pii: jc-18-00039 http://dx.doi.org/10.5664/jcsm.7146

JCSM
Journal of Clinical Sleep Medicine

PRO/CON DEBATE

PRO: Persistent Central Sleep Apnea/Hunter-Cheyne-Stokes Breathing, Despite Best Guideline-Based Therapy of Heart Failure With Reduced Ejection Fraction, Is a Compensatory Mechanism and Should Not Be Suppressed

Matthew T. Naughton, MBBS, MD, FRACP

Department of Respiratory Medicine, Alfred Hospital and Monash University, Melbourne, Victoria, Australia

INTRODUCTION

The question being debated is whether *persistent* central sleep apnea with Hunter-Cheyne-Stokes breathing (CSA-HCSB), despite *best* guideline-based therapy of heart failure with reduced ejection fraction (HFrEF) is a compensatory mechanism *and* should not be suppressed. I have been asked to provide the "pro" argument; however, there are a number of components to this question that need to be defined and require elaboration.

WHAT IS CSA-HCSB?

CSA-HCSB is best described as an oscillatory pattern of respiration associated with similarly cyclic changes in blood pressure, heart rate, and sleep[1] (**Figure 1**). It occurs during stage N1 and N2 sleep when ventilation is under "chemical control" (ie, the partial pressure of carbon dioxide) and rarely in stage N3 or R sleep. Occasionally, CSA-HCSB occurs during wakefulness and/or at the commencement of exercise. It is associated with advanced heart failure (HF) of any cause and can be predicted by abnormal markers of cardiac (low left ventricular ejection fraction [LVEF], high pulmonary capillary wedge pressure [PCWP], high brain natriuretic peptide), autonomic (high norepinephrine activity) and pulmonary function (low $PaCO_2$, increased ventilatory response to CO_2, small lung volumes, impaired diffusing capacity, increased work of breathing). The severity of HF is paralleled by the CSA-HCSB apnea-hypopnea index (AHI). Treatment of the underlying HF results in attenuation of CSA-HCSB.

The prevailing hyperventilation (increased minute volume of ventilation despite central apneas) and secondary low $PaCO_2$ that characterize CSA-HCSB is thought to be caused by at least four potential mechanisms. The first mechanism is pulmonary venous congestion stimulating afferent pulmonary vagal J fibers. However, this mechanism is unlikely to be absolute because patients with denervated lungs resulting from lung transplantation can still exhibit CSA-HCSB.[2] The second mechanism is increased sympathetic activity[3] caused by the HF and/or underlying CSA-HCSB. We have compared the contribution of both HF and CSA-HCSB severity to the development of sympathetic overactivity and found the former to be the main contributor.[4] The third mechanism relates to loss of endothelial nitric oxide activity in the carotid bodies associated with hyperventilation, which has been documented in rabbit models of HF.[5] A final mechanism relates to increased physiological pulmonary dead space in patients with HF (identified as having a low diffusing capacity) which contributes to wasted ventilation.[6] Hypoxemia does not appear to play a role in the development of CSA-HCSB.

The classic periodic breathing seen in HF begins with an arousal or sleep state change and a rise in ventilation followed by a 1- to 2-mmHg drop in transcutaneous PCO_2 ($PtcCO_2$). Thereafter, a crescendo-decrescendo ventilatory pattern develops lasting several minutes, with an arousal at the peak of ventilation, often snoring (and/or oral breathing) during the hyperventilation period followed by a central apnea. The ventilatory length (VL) and apnea length (AL) are about 30 seconds each. The central apnea in reality is a prolonged expiration (as indicated by elevated end-tidal PCO_2) that may abruptly stop midway, indicating upper airway closure. Intrathoracic pressure at this point may rise around 5 to 10 mmHg from this timepoint until ventilation resumes (see **Figure 2**). Often there are two to three obstructed efforts to breath before the upper airway reopens. The VL and AL combine to make the cycle length (CL).

Symptomatically, patients with CSA-HCSB complain of insomnia and fatigue, occasionally orthopnea and sometimes paroxysmal nocturnal dyspnea. Commonly they are males older than 60 years with atrial fibrillation and recurring episodes of acute pulmonary edema.

