Transvenous phrenic nerve stimulation for central sleep apnoea in heart failure: chicken or egg?

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This editorial refers to ‘Transvenous phrenic nerve stimulation for the treatment of central sleep apnoea in heart failure’[†], by P. Ponikowski *et al.*, on page 889

The prevalence of central sleep apnoea (CSA) is 100-fold greater in chronic heart failure (HF) due to impaired systolic function than in the general population.¹ It afflicts principally elderly male patients who have atrial fibrillation, implanted pacemakers, low arterial P_{CO_2} when awake, or high diuretic requirements.¹ Its presence identifies HF patients with higher night- and day-time sympathetic nervous system activity,² at increased risk of malignant ventricular arrhythmias,³ whose survival is foreshortened.⁴

The primary abnormality in CSA is neither the upper airway collapse of obstructive sleep apnoea (OSA), which can be treated quite effectively with continuous positive airway pressure (CPAP), nor a paucity of ventilation, but rather the compromise of mechanisms that normally stabilize breathing due to the confluence of pulmonary congestion, circulatory delay, altered cerebrovascular blood flow, and enhanced central sensitivity to CO_2 , all predisposing to hyperventilation.⁴ Although the reality is more complex, to simplify, in HF the cyclical oscillations between hyperpnoea and apnoea, known commonly as Cheyne–Stokes respiration, are initiated by the hyperpnoea, which can be stimulated by spontaneous arousal from sleep, or by pulmonary congestion. During sleep, the latter is exacerbated both by fluid shifts from the periphery to the cardiopulmonary reservoir,⁵ and by pre-existing pulmonary–cardiac–chemoreceptor circulatory delay. Thus, when increases in pulmonary capillary and venous pressures stimulate pulmonary irritant receptors, triggering a bout of hyperpnoea, the already low Pa_{CO_2} is driven below the patient’s apnoeic threshold. Central drive to the muscles of breathing pauses until the rising Pa_{CO_2} and falling Pa_{O_2} are sensed, eventually, by chemoreceptors, which then initiate a new cycle of hyperpnoea,

hypocapnia, and apnoea. CSA is more likely to develop if increased chemoreceptor reflex gain destabilizes ventilatory control. Once established, the duration of hyperpnoea within each cycle relates inversely to cardiac output.⁴

CSA concerns the cardiologist because of its pathological consequences for the failing heart: hypoxaemia during apnoea, and clustered intense sympathetic nerve firing and ventricular arrhythmias during hyperpnoea.^{4,6} These disturbances may be particularly ominous for patients with ischaemic cardiomyopathy.⁷

Since this pattern of periodic breathing is the hallmark of CSA, treatments have focused on its direct or indirect stabilization. However, therapy remains problematic, and there is currently equipoise as to whether CSA, independently of HF, should be treated at all^{2,8} and, if so, whether its target should be the hyperpnoea, the apnoea, the arousals from sleep, the pre-disposing circulatory pathophysiology, or all of the above. Foreshortening apnoea by increasing inspired CO_2 restores rapidly normal breathing,⁹ but this knowledge has yet to be translated into practical therapy. Supplemental O_2 , which does not address specifically the underlying pathophysiology,⁹ attenuated CSA in one clinical trial and also improved functional class and quality of life.¹⁰ Theophylline, which targets chemosensitivity, has only been evaluated in very brief studies. The concept of suppressing CSA has attracted the interest of several device manufacturers. However, biventricular resynchronization pacing provides only short-term relief,³ and attempts to attenuate CSA by atrial pacing have proven unsuccessful.¹¹

In small randomized trials of 3 months duration, nocturnal CPAP suppressed CSA, reduced overnight noradrenaline excretion and daytime plasma noradrenaline, lessened mitral regurgitant fraction, and improved left ventricular ejection fraction (LVEF).⁴ However, in a randomized outcome trial, involving 258 participants with CSA and a mean LVEF of 24.5% treated with CPAP on average for 216 min/night over 2 years, the primary composite endpoint

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Figure 1 Two strategies to treat central sleep apnoea in heart failure. Adaptive servo-ventilation (left) targets both hyperpnoea and apnoea (two arrows). Positive airway pressure (+) maintains airway patency, attenuates reflex pulmonary afferent nerve initiation of hyperpnoea by lung congestion, and, by reducing both left ventricular afterload and end-diastolic wall stress, augments stroke volume to shorten the hyperpnoea cycle length and diminish hypocapnoea-induced apnoea. If apnoea is detected, back-up inspiratory support is provided. Transvenous phrenic nerve stimulation (right), as applied by Ponikowski *et al.*,¹⁵ stabilizes breathing specifically by preventing apnoea (single arrow). Intrathoracic pressure remains subatmospheric (–).

of transplant-free survival was identical in treated and untreated patients.¹² This neutral result was attributed to the failure of CPAP to suppress severe CSA in a large proportion.¹³ There are now more effective non-invasive methods of stabilizing breathing. Adaptive servo-ventilation (ASV), which synchronizes delivered pressure to the breathing phase, is significantly superior to CPAP in reducing the number of central apnoeas and hypopnoeas occurring during sleep.¹⁴ Two large multicentre clinical trials (NCT00733343 and NCT01128816) testing the hypothesis that in HF patients with sleep apnoea ASV will improve outcome are currently enrolling participants.

