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Therapeutic options for the treatment of Cheyne-Stokes respiration

Winfried J. Randerath

Institute of Pneumology at the University Witten/Herdecke, Clinic for Pneumology and Allergology, Centre of Sleep Medicine and Respiratory Care, Bethanien Hospital, Solingen, Germany

Summary

The awareness of Cheyne-Stokes respiration (CSR) and of the co-existence of the obstructive sleep apnoea syndrome and central breathing disturbances has rapidly grown in recent years. CSR is defined by a waxing and waning pattern of the breathing amplitude. Sleep related breathing disorders in patients with heart failure are associated with impaired clinical outcome and survival. While continuous positive airway pressure treatment (CPAP) is widely used to treat CSR, it has failed to improve overall survival of heart failure patients. Nevertheless, it has been shown that CPAP reduces mortality if breathing disturbances were sufficiently eliminated. Therefore, optimal suppression of CSR is critical. While CPAP reduces CSR by 50% on average, adaptive servo-ventilation (ASV) normalises CSR in most patients. ASV devices apply different levels of pressure support: during periods of hypoventilation the inspiratory pressure is increased while it is reduced to the lowest possible level during hyperventilation. The devices deliver an expiratory pressure to overcome upper airways obstruction. Pressure support is defined by the difference between expiratory and inspiratory pressure. Thus, while pressure support is fixed in bilevel devices, it varies under ASV. However, the hypothesis that ASV might improve survival in CSR patients has to be proved in prospective studies in CPAP non-responders. There is a lack of evidence on the use of bilevel devices in CSR. However, ASV has proven both to effectively treat CSR and to be superior to CPAP in respiratory and sleep parameters in short term and medium term studies. Nevertheless, data on the long term use and the influence on cardiac parameters are necessary.

Key words: Cheyne-Stokes respiration; central sleep apnea; obstructive sleep apnea; complex sleep apnea; adaptive servo-ventilation; anticyclic modulated ventilation

Introduction

Sleep-related breathing disorders have been a source of major interest to the medical community since the late 1970s. Sullivan described the effective treatment of the obstructive sleep apnoea syndrome (OSAS) with continuous positive airway pressure (CPAP) [1]. However, OSAS is not the only sleep related breathing disorder. It has to be distinguished from central breathing disturbances, such as the hypoventilation syndromes, central sleep apnoea (CSA), and Cheyne-Stokes respiration (CSR) [2]. Cheyne-Stokes respiration results from instability of the respiratory control system [3]. During sleep, respiration depends mainly on the level of $PaCO_2$. If the $PaCO_2$ falls below the apnoea threshold, central apnoea occurs. CSR is characterised by cyclical recurrence of central apnoeas. The respiratory control system is destabilised by chronic hyperventilation with $PaCO_2$ close to the apnoea threshold. In heart failure the $PaCO_2$ is lower in patients with CSR as compared to those without CSR due to stimulation of pulmonary irritant receptors by pulmonary congestion and increased chemosensitivity. In patients with heart failure and CSR the apnoea threshold but not the $PaCO_2$ increases during sleep onset. CSR occurs to the greatest extent during NREM sleep in which respiration is mainly under metabolic control. In NREM sleep arousals are associated with abrupt hyperventilation and decrease of $PaCO_2$. The smaller the difference between the apnoea threshold and $PaCO_2$, the more likely central apnoeas are to occur. Arousals thereby destabilise the ventilatory control system in CSR. The pathophysiology of CSR is not completely understood. Additional factors such as instability of the upper airways, lung function, gas exchange and metabolic alkalosis may contribute to the instability of the ventilation [3]. Clinically the typical figure of waxing and waning of the flow amplitude in Cheyne-Stokes respiration results (fig. 1).

