoventilation is diagnosed if diseases of lung parenchyma, airways, pulmonary vessels, chest volume or neuromuscular diseases (NMD), drug treatment, obesity or congenital hypoventilation can be excluded (3,5). Several questions on idiopathic central alveolar hypoventilation are unresolved. The pathophysiology is unclear although an impairment of the hypercapnic and hypoxic chemoresponsiveness and respiratory drive has been discussed.

Late-onset central hypoventilation with hypothalamic dysfunction is a disorder of the central control of ventilation (3). It can be diagnosed if sleep related hypoventilation develops after the first years of life. The patients present with obesity, endocrine abnormalities of hypothalamic origin, severe emotional or behavioral disturbances or a tumor of neural origin (two of these four findings are required). Moreover, mutations of the PHOX2B-gene and other disorders explaining hypoventilation have to be excluded. Although the disease is associated with hyperphagia, hypoventilation persists even if patients lose weight. Diabetes insipidus, inappropriate antidiuretic hormone hypersecretion, precocious puberty, hypogonadism, hyperprolactinemia, hyperthyroidism and decreased growth hormone secretion are associated endocrine dysfunctions (3,5).

In contrast to these rare disorders, the OHS and chronic hypoventilation due to medical disorders or pharmaceutical influences represent the huge majority of chronic and SRH. OHS patients are characterized by obesity ( $\text{BMI} > 30 \text{ kg/m}^2$ ) and wakefulness hypercapnia. Hypoventilation in OHS cannot primarily be explained by other thoraco-pulmonary, neuromuscular or idiopathic diseases or pharmaceutical influences (3,5,8,9) (Table 1).

Sleep related hypoventilation due to a medical disorder is diagnosed in patients with underlying diseases of the lung parenchyma or the airways, the pulmonary vessels or neurological or musculo-skeletal disorders. In addition, SRH can be induced by drugs which depress ventilatory drive or impair muscle function. Long-acting narcotics, anesthetics, sedatives and muscle relaxants and also alcohol have been discussed (3,5). Chronic opioid intake may be associated with central apnoeas, atactic respiration but also

**Table 1** Characteristics of the obesity hypoventilation syndrome (OHS)

Definition criteria	Description
Chronic hypoventilation	Hypercapnia in wakefulness and sleep ( $\text{PaCO}_2 \geq 45$ mmHg or 6 kPa)
Obesity	Body mass index (BMI) $\geq 30$ kg/m <sup>2</sup>
Absence of other causes of hypercapnia	Diseases of the lung parenchyma, airways, pulmonary vessels Neurological, musculo-skeletal or other idiopathic disorders Congenital central alveolar hypoventilation syndrome (CCHS) Medication or drugs
Sleep-related breathing disorders	Obstructive sleep apnea (OSA) with or without coexisting sleep-related hypoventilation in 90% of patients Non-obstructive (apnea-hypopnea index $< 5$ events/hours) sleep-related hypoventilation in about 10%

sustained hypoxemia and hypoventilation (10).

### Diagnosis of chronic and sleep related hypoventilation

Due to the broad variety of underlying diseases and pathophysiological mechanisms, there are no single typical clinical signs or symptoms which confidentially indicate or predict chronic or sleep related hypoventilation. Thus, a comprehensive clinical assessment, including a detailed history on sleep quality, morning symptoms, daytime fatigue or dyspnoea on exertion and a careful examination are crucial. Firstly, impaired alveolar ventilation becomes evident during sleep or exertion. Sleep is associated with a reduction of the minute ventilation even in healthy persons, while physical stress increases  $\text{CO}_2$  production. Hypoventilation during sleep may be associated with poor sleep quality, excessive daytime sleepiness and morning headaches. However, a relevant portion of patients reports no or only minor complaints. Typical clinical symptoms include reduced exercise capacity and dyspnoea. However, there are huge interindividual differences in clinical findings also depending on the underlying disease (6,11).

Chronic hypercapnic respiratory failure and hypoventilation during exertion can easily be diagnosed by arterial or capillary blood gas analysis during wakefulness. However, monitoring of respiration and carbon dioxide levels during sleep are needed to establish the diagnosis of SRH. Polysomnography (PSG) reveals the gold standard of investigating sleep and respiration. It is the only technique which allows to differentiate sleep and wakefulness and to diagnose electroencephalographic arousals and their relation to breathing disturbances. Sleep-wake transitions

and arousals substantially influence respiration, leading to central breathing disturbances and propagation of periodic breathing (12-14). Thus, PSG is crucially important to precisely define the disease in individual patients and understand the underlying pathophysiology. Moreover, optimal therapy of chronic hypoventilation should not only focus on improvement of oxygen saturation and normalization of hypercapnia, but also in stabilization of the sleep profile. Therefore, we recommend PSG in the diagnostical work up of patients with chronic hypoventilation and in the follow-up of patients with persisting fatigue, sleepiness and morning headache under treatment. Nevertheless, if PSG is not available or cannot be performed due to comorbidities or complicated circumstances, multi-channel respiratory studies may suffice (15). When combined with actigraphy, they may also allow to separate sleep from wake periods (16).