It is important to consider the differential diagnosis when one sees CSA-HCSB on a polysomnogram. Classic CSA-HCSB has a long CL (45 to 75 seconds) and is indicative of HFrEF, whereas a short CL (< 45 seconds) can occur with atrial fibrillation with HFrEF, narcotics, pulmonary hypertension, renal failure, premature infancy, high altitude, and stroke. In approximately 1% of patients initiating continuous positive airway pressure for obstructive sleep apnea, CSA can develop (related to high pressures, readjustment of chemical drive),

which resolves in approximately 1 to 3 months. This scenario is referred to as treatment-emergent apnea.

GUIDELINES

What is meant by "persistent…despite best guideline-based therapy"? Best guideline-based therapy is the holy grail for all chronic disease management. The European and North American cardiac societies are in agreement with this assessment.[7] Whether most patients are treated according to the guidelines 100% of the time is a topic of debate!

TYPES OF HEART FAILURE

What is "heart failure with reduced ejection fraction" and is this the only classification? The classification of HF is complex.[3] Symptoms are categorized according to the New York Heart Association class (1 to 4), the prognostic severity by the American Cardiac and American Heart Associations (A to D), and a further categorization is based on LVEF (preserved, midrange, or reduced). Forrester had a simple classification to guide individualized therapy and prognosis based upon filling pressure (PCWP) and forward cardiac output.[7] Moreover, various pathologies can contribute to HF and interfere with pump, valve, or rhythm (eg, amyloid, sarcoid, toxic drugs, infections, and radiation), which may require biopsy confirmation. Interestingly, 30% of elderly patients (older than 75 years) with HFrEF in the United States[8] have amyloid cardiomyopathy (based on postmortem examinations) for which diagnosis and treatment are difficult and prognosis is poor. Thus, when CSA-HCSB is seen, all types and causes of HF (pump, valve, rate, and rhythm) must be considered and the patient treated accordingly. Moreover, CSA-HCSB should be viewed as a sign of significant HF. Just as an elevated body temperature reflects sepsis, CSA-HCSB reflects HF. Some patients, particularly the elderly, will have intractable HF.

COMPENSATORY MECHANISM

What evidence is there that "CSA-HCSB…is a compensatory mechanism for heart failure"? I would like to preface that CSA-HCSB indicates the presence of HF and that treatment of the underlying HF should be initiated. Treatment options might include pharmacological (at least six drug classes), physical, and dietary manipulation, correction of underlying associated medical conditions (eg, anemia or renal failure, both common in HF) and devices and surgery (valve repair, replacement, or transplantation).

However, if CSA-HCSB continues despite the "optimal therapy," I would argue that CSA-HCSB is, in itself, a compensatory mechanism to offset the adverse effects of HF.

The compensatory aspects of CSA-HCSB offset the known adverse effects of HF, namely edematous lungs with restricted lung volumes, exhaustion due to an increased work of breathing, bronchial wheeze due to the edematous small airways, the desire to sit upright, and difficulty sleeping.

A cardinal feature of CSA-HCSB is periodic rest interspersed with periodic hyperventilation (increased work of breathing). The dyspnea of HF is akin to walking up a steep hill, and CSA-HCSB is akin to stopping periodically to "catch your breath." Although work of breathing (pressure volume product) is increased, efficiency of breathing (pressure time product) with CSA-HCSB is improved.[9]

Unobstructed hyperventilation, as seen with CSA-HCSB, can assist forward cardiac output. It is known that the pleural pressure swings that can develop in humans range from approximately −150 to +150 mmHg, and are only slightly reduced in patients with HF.[10] The swings in pleural pressure caused by coughing when the heart is asystolic have been shown to maintain cardiac output for several minutes.[11] Stroke volume has been shown to increase during the hyperventilation period compared with the apneic period.[12] Thus, the respiratory pump muscles can act as a secondary cardiac pump if and when needed and there is evidence that this occurs during CSA-HCSB.

Characteristically, patients with CSA-HCSB have respiratory alkalosis (low $PaCO_2$ and high pH). An alkalotic environment has been shown to protect the failing heart, exposed to hypoxia, from decompensation.[13] An acidotic pH is associated with reduced cardiac output. Thus, in the event of a further deterioration of HF (eg, pneumonia aspiratory or progression of HF) an alkalotic pH provides a buffer from an acidotic pH.

