About 50% of patients with chronic heart failure suffer from sleep disordered breathing (1). The prevalence of obstructive sleep apnea (OSA) and central sleep apnea with Cheyne-Stokes respiration (CSR) differs in terms of chronic heart failure severity, with increasing prevalence of CSR with more advanced heart failure (1–4). Whereas OSA seems to be a risk factor for the manifestation and deterioration of heart failure per se (5,6), CSR is likely to mirror cardiac function and may further deteriorate cardiac function and prognosis (3,4,7,8).

In the past 25 years, research efforts were made to understand pathophysiology, cardiovascular consequences, and therapeutic options of both types of sleep disordered breathing. Although the impact of OSA on cardiovascular diseases (9) and the indications for treatment by continuous positive airway pressure ventilation is widely accepted and recommended by current guidelines (10), the pathophysiology of CSR is not fully understood, and guidelines yet do not address therapeutic consequences.

Whereas OSA is caused by repetitive occlusion of the upper airway (11), central sleep apnea with CSR is caused by intermittent cessation of inspiratory drive due to a fall in partial pressure of CO₂ (pCO₂) below the (altered) apnea threshold (12,13). However, CSR with the typical waxing and waning ventilation pattern followed by central apnea represents only 1 expression of respiratory instability seen in advanced heart failure. Other manifestations are increased $V_E/V_{CO_2}$ slope and/or oscillatory breathing pattern during cardiopulmonary exercise (14–16) or at rest (17).

All these conditions can be characterized by inappropriate (hyper)ventilation with low arterial pCO₂, increased sensitivity of central and peripheral receptors to CO₂, and an altered apnea threshold or a narrowed Δend-tidal pCO₂ between spontaneous breathing and apnea threshold, respectively (13,16,18,19).

In this issue of the Journal, Giannoni et al. (20) present a small proof-of-concept study supporting the following theory: Dynamic CO₂ administration resulted in markedly improved oscillations in end-tidal CO₂ and ventilation. By administration of CO₂ during the peak of ventilation, periodic breathing (oscillation of ventilation) was reduced during voluntary periodic breathing in healthy subjects as well as in heart failure patients with spontaneous periodic breathing. In parallel, mean oxygen saturation was increased and magnitude of desaturation reduced. In previous studies, CO₂ administration was performed with a constant (static) flow, not annoying the phase of ventilation (waxing, hyperventilation, waning, hypopnea, or apnea). However, even with this continuous flow of CO₂, oscillatory ventilation was reduced, supporting the concept of pCO₂ dependency of periodic breathing. In contrast to the present study, previous studies using static CO₂ administration were associated with an increase in end-tidal CO₂ ventilation, and sympathetic activity. The latter was not directly and reliably measured in the present study, but no effects of dynamic CO₂ administration on heart rate, blood pressure, or ventricular ectopy were documented. Further studies are warranted to investigate the effects of dynamic CO₂ administration on ventilation, sleep, and sympathetic activity in heart failure patients with nocturnal CSR.

Whereas the first studies using adaptive servoventilation to treat nocturnal CSR in heart failure patients revealed good response regarding compliance (21), sleep parameters (22), and cardiac function (23–26), its impact on long-term outcome is still unknown and part of ongoing clinical outcome trials. In addition, the algorithms of some available adaptive servoventilation devices are designed to decrease patient’s spontaneous minute ventilation and increase pCO₂, which may result in improved respiratory stability.

Giannoni et al. (20) suggest dynamic CO₂ administration as an alternative to positive airway pressure ventilation therapy applied via nasal or full-face masks. However, in this case, CO₂ administration needs to be performed using nasal cannula and ventilation needs to be reliably measured without using a pneumotachograph—a method not tested so far.

We congratulate Giannoni et al. (20) for their proof-of-concept study pointing out the crucial role of CO₂ in the pathophysiology of respiratory instability seen in heart failure patients. We encourage them to set up a pilot study, investigating not only the ventilatory effects of dynamic CO₂ administration, but also the effects on sympathetic activation, sleep, and heart failure parameters.
REFERENCES


Key Words: carbon dioxide • central sleep apnea • Cheyne-Stokes • periodic breathing • treatment.