Different invasive and non-invasive techniques are available to measure the carbon dioxide level. Arterial blood samples or samples from arterialized ear lobe represent the state of the art techniques for assessment of the  $\text{PCO}_2$ . However, blood sampling during the night disrupts patients' sleep, which may be associated with hyperventilation. Moreover, as a snapshot, single samples may not reflect the ventilator status of the whole night (17). Monitoring of the end-tidal  $\text{CO}_2$  ( $\text{PetCO}_2$ ) and of the transcutaneous  $\text{CO}_2$  ( $\text{PtcCO}_2$ ) allow for non-invasive and continuous measurement.  $\text{PetCO}_2$  is known to be influenced by nasal congestion and secretion. Moreover, it may substantially be limited by oxygen insufflation, non-invasive ventilation (NIV) and mask leaks (18,19).  $\text{PtcCO}_2$  allows for reliable and continuous measurement of the changes of the parameter.  $\text{PtcCO}_2$  correlates with  $\text{PaCO}_2$

although absolute figures often differ substantially. Actually, PtcCO<sub>2</sub> represents a different parameter as it is influenced by the metabolism of the skin cells and the heating of the skin. Thus, PtcCO<sub>2</sub> is systematically higher than PaCO<sub>2</sub>, which has to be considered when interpreting the results. In addition, there might be a shift of the PtcCO<sub>2</sub> during long term measurements, although this problem seems to be less relevant with modern devices (17,20).

Numerous definitions of SRH have been introduced; they impair the comparison of studies and may have impact on clinical decisions. Previous definitions included increases of the PaCO<sub>2</sub> >50 mmHg for >5% of measuring time or 10 mmHg rise or peak PtcCO<sub>2</sub> >6.5 kPa (49 mmHg) (15). The most recent revision of the American Academy of Sleep Medicine (AASM) scoring criteria suggest to score SRH in case of:

- PCO<sub>2</sub> >55 mmHg for ≥10 minutes during sleep or;
- Increases of the PCO<sub>2</sub> ≥10 mmHg as compared to awake supine value up to a level of >50 mmHg for ≥10 minutes (21);
- In children, hypoventilation is scored if the PaCO<sub>2</sub> or surrogate parameter increase >50 mmHg for >25% of total sleep time (21).

Hypoventilation is usually associated with a long term oxygen desaturation so that a decreased of the oxygen saturation (SaO<sub>2</sub>) <90% for >5 minutes with a nadir of ≤85% may also indicate hypercapnia and should urge to further diagnostical work up. Finally, as mentioned above, elevated levels of HCO<sub>3</sub><sup>-</sup> after awakening suggest sleep hypoventilation even if the PaCO<sub>2</sub> is within the normal range during wakefulness.

### Identification of patients at risk for hypercapnic respiratory failure

An inversed breathing pattern in supine position may indicate a relevant deterioration of ventilatory muscle capacity in NMD. The change of the forced vital capacity (FVC) from erect to supine position may deliver additional information: while FVC decreases approximately by 8-10% from upright to supine position in healthy subjects, Allen *et al.* showed that a decrease >25% indicates an impaired diaphragmatic function (22). Ragette *et al.* found a correlation between inspiratory vital capacity (IVC) with respiratory muscle function and CO<sub>2</sub> elimination in NMD during day and night. Onset of sleep disordered breathing was noticed with IVC <60%, while a figure below 40% was associated with continuous hypoventilation during sleep, respiratory