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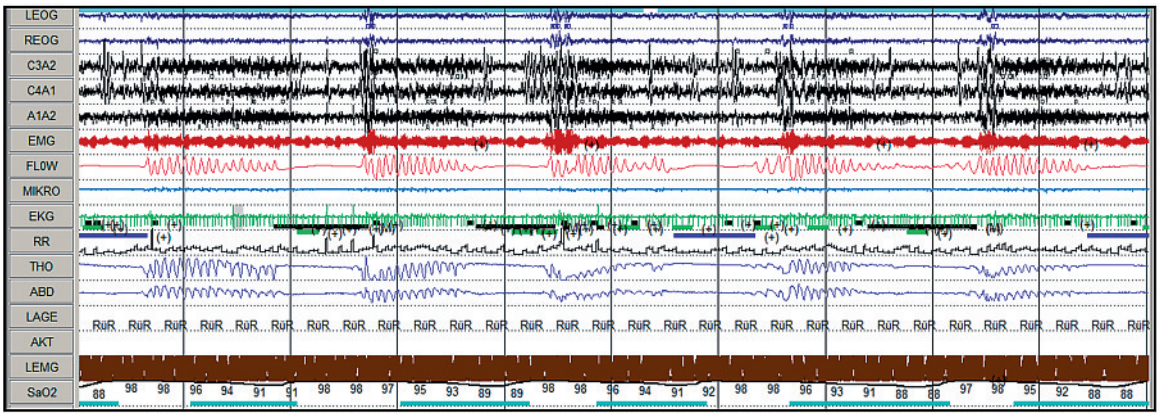

Figure 1

Cheyne-Stokes respiration.
The figure presents a 5-min-period of a polysomnography with Cheyne-Stokes respiration. The flow and effort (THO = thorax, BD = abdomen) channel show the typical pattern of waxing and waning amplitude. The arousals (increases of amplitude in the EEG channels (C3A2, C4A1) are found at the peak flow amplitude in most events. The respiratory disturbances are accompanied by decreases of oxygen saturation (SaO_2).

Up to 50% of patients with heart failure suffer from sleep-related breathing disorders with CSR being the most frequent finding [4]. Unfortunately, CSR patients often do not present with the typical signs as in OSAS. Fatigue and reduced exercise capacity are often leading symptoms of heart failure and are not brought together with sleep related breathing disorders. It has been shown that CSR is marker of poor prognosis in heart failure patients [5, 6]. On the other hand, the CanPAP post-hoc analysis found out that patients with suppression of CSR under CPAP experienced better transplant-free survival as compared to those with unsuppressed CSR [7]. However, these results have to be confirmed in prospective trials. This leads to several conclusions for clinical practice:

- Heart failure patients should systematically be screened for sleep related breathing disorders, even if they do not suffer of daytime sleepiness or witnessed apnoeas.
- Cardiac treatment with drugs or interventions should be optimised.
- If breathing disorders still remain positive, pressure treatment should be applied as soon as possible despite the limitations mentioned above.

Continuous positive airway pressure in Cheyne-Stokes respiration

What does the application of positive pressure mean to the heart? In healthy persons CPAP slightly – but not relevantly – reduces the venous return, preload, and consequently cardiac output. However, this effect is missing in heart failure patients. CPAP reduces the left ventricular transmural pressure and therefore the afterload. Moreover, oxygen demand is improved by reducing breathing effort and the oxygen supply is improved by optimising the relationship between ventilation and perfusion in the lungs. Thus, CPAP has been demonstrated to improve the left ventricular ejection fraction [8–19]. Additionally, Sin et al. retrospectively found an improvement in the survival in those heart failure patients with CSR who were treated with CPAP [20]. However, Bradley et al. failed to prove these findings in the prospective randomised CPAP controlled CanPAP trial. Although several cardiac and polysomnographic parameters improved, the overall survival did not differ significantly between the CPAP and placebo group [21]. This was partly due to the fact that mortality in the CPAP group was higher in the first months of the trial which was balanced over three years. Several reasons for the increased mortality in the early treatment period have been discussed: central sleep apnoea non-responsive to CPAP, reduced cardiac output in preload-dependent heart failure, and pharmacological aspects such as volume depletion by diuretics [22]. Arzt et al. most recently performed a *post-hoc* analysis of the CanPAP data and showed relevant differences between subgroups: those patients whose breathing disturbances were sufficiently reduced had a survival benefit as compared to those without improvement of respiratory disturbances. This leads to the conclusion that optimal suppression of respiratory disturbances is essential in CSR patients [7].