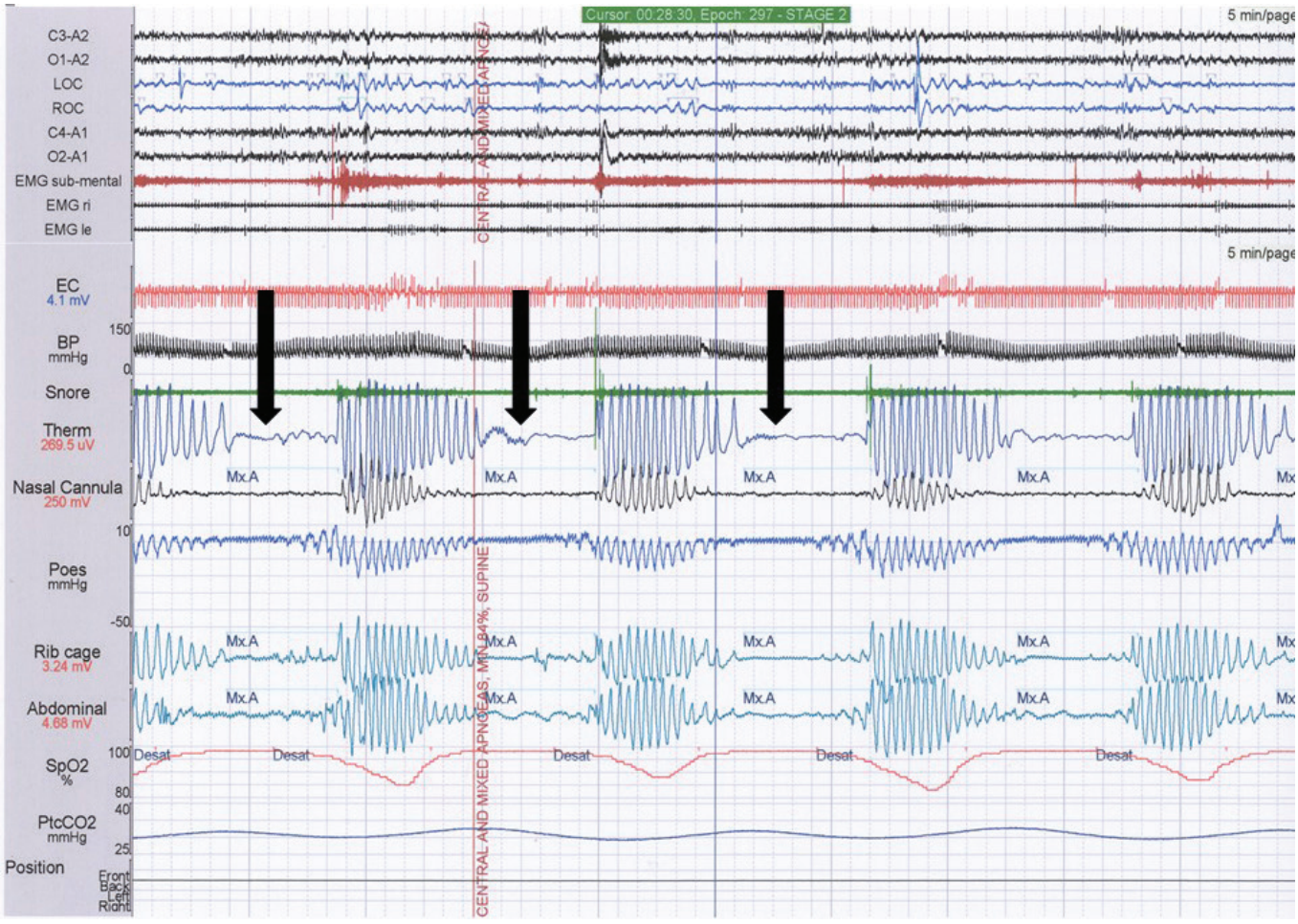
The period of hyperventilation is associated with an increase in end-expiratory lung volume of approximately 1 L.[14] This will increase oxygen stores (note approximately 50% of the body's oxygen is stored in the lungs) and assist in overcoming the restrictive ventilatory defect, especially when exacerbated when the patient with CSA-HCSB is supine or semirecumbent.

Following the period of hyperventilation, there is a prolonged apnea. Strictly speaking, this is a prolonged expiration with an open airway for about half the apnea duration (as measured by thermistor—see **Figure 1** and **Figure 2**—end-tidal PCO_2 or via nasendoscopy).[15] The upper airway may close about 50% to 75% through the apneic phase, at which time the exhalation continues against a closed upper airway and thereby creates a small amount of positive end-expiratory pressure. Sometimes the airway remains open throughout. If the airway closes, there is a small rise in positive end-expiratory pressure, about 5 to 10 mmHg. This is of similar magnitude to that seen with chronic obstructive pulmonary disease (intrinsic positive end-expiratory pressure) and may be helpful in preventing bronchial and alveolar collapse (**Figure 2**).