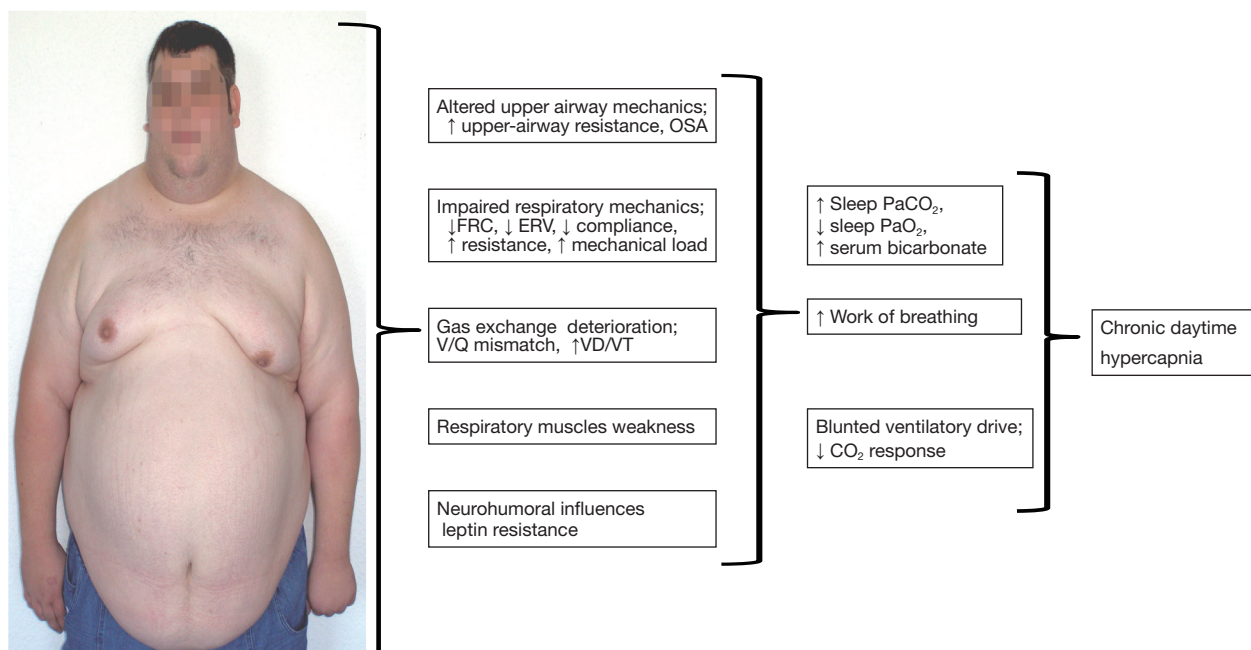
failure both during sleep and wakefulness was likely below 25% (23). The sniff nasal pressure was superior to vital capacity (VC) in predicting reduced respiratory muscle strength in ALS without significant bulbar involvement (24). In addition, children with NMD exhibit significantly more often sleep related hypoventilation when they also suffer from scoliosis (25). Lung function parameters indicating a high respiratory load and low muscle capacity are major predictors of daytime hypercapnia in COPD (26). Forced expiratory volume in one second (FEV<sub>1</sub>) correlates with chronic hypercapnia in most studies. Montes de Oca and Celli studied 33 severe COPD patients, including 14 with daytime hypercapnia, and 20 controls. The likelihood of hypercapnia increased substantially if FEV<sub>1</sub> was <0.5 liters (27). Hypercapnia was more probable in patients with a FEV<sub>1</sub> <40% and in hyperinflation as demonstrated by Rodríguez-Roisin *et al.* (28). and Saure *et al.* (29).

Increased levels of HCO<sub>3</sub><sup>-</sup> may indicate chronic or intermittent hypoventilation. It has been shown, that an elevated HCO<sub>3</sub><sup>-</sup> level sufficiently predicts hypercapnia in obese subjects (30). The careful examination of the relation between PaCO<sub>2</sub> and body-mass-index (BMI) may prevent underdiagnoses of OHS. Bülbül *et al.* found a ratio below 1.5 to be strongly predictive of the disease (31). In addition, oxygen saturation during sleep or wakefulness may also serve as an indicator of chronic hypercapnia. Basoglu *et al.* found an independent association of hypercapnia with reduced daytime SaO<sub>2</sub> in OHS as compared to matched patients with obstructive sleep apnoea (OSA) (32). Parameters of lung function may reveal a restrictive pattern in morbidly obese patients including reduced VC and FEV<sub>1</sub> which may be amplified in patients with OHS (33).

### Pathophysiology of chronic hypoventilation

Although the reduction of the minute volume is the common characteristic of all chronic hypoventilation disorders, the underlying pathomechanisms differ substantially between the entities and can be complex in individual cases (exemplary shown for OHS in Figure 1).

Respiratory mechanics importantly contribute to chronic hypoventilation in many conditions. Inspiratory muscle strength diminishes during the course of NMD with diaphragmatic involvement. Scoliosis and thoracic hyperkyphosis—idiopathic or secondary to NMD—may impair the diaphragm capacity and contribute to thoracopulmonary restriction.