Although CPAP is widely used in the treatment of CSR it has proved to reduce the numbers of apnoeas and hypopnoeas per hour (the AH index) only by 50% both in short and long term studies [21, 23]. Several other treatment options are under discussion: there are controversial results on the supplementation of oxygen during the night or the treatment with the carbonic anhydrase inhibitor acetazolamide [24–29]. Therefore, both approaches cannot reasonably be recommended with OSAS or CSA/CSR.

Bilevel

In contrast to CPAP, bilevel positive pressure devices do not apply one single pressure throughout the whole breathing cycle but a higher level during inspiration and a lower one during expiration. Bilevel devices can be used for support of the spontaneous breathing of the patient (bilevel S) or can apply mandatory (timed) breaths in case of breathing pauses (bilevel ST or T). The two predefined pressure levels do not vary during the night. Köhnlein et al. studied the efficacy of bilevel ST as compared to CPAP in patients with chronic congestive cardiac failure and CSA and found equal improvements with both options [30]. However, there is limited evidence for the treatment with bilevel in CSR. Moreover, the fixed pressure support does not allow for counterbalancing the waxing and waning of the flow amplitude.

Adaptive servo-ventilation

Adaptive servo-ventilation (also called auto servo-ventilation or anticyclic modulated ventilation) (ASV) has been developed to more effectively improve CSA/CSR. It aims at reducing the number of central breathing disturbances more effectively than CPAP by providing an expiratory positive airway-pressure to eliminate obstructive apnoea and hypopnoea, and modulating the inspiratory positive airway-pressure to overcome central apnoea and hypopnoea when required. ASV should reduce hypoxia and hypocapnia and normalise the instability of respiration in CSR.

The algorithms analyse the patients' breathing pattern and modulate anticyclically the pressure support. While bilevel devices apply one predefined difference between inspiration and expira-