If CSA-HCSB is detrimental, one might expect to observe the severity of HF and CSA-HCSB to worsen across the night (or from night to night). We observed no significant differences in any marker of HF or CSA-HCSB severity comparing the first and last quarter of the night (AL, CL, VL, hypoxia, and sympathetic activity measured by heart rate variability) in 13 patients with a mean LVEF of 27%.[16]

Is HCSB associated with poor prognosis? Small studies were ambiguous and clouded by multiple causes of death. Our

Figure 1—Five-minute montage of stage N2 sleep with CSA-HCSB illustrating four apneas, with oscillating SpO_2, $PtcCO_2$, systemic blood pressure, and esophageal pressure.



Note thermistor (therm) trace with cardiac oscillation which stops abruptly in three of four apneas (see three vertical arrows). CSA-HCSB = central sleep apnea with Hunter-Cheyne-Stokes breathing.

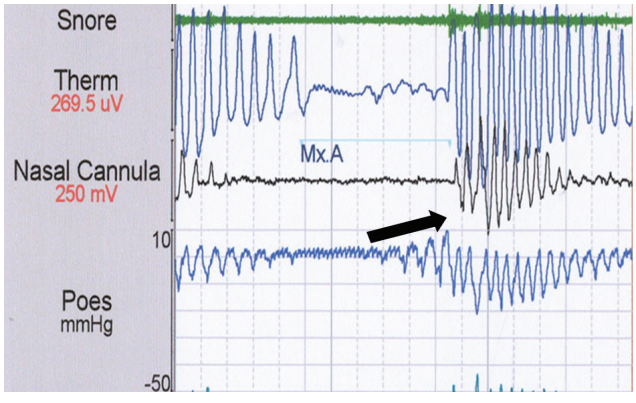
data were unable to confirm the answer to the question.[1] Three of the four recent longer term studies suggested increased mortality; however, all studies did not control for all factors and could well be explained by simply representing HF in patients with end-stage HF.[1]

SUPPRESSION OF CSA-HCSB

The final piece to be addressed is whether or not CSA-HCSB should be suppressed. This is the crux of the debate, which I will place in the context that the HF has been optimally diagnosed, etiology or etiologies and comorbidities identified, and "best guideline-based" treatment initiated for a sufficient period of time.

Thereafter, should CSA-HCSB be suppressed *by drugs that stimulate ventilation* (eg, acetazolamide or theophylline)? Theophylline prescribed for 5 days reduced group mean AHI from 47 to 18 events/h and decreased $PaCO_2$ (37 to 36 mmHg) while leading to increased cardiac arrhythmias[17] in 15 males with a mean LVEF 26%.

Figure 2—Closer look at first apnea from Figure 1.



Note that the first apnea from Figure 1 with respiratory efforts provide a positive end-expiratory pressure of about 10 mmHg as indicated by the arrow.

Similarly, acetazolamide (250 mg daily for 6 days) reduced mean AHI from 54 to 34 events/h while $PaCO_2$ fell from 37 to

34 mmHg in 12 males with a mean LVEF of 20%.[18] These pharmacological approaches were important contributions to our understanding; however, they have not achieved widespread acceptance partly because of the increase in periods of ventilation and reduction in apneic rest periods. These drugs reduce $PaCO_2$ and increase pH and are likely to disturb electrolytes or possibly induce laryngeal spasm during sleep.[19] These drugs are associated with cardiac arrhythmias. In my opinion, and based on the published literature, I do not routinely favor these drugs. I can, however, appreciate that if diuretic usage is required to treat the HF that a carbonic anhydrase inhibitor diuretic could be considered as an alternative to loop (furosemide), thiazide, or aldosterone inhibitor (eg, spironolactone). Note spironolactone, but not acetazolamide, is listed in the guidelines of HF management.[7]

Other methods by which ventilation is stimulated (inhaling carbon dioxide or using a device that increases dead space) will similarly increase minute ventilation, and replace the periods of central apneic rest with persistent and unrelenting hyperventilation. They are also associated with worse quality of sleep and no improvement in cardiac function.[20]

Should drugs that suppress ventilation be used? Benzodiazepines have been tried in an attempt to reduce arousability and/or the ventilatory response to CO_2 and thereby attenuate CSA-HCSB.[21] This report identified a fall in arousal index but no change in percent of time spent with CSA-HCSB, hypoxemic time, or total sleep time. In my opinion, benzodiazepines can be used for acute insomnia management while the underlying HF is being managed. However, they should not be prescribed for long-term use to treat the CSA-HCSB.