**Figure 1** Possible mechanisms by which obesity can lead to chronic daytime hypercapnia. CO<sub>2</sub>, carbon dioxide; ERV, expiratory reserve volume; FRC, functional residual capacity; OSA, obstructive sleep apnea; PaCO<sub>2</sub>, arterial carbon dioxide partial pressure; PaO<sub>2</sub>, arterial oxygen partial pressure; Q, perfusion; V, ventilation; VD, dead space volume; VT, tidal volume.

Obesity adds additional mass load to the respiratory system and reduces lung volume, especially when severe and predominantly centrally distributed (34). It increases the resistance of the upper and lower airways and reduces the compliance of the respiratory system. Sharp *et al.* showed in the 1960s that the compliance is reduced by 60% in OHS patients as compared to non-obese patients and by 20% as compared to normocapnic obese patients (35). The small airways tend to collapse at low tidal volumes leading to trapping of the air and increasing intrinsic end-expiratory pressure (PEEPi) (36). All these factors elevate the work of breathing in OHS patients, both in upright and supine position (37). On the other hand, obesity reduces the expiratory reserve volume, leading to ventilation perfusion mismatch and abnormalities of the gas exchange (38).

Similar effects on PEEPi limit the VC in COPD patients with severe hyperinflation. The flattening of the diaphragm impairs its mechanical properties and increases the work of breathing (39).

In addition to alterations of the thoraco-pulmonary mechanics, the ventilatory control system contributes substantially to chronic hypercapnic failure and sleep related hypoventilation. While respiration is primarily driven by the carbon dioxide level in healthy subjects, the response

to hypercapnia is usually altered in chronic hypercapnia. Radwan *et al.* compared patients with overlap of COPD and OSA with patients with OSA alone. Plasma bicarbonate concentration was significantly elevated in overlap patients, indicating chronic or long term nocturnal hypoventilation. Moreover, the hypercapnic ventilatory response was reduced in overlap patients, while it was normal in awake OSA patients (40).

Hypoxic and hypercapnic ventilatory response is also blunted in OHS patients as compared to normocapnic OSA patients (41). There is no evidence of impaired chemoresponsiveness in first degree relatives of OHS patients making an inherited condition improbable (42). However, the reduced chemoresponsiveness discriminates OHS patients from normocapnic obese individuals and OSA patients.

An impairment of the hypercapnic ventilatory response also contributes to the pathophysiology of NMD (15). This hypothesis is supported by findings of Nickol *et al.* in patients with hypercapnic respiratory failure due to restrictive thoracic diseases (NMD or chest wall disorders). Nocturnal NIV effectively controlled daytime PaCO<sub>2</sub>, although neither muscle strength, nor lung function or respiratory compliance significantly increased. Therefore, the authors



concluded that the normalization of the chemosensitivity is the principal mechanism improving gas exchange under NIV (43).

The impairment of the central ventilatory drive may be the exclusive pathophysiological factor in rare cases, such as CCHS. They present with diminished minute ventilation both, during wakefulness and sleep which is most pronounced in non-rapid-eye-movement (NREM) sleep (44).

*Leptin* is a protein specifically produced by adipose tissue. *Leptin* crosses the blood-brain barrier and interacts with specific receptors in various areas of the brain and—among other effects—stimulates ventilation (45). Its contribution to the pathophysiology of OHS has intensively been discussed in recent years. The serum *leptin* concentration is elevated, associated with increased ventilation in obese individuals. This is thought to compensate for the increased CO<sub>2</sub> production by excess body-mass (33). Shimura *et al.* compared circulating levels of *leptin* in OSA patients with and without hypercapnia. Serum *leptin* correlated with the BMI and was the only predictor for hypercapnia (46). However, *leptin* failed to adequately stimulate ventilation in hypercapnic individuals, which has been interpreted as a central *leptin* resistance contributing to the pathophysiology of OHS (11).

Obstructions of the upper airways additionally stress the ventilatory system and may impede CO<sub>2</sub> elimination especially during sleep. Obstructive apnoeas and hypopnoeas are associated with transient episodes of acute hypercapnia. While eucapnic OSA patients hyperventilate between obstructive episodes and therefore eliminate the accumulated CO<sub>2</sub> (47), the duration of the interval and increase of the minute ventilation may not allow for normalization of CO<sub>2</sub> in patients with sleep related hypoventilation (48). Computer models suggest, that CO<sub>2</sub> accumulates over the long term, when apnoea episodes become more than 3 times longer than the hyperventilation period between them (15). Obstructions of the upper airways may also be involved in patients with neuro-muscular diseases. The muscle of the upper airways may directly be involved if bulbar nerves and depending muscles are affected. The function of the upper airway muscles can be impaired in myopathic disorders or under pharmaceutical influences (long-term use of corticosteroids). Fat deposition and fluid retention may narrow the diameter of the upper airways. Peripheral edema and fluid overload frequently occur in patients with right heart failure in COPD or OHS. The fluid may shift from the lower limbs to the upper body

components during recumbency. Redolfi *et al.* showed in non-obese men that the severity of OSA strongly correlates with the reduction of leg fluid volume and concomitant increase in neck circumference (49). In addition to the increased load to the upper airways, they may collapse in central breathing disturbances (50). The capacity of the muscles may be insufficient to compensate for the additional load and the increased resistance in patients with NMD or thoraco-skeletal disorders.