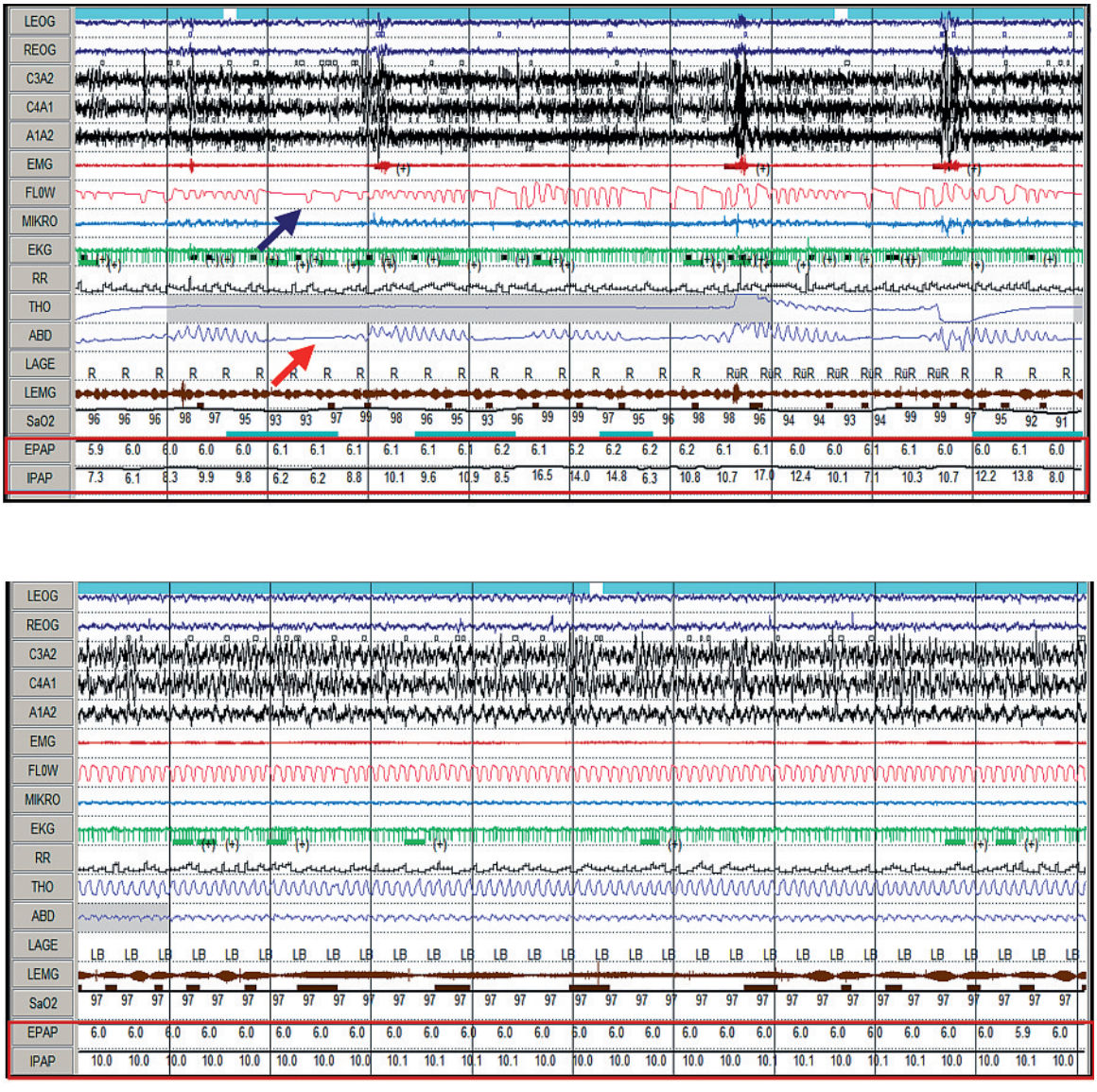

Figure 2

Treatment of Cheyne-Stokes respiration with adaptive servo-ventilation
Figure 2a gives an example of 5 min during the first treatment with ASV. The red arrow points at a central apnoea which indicates the underlying central breathing disorder. The device applies a mandatory breath (blue arrow). The expiratory pressure is fixed at 6 mbar, the inspiratory pressure varies between 6 and 16.5 mbar to add pressure support. Figure 2b presents the normalisation of breathing under ongoing treatment with ASV. The pressure levels are stable.

tion and therefore deliver one fixed tidal volume, it changes continuously under adaptive servo-ventilation. The inspiratory pressure increases during hypopnoea and falls during hyperventilation. ASV devices use three pressure levels:

– The **expiratory pressure** serves to sustain upper airway patency.
– The **minimal inspiratory pressure** describes the lower limit during inspiration under which the pressure cannot fall.
– The actual inspiratory pressure cannot increase over the **maximum inspiratory pressure**. The difference between the actual inspiratory pressure and the expiratory pressure defines the tidal volume. It therefore is essential to overcome CSR.