Oxygen therapy has also been used to alleviate dyspnea and thereby attenuate CSA-HCSB. Supplemental oxygen (2–4 liters per minute) for a single night decreased AHI from 49 to 29 events/h without reports of cardiac function.[22] However, two well-performed studies[23,24] have shown oxygen at super normal amounts further impairs cardiac function. Importantly, CSA-HCSB can occur without hypoxemia. Thus, the role for supplemental oxygen is unproven and not recommended in HF guidelines.[25]

Transvenous phrenic nerve stimulation has been proposed as another mode of therapy for CSA-HCSB.[26] This is based on the premise that stimulating a diaphragm to contract during periods of rest is accompanied by the expectation that cardiac function will improve. The physiological explanation for this relationship remains to be clarified. Recent industry-sponsored publications have stimulated single and bilateral diaphragms to reduce AHI (incompletely); however, with a risk of serious adverse side effects in 1 in 10 patients. No improvements in cardiac function were reported.

Continuous, fixed-level positive airway pressure (CPAP) has been known to alleviate HF and reduce intubation and in-hospital mortality in acute cardiogenic pulmonary edema[7] when coexistent with chronic obstructive sleep apnea. There are several mechanisms by which CPAP may help alleviate HF, including prevention of upper and lower airway collapse, increase lung volumes, assistance with respiratory pump muscle, and reduced preload and afterload of left ventricle.[27]

The downstream effects of CPAP in patients with CSA-HCSB from a single center were an approximate 35% fall in mean minute volume of ventilation, a rise in mean $PtcCO_2$ (around 35 to 41 mmHg), an approximate 35% rise in LVEF, and an approximate 40% fall in norepinephrine levels.[22] The beneficial effects of a single night's CPAP on CSA-HCSB were confirmed by Javaheri who described a fall in AHI to fewer than 15 events/h in approximately 45% of patients associated with an attenuation of cardiac arrhythmias.[28] Patients likely to show improvement are those with an elevated PCWP.[29]

However, an eight-center randomized controlled trial across North America and Europe of CPAP in 258 patients with CSA-HCSB failed to demonstrate a reduction in transplant-free survival at 24 months, although AHI, LVEF, catecholamine levels, and 6-minute walk distances improved.[30]

Of interest, however, was a *post hoc* analysis in those patients who underwent 3-month polysomnography testing that indicated that approximately two-thirds of patients experienced a reduction in AHI to fewer than 15 events/h and a transplant-free survival benefit.[31] Patients with persistent CSA-HCSB at 3 months despite CPAP and optimal medical therapy had a greater mortality.

With the aforementioned knowledge of CPAP, a new form of positive airway pressure called adaptive servoventilation (ASV) was developed to stimulate ventilation during the central apneas.[32] The aim was to maintain approximately 80% of the prevailing minute ventilation by providing background of CPAP (eg, 8 cmH_2O) plus periodic ventilatory support (eg, 3–8 cmH_2O). A reduction in minute ventilation was argued to result from fewer arousals and greater amounts of stage N3 and R sleep. During sleep, the cumulative positive airway pressure would range from 8 to 16 cmH_2O with ASV.

Two manufacturers have developed their own proprietary devices that were clinically assessed under two independent studies: one now complete[32] and the second ongoing at the time of this writing.[33] Common to both propriety products is that they provide a baseline of CPAP on which ventilator assistance is provided during the central apneas: in other words, a hybrid of CPAP and ventilatory assistance.