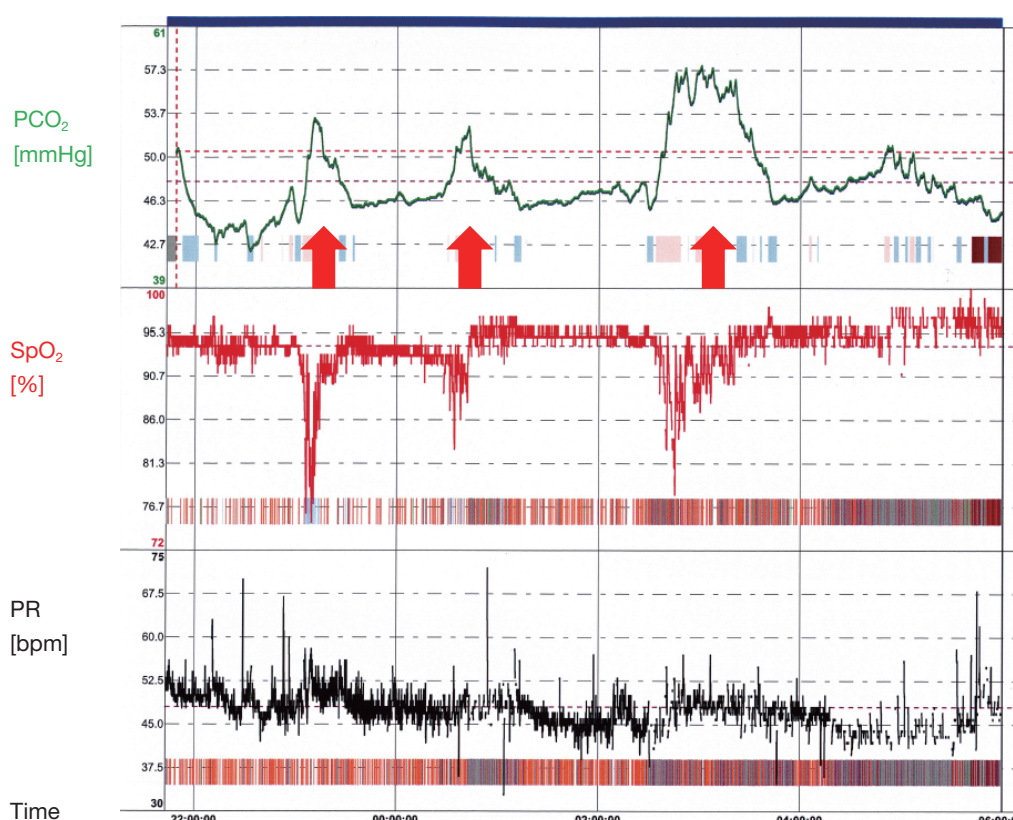
As mentioned before, pharmaceutical therapy can also negatively impact ventilation. Steroid myopathy is an adverse effect of high dose, long-term use of systemic corticosteroids. Although corticosteroid-induced muscle atrophy affects predominantly type II b muscle fibers (51), additional effects on accessory respiratory muscles have to be discussed. Moreover, the long-term systemic treatment with glucocorticosteroids is a risk factor for the development and worsening of osteoporosis. The prevalence of osteoporosis in COPD varies between 9-69% and exceeds prevalence in healthy subjects (52). However, the causal relationship between corticosteroids and osteoporosis in COPD has not undoubtedly been demonstrated. Vertebral fractures due to osteoporotic sinterings and consecutive reductions of the weight diminish the efficiency of respiratory muscles. Recently, Watanabe *et al.* found an association between osteoporosis on the one hand and deterioration of pulmonary function on the other in Japanese male patients with COPD (53).

Opioids are often prescribed for chronic pain or palliation of dyspnoea in patients with severe, symptomatic lung disorders. They influence ventilation by blunting the hypercapnic ventilatory response, reducing breathing frequency, inducing the collapse of the upper airways and diminishing the activity of peripheral muscles (54). In addition to short term apnoeas and hypopnoeas, sustained hypoxia during sleep may delay arousals and increase the arousal threshold in NMD, COPD and OHS (55).