These levels have to be determined by the physician. The maximum inspiratory pressure depends on the suspected cardiovascular side-effects. For testing it is advisable to apply the maximum inspiratory pressure during wakefulness and control the arterial blood pressure. In patients with severely reduced left ventricular function monitoring of the blood pressure during the night may be advisable under any positive airway pressure treatment. The expiratory pressure is set based on the suppression of obstructive hypopnoea, apnoea, snoring and flattening. In clinical practice a CPAP titration trial can be recommended before indicating treatment with ASV. This is helpful for two reasons: If CPAP sufficiently suppresses the respiratory disturbances, the patient can stay on this option. If CSR is incompletely resolved, the CPAP level which eliminates obstructive disturbances serves as the expiratory pressure under adaptive servo-ventilation.

Three devices are available (AutoSet® CS by ResMed, BiPAP AutoSV® by Respironics, SOMNOVent CR® by Weinmann). They differ in terms of the target parameter, back-up frequency and the pressure levels which can be applied. One device (AutoSet CS) always delivers pressure support of at least 3 mbar. This might be helpful in those patients with pure CSR. The others can apply the same pressure during inspiration and expiration (that means CPAP) in periods of stable breathing which is an interesting feature in the patients with co-existing CSR and OSAS. One algorithm (SOMNOVent CR®) combines both automatic CPAP and adaptive servo-ventilation. Thus, the device varies not only the pressure support but also the expiratory pressure to overcome upper airways obstructions on its own.

Although there are no studies comparing the different algorithms and although long-term prospective studies are missing at this point, data on the efficacy of adaptive servo-ventilation from short-term and small-sized trials are available. Teschler et al. have demonstrated significant improvements in the central respiratory disturbances during sleep under ASV therapy. They compared several treatment options: oxygen, CPAP, bilevel, and ASV, for one night each [23]. As in the CanPAP trial, they found a reduction of the AHI by half under CPAP while ASV improved the respiratory disturbances by >80%. The effect of CPAP was similar to oxygen which confirmed previous findings [23, 29]. Pepperell et al. focussed on quality of life in a randomised prospective study comparing therapeutic and subtherapeutic ASV in 30 patients with chronic heart failure and mild CSR. They found a significant improvement of excessive daytime sleepiness, the level of brain natriuretic peptide and metadrenaline excretion under therapeutic ASV [31]. In addition, Philippe et al. demonstrated that heart failure patients preferred ASV as compared to CPAP [32].

Teschler's results have been confirmed in a group of patients suffering of chronic heart failure with an impaired left ventricular function and pure CSA/CSR using a different ASV device [33]. Using the same device, we most recently demonstrated a sufficient improvement of all types of respiratory disturbances in patients with co-existing OSAS and CSR [34]. Morgenthaler et al. retrospectively analysed the efficacy of different therapeutic approaches in their patients with CSA but did not only include patients with pure CSA [35]. They found that ASV was superior to oxygen, CPAP and bilevel therapy. The same group compared ASV and non-invasive positive pressure ventilation (NPPV) in patients with CSA/CSR, complex sleep apnoea and mixed sleep apnoea. Both options sufficiently improved respiratory disturbances while ASV was more effective than NPPV [35]. Very promising preliminary data were found on the combination treatment of automatic positive airway pressure and adaptive servo-ventilation [36].

Conclusions

Cheyne-Stokes respiration promises to become one of the major challenges in sleep medicine due to demographic changes, the increasing number of cardiovascular comorbidities and the higher level of awareness, especially in patients with arterial hypertension and chronic heart failure. Preliminary data awaiting further confirmation show that CPAP improves survival in patients in whom the respiratory disturbances can sufficiently be suppressed. However, CPAP reduces CSR only by 50% in mean. Adaptive servo-ventilation more effectively improves CSR in patients with or without heart failure and might become the new standard of treatment. However, data on the long-term efficacy, the influence on cardiovascular parameters and the survival are missing.

Correspondence:
Prof. Dr. Winfried J. Randerath, FCCP
Clinic for Pneumology and Allergology
Center of Sleep Medicine and Respiratory Care,
Bethanien Hospital
Aufderhöherstraße 169-175
42699 Solingen, Germany
E-Mail: randerath@klinik-bethanien.de

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