The SERVE-HF trial[32] included 1,325 patients from 91 centers with HFrEF on optimal therapy with an AHI > 15 events/h and most instances of sleep apnea due to CSA-HCSB randomized to medical therapy or medical therapy plus ASV. The study failed to show a significant difference in the primary composite outcome at the mean follow-up time of 31 months, namely all-cause mortality, lifesaving cardiovascular intervention, or unplanned admission for HF. There were important secondary outcomes that worsened with ASV, such as all-cause and cardiovascular mortality. Basic variables (heart rate, arousal frequency, and sleep quality) were not reported. There appeared to be a greater risk of sudden death with ASV, the cause of which can only be speculated. Possibilities include mismatching for antiarrhythmic usage at study entry (13.5% in control versus 19.2% in ASV group), aggravation of arrhythmias by ASV (greater ventilation, lower $PaCO_2$ and rise in pH with electrolyte change), or simply inadequate use of ASV (around 3.7 h/night). One factor that was indicative of better survival was the greater amount of CSA-HCSB at the time of randomization, strongly suggestive that CSA-HCSB was associated with greater survival.

The second ASV trial, the ADVENT-HF, is ongoing at the time of this writing.[33] It has important differences in comparison with the SERVE-HF trial,[32] namely enrolling patients who do not have excessive daytime sleepiness with AHI > 15 events/h of which more than 50% of events are central. In addition, the ASV device settings used in the SERVE-HF and ADVENT-HF differ in terms of lower end-expiratory pressures (4 versus 5 cmH_2O) and minimal pressure support (zero versus 3 cmH_2O).

SUMMARY

In summary, HF is a complex disease with multiple causes and associated conditions that are commonly associated with central and obstructive sleep-disordered breathing. Positive airway pressure has a role to play in both apnea types. Despite optimal guideline-directed therapies directed at HF and associated comorbidities, persistent underlying CSA-HCSB occurs. Evidence suggests that persistent CSA-HCSB is a marker of persistent HF. The unique characteristics of CSA-HCSB provide a natural compensatory mechanism to offset the adverse effects of HF, in some ways similar to that seen with CPAP. The adverse outcome of the SERVE-HF trial provides an outstanding opportunity to interrogate the data and solve mysteries. One important question is whether there was a difference in survival between those with controlled versus persistent CSA-HCSB at the 1- to 3-month mark? Data from the devices may be able to provide an answer.

CITATION

Naughton MT. Pro: persistent central sleep apnea/Hunter-Cheyne-Stokes breathing, despite best guideline-based therapy of heart failure with reduced ejection fraction, is a compensatory mechanism and should not be suppressed. *J Clin Sleep Med*. 2018;14(6):909–914.