### Influence of sleep on ventilation

Hypercapnia manifests during sleep prior to wakefulness as a consequence of physiological and pathophysiological changes of ventilation. The minute ventilation decreases from wakefulness to NREM sleep and further to rapid-eye-movement (REM) sleep by about 15% in healthy subjects (56).

The reduction of the minute ventilation during sleep is predominantly due to a lower tidal volume, which is not fully compensated by an increase of breathing frequency. The



**Figure 2** Nocturnal transcutaneous CO<sub>2</sub> monitoring shows three sustained episodes of elevated PCO<sub>2</sub> levels (red arrows) and corresponding decreases in SpO<sub>2</sub>. Polysomnography (not shown in this figure) revealed rapid eye movement (REM) sleep during these episodes. PCO<sub>2</sub>, carbon dioxide partial pressure; SpO<sub>2</sub>, oxygen saturation; PR, pulse rate.

underlying pathophysiological mechanisms are complex: the tone of the thoracic muscles is reduced during sleep, reaching its lowest level during REM. The muscle relaxation also increases the upper airway resistance (50) and thus predisposes to upper airway obstruction. As discussed above, obstructive breathing disturbances account for further CO<sub>2</sub> loading in obese patients and patients with NMD.

The muscle atonia during REM sleep affects primarily the accessory breathing muscles, whereas diaphragm contraction is saved. However, lung hyperinflation in COPD reduces the efficiency of the diaphragm, leading to a reduction of the tidal volume and the minute ventilation (9,57). It may also be reduced in diseases, in which accessory breathing muscles contribute substantially to ventilation.

In addition, hypoxic and hypercapnic ventilatory responses are also blunted during REM sleep, leading to insufficient reactions to changes of the blood gases. Respiratory derailments during REM as well as NREM

sleep trigger arousals, resulting in sleep fragmentation and diminished sleep efficacy. Thus, taking all these aspects together, sleep related hypoventilation manifests during REM sleep at first (*Figure 2*). PSG analyses in NMD showed a significant reduction of the REM proportion which might be regarded as protective mechanism to respiratory problems during REM sleep (58).

In clinical practice, it is not uncommon, that patients present with both, different entities of sleep related hypoventilation and other breathing disturbances during sleep. Ninety percent of OHS patients exhibit OSA (11). Nocturnal hypercapnia is more prevalent in COPD patients if they suffer from comorbid OSA (59). Their coexistence is referred to as the overlap syndrome and may be associated with pulmonary hypertension and right heart failure (60). Breathing disturbances in patients with Duchenne muscular dystrophy may begin with OSA (61), followed by sleep related hypoventilation when diaphragmatic weakness

becomes critical and end with chronic hypoventilation. Several investigators have focused on breathing disturbances under chronic opioid use in recent years. Rose *et al.* showed chronic hypercapnic failure in patients with chronic pain and long term opioid therapy. In addition to hypoventilation, up to 50% of the patients presented with severe sleep apnoea, predominantly of central origin (62). CCHS is characterized by disturbed central chemical respiratory drive. However, central apnoeas and hypopnoeas have been described in PSG-studies of affected patients so that CCHS may present as predominant central sleep apnoea in individual cases (63).

### Treatment of chronic hypoventilation

It is a general principle in medicine to treat any causative factors if possible. In terms of chronic hypoventilation this includes the cessation or reduction of drugs affecting breathing regulation, neural transmission or muscular function. Opioids, benzodiazepine and other psychotropic drugs have to be reviewed critically. The muscles should be unloaded or their efficiency improved. Therefore, weight reduction, stabilization of vertebral fractures, orthopedic and surgical methods in kyphoscoliosis should be discussed. Electrical stimulation of the diaphragm can improve ventilation in individual cases (64,65).

However, causal treatment options will not suffice for the huge majority of patients with chronic or sleep related hypoventilation so that symptomatic therapy with mechanical ventilation becomes necessary. During the poliomyelitis pandemics in the 20<sup>th</sup> century, negative pressure ventilators—popularly named iron lungs, or steel cocoons—saved the life of thousands of patients afflicted with respiratory muscle paralysis (66). Negative pressure ventilation has completely been replaced by devices, which non-invasively apply ventilatory support via a nasal or oral-nasal mask to the patient. NIV generates the tidal volume by a fixed difference between inspiratory and expiratory pressure (pressure support, pressure controlled ventilation) or a predefined volume (volume support, volume controlled ventilation).