A team of Polish and American investigators from six centres, led by Dr Ponikowski, have now taken a different tack (*Figure 1*). Their proof-of-concept study evaluated the impact on CSA during sleep of a single night of unilateral transvenous phrenic nerve stimulation.¹⁵ If CSA is, in general, a condition of hyperventilation,⁴ a strategy of stimulating ventilation further might at first seem counterintuitive. However, the objective of these authors was to stimulate the diaphragm to prevent apnoea, thereby pre-empting hyperpnoea. As hypothesized, stimulation (mean 251 min) virtually abolished central apnoeic events as compared with a single control night. Occurrences of O₂ desaturation and arousal were also reduced significantly. The procedure was described as well tolerated.

The concept of supporting ventilation by chronic phrenic nerve stimulation is not new, but in the present context its acute transvenous application to treat the CSA of heart failure is indeed novel. Clearly, it is also challenging. An unknown number of subjects were screened to identify 31 participants, all men, eligible for study; however, according to the investigators' unpublished site-specific data, in the three centres with the highest enrolments, phrenic

nerve stimulation was achieved successfully in only 41, 71, and 25% of consented subjects (16 overall). Thus, before deploying this technique in other centres it would be important to learn whether further operator experience will lead to greater success in achieving phrenic capture. Nonetheless, the authors are to be congratulated for completing this insightful study.

If future protocols are envisaged, it is hoped that several aspects of that of Ponikowski *et al.* will be remedied. Many HF-CSA patients are pacemaker dependent, but this population was excluded. Polysomnographic data were interpreted blindly, but the sequence of study nights (control, stimulation) was not randomized, out of concern that a stable stimulation site could not be sustained. Although an equal number of subjects received right- and left-sided phrenic nerve stimulation, which apparently achieved similar success, this distribution also was not random, but determined by the investigator, whose choice in four participants may have been constrained by pre-existing defibrillator implants.

This being only a single-night study, it is unknown whether the acute impact of phrenic nerve pacing on CSA can be sustained long term without engendering complications or patient discomfort. Concerning the algorithm applied, we are informed that an observer intervened to 'titrate' stimulation 'with the goal of eliminating centrally mediated apnoeic events without arousing the patient from sleep'. Although judicious titration facilitates successful suppression of CSA by all positive pressure devices, an effective automated sensing–intervention feature would be required if this technology is to advance to permanent implantation mode, where presumably it could also address the less common but even more concerning phenomenon of Cheyne–Stokes breathing during wakefulness.

Will suppressing breathing cycles in this way improve the underlying HF state, or counter the pathophysiology of its progression? Not studied or reported were several effects or potential effects of phrenic nerve stimulation that would provide assurance that this intervention is not simply cosmetic, but indeed represents an important therapeutic innovation. Confirmation that stimulated suppression of CSA reduces sympathetic activation and hyperpnoea-induced ventricular arrhythmias in parallel would be encouraging. Arousals from sleep, which can trigger hyperpnoea, were reduced significantly, but the impact of abolishing apnoea by phrenic nerve stimulation on the destabilizing triad of high cardiac filling pressures, low cardiac output, and enhanced chemosensitivity was not examined, and transcutaneous PCO₂, a variable critical to the understanding of CSA pathophysiology, was not recorded. It is conceivable that eliminating hyperpnoea will also abolish the transient boost its 'bellows effect' provides to cardiac output.⁴ Since nocturnal fluid shifts also exacerbate OSA, probably through reduction of upper airway cross-sectional area by jugular venous distension,⁵ the four-fold rise in the median value for the obstructive apnoeic index ($P = 0.056$) raises the possibility that phrenic pacing might exacerbate lung congestion. This concern warrants exclusion before long-term studies are initiated.

The authors rightly conclude that this novel intervention, with immediate effect on CSA, merits further investigation. However, if the goal of therapy is to improve the outlook of such patients, will a strategy focused solely on stabilizing breathing by targeting apnoea be sufficient? Alternately, will stabilizing breathing solely by targeting hyperpnoea or by improving cardiac performance be sufficient? Current experience with biventricular pacing would suggest not. In contrast, suppression by CPAP of CSA, which often requires days to weeks, has been attributed to a combination of factors, including prevention of hyperpnoea by decreasing lung water, attenuating apnoea by subtly raising PaCO₂, and augmenting stroke volume by diminishing left ventricular end-diastolic wall stress, left ventricular end-systolic transmural pressure (afterload), and mitral regurgitation.⁴ Now that ASV (which, like phrenic nerve stimulation, times pressure load to the breathing cycle so as to interrupt apnoea) has been shown capable of suppressing CSA in CPAP-resistant patients, and increasing LVEF with long-term use,¹⁴ this Editorialist's bias favours a multifaceted, rather than a single-target, therapeutic approach if the current equipoise concerning the merits of treating CSA specifically in HF is to be resolved by clinical trials.

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