REFERENCES

1. Naughton MT, Kee K. Sleep apnoea in heart failure: to treat or not to treat? *Respirology*. 2017;22(2):217–229.
2. Solin P, Snell GI, Williams TJ, Naughton MT. Central sleep apnoea in congestive heart failure despite vagal denervation after bilateral lung transplantation. *Eur Respir J*. 1998;12(2):495–498.
3. Heistad DD, Wheeler RC, Mark AL, Schmid PG, Abboud FM. Effects of adrenergic stimulation on ventilation in man. *J Clin Invest*. 1972;51(6):1469–1475.
4. Mansfield D, Kaye DM, Brunner La Rocca H, Solin P, Esler MD, Naughton MT. Raised sympathetic nerve activity in heart failure and central sleep apnea is due to heart failure severity. *Circulation*. 2003;107(10):1396–1400.
5. Sun SY, Wang W, Zucker IH, Schultz HD. Enhanced activity of carotid body chemoreceptors in rabbits with heart failure: role of nitric oxide. *J Appl Physiol*. 1999;86(4):1273–1282.
6. Kee K, Stuart-Andrews C, Ellis MJ, et al. Increased dead space ventilation mediates reduced exercise capacity in systolic heart failure. *Am J Respir Crit Care Med*. 2016;193(11):1292–1300.
7. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137–e161.
8. Mirzoyev SA, Edwards WD, Mohammed SF, et al. Cardiac amyloid deposition is common in elderly patients with heart failure and preserved ejection fraction [abstract]. *Circulation*. 2010;122:A1792.
9. Kee K, Sands S, Stuart-Andrews C, et al. Effect of apnea type on work of breathing and respiratory fatigability during sleep in humans with heart failure [abstract]. *Am J Respir Crit Care Med*. 2014;189:A3892.
10. Granton JT, Naughton MT, Benard DC, Liu PP, Goldstein RS, Bradley TD. CPAP improves inspiratory muscle strength in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med*. 1996;153(1):277–282.
11. Criley JM, Blaufuss AH, Kissel GL. Cough-induced cardiac compression. Self-administered from of cardiopulmonary resuscitation. *JAMA*. 1976;236(11):1246–1250.
12. Yumino D, Kasai T, Kimmerly D, Amirthalingam V, Floras JS, Bradley TD. Differing effects of obstructive and central sleep apneas on stroke volume in patients with heart failure. *Am J Respir Crit Care Med*. 2010;187(4):433–438.
13. Bing OH, Apstein CS, Brooks WW. Factors influencing tolerance of cardiac muscle to hypoxia. *Recent Adv Stud Cardiac Struct Metab*. 1975;10:343–354.
14. Brack T, Jubran A, Laghi F, Tobin MJ. Fluctuations in end-expiratory lung volume during Cheyne-Stokes respiration. *Am J Respir Crit Care Med*. 2005;171(12):1408–1413.
15. Badr MS, Toiber F, Skatrud JB, Dempsey J. Pharyngeal narrowing/occlusion during central sleep apnea. *J Appl Physiol*. 1995;78(5):1806–1815.
16. Szollosi I, Krum H, Kaye D, Naughton MT. Sleep apnea in heart failure increases heart rate variability and sympathetic dominance. *Sleep*. 2007;30(11):1509–1514.
17. Javaheri S, Parker TJ, Wexler L, Liming JD, Lindower P, Roselle GA. Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med*. 1996;335(8):562–567.
18. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. *Am J Respir Crit Care Med*. 2006;173(2):234–237.
19. Jounieaux V, Aubert G, Dury M, Delguste P, Rodenstein DO. Effects of nasal positive-pressure hyperventilation on the glottis in normal sleeping subjects. *J Appl Physiol*. 1995;79(1):186–193.
20. Szollosi I, O'Driscoll DM, Dayer MJ, Coats AJ, Morrell MJ, Simonds AK. Adaptive servo-ventilation and deadspace: effects on central sleep apnoea. *J Sleep Res*. 2006;15(2):199–205.
21. Biberdorf DJ, Steens R, Millar TW, Kryger MH. Benzodiazepines in congestive heart failure: effects of temazepam on arousability and Cheyne-Stokes respiration. *Sleep*. 1993;16(6):529–538.
22. Javaheri S, Ahmed M, Parker TJ, Brown CR. Effects of nasal O2 on sleep-related disordered breathing in ambulatory patients with stable heart failure. *Sleep*. 1999;22(8):1101–1106.
23. Haque WA, Boehmer J, Clemson BS, Leuenberger UA, Silber DH, Sinoway LI. Hemodynamic effects of supplemental oxygen administration in congestive heart failure. *J Am Coll Cardiol*. 1996;27(2):353–357.
24. Mak S, Azevedo ER, Liu PP, Newton GE. Effect of hyperoxia on left ventricular function and filling pressures in patients with and without congestive heart failure. *Chest*. 2001;120(2):467–473.
25. Clark AL, Johnson MJ, Squire I. Does home oxygen benefit people with chronic heart failure? *BMJ*. 2011;342:d234.
26. Costanzo MR, Ponikowski P, Javaheri S, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. *Lancet*. 2016;388(10048):974–982.
27. Kee K, Naughton MT. Heart failure and sleep-disordered breathing: mechanisms, consequences and treatment. *Curr Opin Pulm Med*. 2009;15(6):565–570.
28. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. *Circulation*. 2000;101(4):392–397.

29. De Hoyos A, Liu PP, Benard DC, Bradley TD. Haemodynamic effects of continuous positive airway pressure in humans with normal and impaired left ventricular function. *Clin Sci*. 1995;88(2):173–178.
30. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med*. 2005;353(19):2025–2033.
31. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation*. 2007;115(25):3173–3180.
32. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med*. 2015;373(12):1095–1105.
33. Bradley TD, Floras JS. Adaptive servo-ventilation and the treatment of central sleep apnea in heart failure. Let's not throw the baby out with the bathwater. *Am J Respir Crit Care Med*. 2016;193(4):357–359.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January 29, 2018
Submitted in final revised form January 29, 2018
Accepted for publication March 16, 2018
Address correspondence to: Matthew T. Naughton, MBBS, MD, FRACP, Department of Respiratory Medicine, Alfred Hospital and Monash University, 55 Commercial Rd, Melbourne, VIC 3004, Australia; Fax +61 3 9076 3601; Email: m.naughton@alfred.org.au

DISCLOSURE STATEMENT

The author reports no conflicts of interest.