Optimal treatment of patients with chronic hypoventilation with NIV crucially depends on the underlying pathophysiological mechanisms. Algorithms primarily focusing on pressure support are most frequently used. They allow to separately adapting inspiratory and expiratory pressure and back-up frequency. The expiratory positive airway pressure (EPAP) is titrated according to the level of

upper airway obstruction (12). It dilates the upper airways and therefore reduces the work of breathing to overcome upper airway resistance. In addition, the expiratory pressure stabilizes the small airways and may overcome the intrinsic peak, it increases air flow to atelectatic parts of the lungs and improves ventilation perfusion mismatch. The EPAP should be titrated under polygraphic or polysomnographic supervision, aiming at optimizing oxygen saturation, reducing apnoeas, hypopnoeas and flattening of the flow curve and respiration-related arousals. The improvement of sleep quality and the reduction of sleep-wake transitions avoid central breathing disturbances and stabilize ventilation (avoid periodic breathing) (12-14).

Tidal volume and breathing frequency influence the CO<sub>2</sub> elimination and therefore counterbalance chronic or intermittent hypoventilation. Therefore, the inspiratory positive airway pressure (IPAP) is not the primary target of titration but the difference between EPAP and IPAP ( $\Delta$  IPAP—EPAP) which defines the tidal volume. When EPAP has been titrated, the  $\Delta$  IPAP—EPAP (the pressure support) can be adapted aiming at normalization of PaCO<sub>2</sub> or PtcCO<sub>2</sub>.

The back-up frequency eliminates any central apnoeas and overcomes periods of bradypnoea. If the back-up frequency is set above the spontaneous breathing rate, the patient is fully controlled ventilated. In terms of patients' compliance and synchronization, it is often reasonable to set the back-up frequency slightly below the spontaneous breathing frequency of the patient (67).

Taking these aspects together, the ventilator settings should be individually selected based on the underlying pathophysiological components (12):

- Airway obstruction can be addressed by increasing intraluminal expiratory pressure [CPAP, EPAP, bilevel in the spontaneous mode (BiPAP-S)];
- Reduced ventilatory drive (breathing frequency) can be counterbalanced by the application of mandatory breaths;
- Fixed or variable pressure support and mandatory breaths assure the necessary minute ventilation (12).

### Controlled versus assisted NIV

Volume-controlled or pressure-controlled ventilation previously represented two extremes of NIV. While the former applied a fixed, predefined tidal volume, irrespective of the required inspiratory pressure level, the latter delivered a fixed pressure support, independent of the really



applied volume. It has been hypothesized that optimal ventilation depends on maximal unloading of the respiratory muscles. This would allow restoring energy reserves required for spontaneous respiration. Controlled ventilation strategies unload respiratory muscles most intensively, as the ventilator takes over the complete work of breathing (68). However, synchronicity of the patients' breathing rhythm with the ventilator may impact efficacy and tolerance. In addition, studies in animals and invasively ventilated intensive care patients have shown negative impact of controlled ventilation on muscle structure and function. In contrast, assisted ventilation allows the patient to spontaneously trigger pressure or volume support, which may improve synchronicity and may damage muscle fibers in less extent (69-71). In clinical practice, non-invasive pressure support ventilation has become the most favorite therapeutical approach. However, modern NIV devices work in hybrid modes: they apply a defined pressure support, a minimal preset tidal volume and minimal rate of mandatory breaths, combining the advantages and disadvantages of the algorithms.

Specific clinical situations may require variable ventilatory support, e.g., according to changing of the body position, sleep stage or patient's respiratory drive. The most recent algorithms of NIV devices allow for automatically varying the expiratory pressure to overcome upper airway obstruction and adjusting the pressure support in order to ensure a predetermined target: pressure support ventilation with target volume (distributed as: average volume assured pressure support, AVAPS) (72-74). Nevertheless, the physician has to supervise the adaptation process and evaluate the effect on carbon dioxide, sleep parameters and upper airway obstruction. The automatic algorithms with a volume assurance may allow for individualized therapy but have not shown to be superior in general.

### NIV in specific situations

NIV is indicated in neuromuscular and restrictive disorders and OHS if patients present with daytime hypercapnia  $>45$  mmHg. In addition, ventilator support may be introduced in neuromuscular or thoraco-skeletal disorders in symptomatic nocturnal hypoventilation even without daytime hypercapnia (15). Keeping in mind that symptoms of nocturnal hypoventilation are highly variable and non-specific, a careful patient examination is necessary at each follow-up consultation. Additional factors emphasizing NIV include comorbidities with upper airway obstruction or impaired peak cough flow. NIV is indicated

in COPD patients if they present with chronic daytime hypercapnia  $\geq 50$  mmHg or a  $\text{PaCO}_2$  of 46-50 mmHg associated with  $\geq 2$  hospitalizations within the last 12 months due to hypercapnic respiratory failure (75).

