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EDITORIAL

Adaptive servo-ventilation for central sleep apnea: What are the lessons learned?

Heart failure remains a major health challenge despite advancements in medical therapy.[1] Patients with heart failure with reduced ejection fraction (HFrEF) often develop a form of central sleep apnoea (CSA) characterized by recurrent central apnoeas and hypopnoeas interposed by a prolonged crescendo -decrescendo pattern of ventilation, known as Cheyne-Stokes respiration (CSR).[2] Although CSR with CSA (CSR-CSA) is common among patients with HFrEF, it is now clear that obstructive sleep apnoea (OSA) is even more common in such patients.[3] In patients with HFrEF, OSA often presents with a prolonged crescendo-decrescendo pattern of breathing resembling CSR-CSA but with obstructive, rather than central respiratory events.[3] The common underlying cause of this sculpted CSR pattern is lower than normal cardiac output, with prolonged time for changes in PaO_2 and $PaCO_2$ in the lungs during respiratory events to reach the peripheral and central chemoreceptors to stimulate breathing. One of the reasons why both CSA and OSA are more common in patients with HFrEF than in the general population is fluid retention. When upright, patients with HFrEF accumulate fluid in their legs, so that when lying down to sleep at night, gravitation causes some of this fluid to shift to the upper body. If fluid accumulates mainly in the lungs, CSA may emerge due to stimulation of pulmonary vagal irritant receptors provoking hyperventilation that drives $PaCO_2$ below the apnoea threshold. If fluid collects mainly in the neck it may increase peripharyngeal tissue pressure causing the pharynx to narrow, thus predisposing to obstructive events.[4]

Unfortunately, current standard full polysomnography (PSG) may fall short in distinguishing central from obstructive events for at least three reasons. A). While oesophageal pressure detects effort, standard PSG belts detect thoracic and abdominal movements. In apnoeas where upper airway obstruction is present, but thoraco-abdominal motion is subtle, and not obviously out-of-phase, it may be difficult to distinguish such obstructive events from central events in patients with HFrEF. In addition, nasal pressure is not helpful in distinguishing obstructive from central apnoeas because, in either case, there is no signal. B) In most patients with HFrEF, and either CSA or OSA, hypopnoeas rather than apnoeas predominate. Differentiating obstructive from central hypopnoeas is more difficult than classifying apnoeas because thoraco-abdominal motion is present but may not be obviously out-of-phase. Similarly, nasal pressure tracings may not clearly demonstrate flattening as a sign of airflow limitation in the presence of upper airway obstruction. C) Patients with HFrEF may convert from mainly obstructive to mainly central events over a single night due to an overnight decrease in cardiac output, increased lung to chemoreceptor circulation time, and a fall in $PaCO_2$ below the apnoea threshold.[5]

While continuous positive airway pressure (CPAP) is able to abolish OSA, the treatment of CSR-CSA is more challenging. The first large multicenter randomized trial (CANPAP), that evaluated the impact of CPAP in patients with HFeEF and CSR-CSA on a hard endpoint (cardiovascular morbidity and mortality) was neutral.[6] One of the reasons may have been that CPAP only reduced the apnoea-hypopnoea index (AHI) by about 55%. However, a subsequent post hoc analysis suggested a protective effect of CPAP among the sub-group of patients in whom the AHI fell below 15 events/hour while on CPAP.[7]

Adaptive servo-ventilation (ASV) was designed to abolish CSR-CSA by providing variable levels of inspiratory pressure support to counteract decreases or cessation of tidal volume during central hypopnoeas and apnoeas.[8] Essentially, ASV stabilizes breathing by providing pressure support that is a mirror image of the patient's respiratory drive. Adaptive servo-ventilation can be triggered by decrease in minute ventilation, in the case of the original ResMed devices (ASVmv), or peak flow (ASVpf), in the case of the Philips devices. A consistent literature showing the beneficial effects of ASV in patients with HFrEF and CSR-CSA on physiological variables[8,9] justified the next step.

The SERVE-HF trial[10] was the largest multicenter randomized trial designed to test the hypothesis that treating CSR-CSA by ASVmv in patients with HFrEF would reduce the rate

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of the primary composite endpoint: the first event of death from any cause, life-saving cardiovascular intervention, or unplanned hospital admission due to worsening of HF. After a median follow-up of 31 months, the primary outcome was neutral. However, ASVmv induced an increase in all-cause and cardiovascular mortality. In addition, the safety of ongoing studies testing the treatment of CSR-CSA with other forms of ASV, such as ASVpf, was questioned.[11-13]

In this issue of Pulmonology, a statement[14] by the Portuguese Society of Pulmonology and the Portuguese Sleep Association sheds light on this topic by trying to separate the wheat from the chaff. The Portuguese Task Force states that the prescription of ASV plunged after the SERVE-HF publication. SERVE-HF had multiple study design problems that have been described by the Portuguese Task Force and debated in several editorials.[11-13] The Portuguese Task Force[14] raises an important flag by pointing out that ASVmv used in SERVE-HF has a minimum pressure support of 3 cm H_2O on a background minimum expiratory pressure of 5 cm H_2O, even when the patient Is hyperventilating, that may accentuate hyperventilation and be harmful to the patients by amplifying alkalosis related to use of diuretics. If potassium levels are also low, this could facilitate development of malignant cardiac arrhythmias. Another critical point was that the study was over interpreted. SERVE-HF was powered to answer a specific question, and the main result was neutral. SERVE-HF had a large number of secondary endpoints. Regulatory agencies, industry and medical societies, however, have taken a conservative approach, and stated that ASV increases cardiovascular mortality, based on this secondary endpoint.[10] One argument in favor of this approach is that increased cardiovascular mortality is not a trivial secondary endpoint. However, statistics must be interpreted with caution. For instance, the rate of antiarrhythmic drug use at study entry was significantly higher in the ASV group than in the control group (P=0.005) and the excess mortality in the ASVmv treated group was likely due to sudden cardiac death.[10,15] Despite the low p value, this difference must be interpreted with caution as it was not driven by a hypothesis.

In contrast to SERVE-HF, that only recruited patients that were classified as having CSA, the ADVENT-HF trial[16] is a large multicenter randomized trial that was designed to test the impact of the treatment of both OSA and CSA in patients with HFrEF. Unfortunately, after the results of the SERVE-HF trial were published in 2015, regulatory agencies in Germany and France prohibited the ADVENT-HF trial to continue to recruit patients with CSA in their countries. This was a regrettable decision for the following reasons. First, it overruled the data and safety monitoring committee that regularly reviewed outcomes data and clearly stated that there was no discernable safety signal. Second, it caused a significant decrease in recruitment of patients with CSA into the trial, reducing overall enrolment. Third, while the fear of harming patients is legitimate for clinical practice, clinical trials are designed to answer difficult clinical questions. Moreover, the device used in ADVENT-HF differed from that used in SERVE-HF as it is peak flow-triggered with lower default inspiratory and expiratory pressure settings. While the field waits for the final results of ADVENT-HF, it is important to keep clinical practice on track. Adaptive servo-ventilation is still recommended in other settings, for instance among patients with CSA who have heart failure with preserved ejection fraction, or those with idiopathic CSA or CPAP-emergent CSA. In this context, the Portuguese society has taken a step forward and proposed algorithms on how to manage patients with CSA.

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