Volume-targeted algorithms may be favorable in NMD. These patients may suffer from impaired coughing causing mucoid bronchus obliteration so that pressure-targeted systems may not guarantee minimum minute ventilation (76). While patients with neuro-muscular or thoraco-skeletal diseases can often be treated sufficiently with low tidal volumes, high pressure support may be needed in patients with COPD. In both groups, the treatment target is normalization of carbon dioxide so that the term "high pressure ventilation" is misleading. Inspiratory pressure levels above 20 mbar are not primarily intended, but may be required to overcome hypercapnia. Dreher *et al.* compared this approach of high-intensity pressure (NPPV: mean inspiratory pressure  $28.6 \pm 1.9$  mbar) with low-intensity pressure (NPPV: mean inspiratory pressures of  $14.6 \pm 0.8$  mbar) in patients with severe stable hypercapnic COPD. The high-intensity regime was associated with better compliance (mean difference of 3.6 h/d) and was superior in terms of controlling nocturnal hypoventilation (77). Murphy *et al.* demonstrated that the pressure component is the most important factor in controlling hypoventilation, while changes in backup frequency (high versus low) did not relevantly impact  $\text{PaCO}_2$  (78).

Continuous positive airway pressure (CPAP) may be still the first therapeutical approach to patients with OHS. Due to the stabilization of upper airway obstruction, improvement of ventilation perfusion mismatch and lung mechanics, it might sufficiently normalize ventilation and oxygenation in a subgroup of OHS patients. Piper *et al.* randomized OHS patients to receive CPAP or bilevel ventilator support. They excluded patients with persisting severe nocturnal hypoxemia or sleep hypoventilation. Daytime carbon dioxide levels decreased similarly in both groups (79). However a substantial group of OHS patients did not sufficiently respond to CPAP, so that pressure support ventilation is the treatment of choice for the huge majority of patients with chronic hypoventilation. The heterogeneous responses to CPAP and pressure support ventilation might reflect the various contributions of the pathophysiological components (9). Similar to COPD, pressure support ventilation with volume assurance have not proven to generally be superior in OHS patients. Murphy *et al.* failed to demonstrate differences between automated volume assured pressure ventilation (AVAPS) and fixed-level pressure

support in super obese patients (BMI  $50 \pm 7$  kg/m<sup>2</sup>) (72). However, hybrid modes and automatic algorithms may facilitate initiation and allow for individualized treatment (15).

NIV has proven to improve quality of sleep, nocturnal oxygen saturation, diurnal and nocturnal PaCO<sub>2</sub> and quality of life in a broad spectrum of various chronic hypoventilation disorders (67). Moreover, NIV may improve patients' survival (80). Non-invasive positive pressure ventilation added to standard treatment has proven to significantly improve survival in patients with COPD with PaCO<sub>2</sub>  $\geq 7$  kPa (51.9 mmHg) (80). Bourke *et al.* demonstrated improvement of the survival by approximately 7 months in ALS with orthopnea or daytime hypercapnia (81). The median age of death in Duchenne's muscle dystrophy has ameliorated from 18-20 years to nearly 30 years under establishment of NIV (82). In addition, Nowbar *et al.* showed an increased mortality in patients with OHS. Twenty-three percent of OHS patients died within 18 months following hospital discharge as compared to 9% of patients with normocapnic obesity. Only 13% of the OHS patients were treated with NPPV. In addition, untreated OHS patients are more likely to require invasive ventilation and have prolonged hospital stays (83).

Most recently, a multicenter randomized controlled trial on the efficacy of NIV in severe stable COPD was performed. The investigators aimed at reducing hypercapnia by 20% or below a level of 48.1 mmHg. NIV was compared to standard treatment without ventilation. NIV significantly reduced 1 year mortality from 33% to 12% as compared to the control group. Therefore, from our point of view, NIV should be recommended to all COPD patients with chronic hypoventilation (PaCO<sub>2</sub>  $\geq 50$  mmHg) (80,84).

## Conclusions

The huge variety of underlying diseases and pathophysiological factors urge the clinician to individualize treatment. NIV has become the therapy of choice of chronic hypoventilation but has to be adapted according to the specific needs of the patients.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Böing S, Randerath WJ. Chronic hypoventilation syndromes and sleep-related hypoventilation. *J Thorac Dis* 2015;7(8):1273-1285. doi: 10.3978/j.issn.2072-1439.2015.06.10