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PRO/CON DEBATE

Rebuttal to Naughton

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We are surprised at the content of Dr. Naughton's pro manuscript in that approximately one-third of his argument consists of restating current knowledge concerning the description, pathogenesis, clinical characteristics, and types of heart failure (HF), along with a brief comment that "guideline-based therapy" is not uniformly applied. Based on Dr. Naughton's previous publications, we were fairly certain as to the points he would make in his pro manuscript, and our con article adequately addressed the hypotheses that he has heretofore expressed. Therefore, we respectfully refer the reader back to our con presentation[1] and will address herein only the novel arguments brought forward by Naughton in this issue of the *Journal of Clinical Sleep Medicine*.

"What is CSA-HCSB?"

Under this heading, Dr. Naughton reviews the mechanisms underlying central sleep apnea with Hunter-Cheyne-Stokes breathing (CSA-HCSB). We differ with him in certain aspects and have discussed such mechanisms in detail in a publication with Dr. Dempsey.[2] Here we note one point only: he states that "Hypoxemia does not appear to play a role in the development of CSA-HCSB." In this he seemingly contradicts his own previous work demonstrating the exact opposite.[3] The title of this work says it all: "Impaired Pulmonary Diffusing Capacity and Hypoxia in Heart Failure Correlates With Central Sleep Apnea Severity." In that study, the mean PaO_2 (± 1 standard deviation) was reduced at 79 (± 13) mmHg and he reports that "…an independent negative correlation in multivariate analyses was found between PaO_2, and not $PaCO_2$, and the AHI."

"A cardinal feature of CSA-HCSB is periodic rest interspersed with periodic hyperventilation"

We agree that CSA-HCSB itself is restful during the apneic phase, but apnea is only one component of CSA-HCSB. As we discussed in our paper,[1] the overall work of breathing increases in CSA-HCSB as a result of the hyperventilatory phase, and treatment with continuous positive airway pressure (CPAP) decreases the overall ventilation and thereby decreases work of breathing; this very result was reported by Naughton himself!

"Unobstructed hyperventilation, as seen with CSA-HCSB can assist forward cardiac output"

Naughton supports this hypothesis by positing that swings in pleural pressure due to hyperventilation are akin to the maintenance of some degree of cardiac output in conscious but asystolic patients by coughing. He believes that positive end-expiratory pressure is induced by occlusion of the upper airway during the course of central apneas that are characterized by a slow expiration; that this can produce an effect similar to that of a cough; and can therefore augment cardiac output. Although there are indeed substantial pressure swings during the hyperventilatory phase of HCSB, these swings are in both directions, as illustrated in the figures from our article.[1] These positive swings Naughton is referring to are due to increased elastic recoil of the lungs during exhalation and are created by the preceding large negative swings during inhalation. Were pleural pressures limited to only increases, we might consider his hypothesis; however, given that the pressure swings during hyperventilation occur in both positive and negative directions, and thereby are radically different from that produced by a cough, we do not believe this hypothesis to be valid. Further, regarding increases in stroke volume (SV) in association with CSA-HCSB, Naughton refers to a study[4] in which SV was measured during 5-second intervals, once during hyperventilation immediately preceding a central apnea and then during the last 5 seconds of a central apnea prior to the start of the successive hyperventilation. Naughton writes "Stroke volume has been shown to increase during the hyperventilation period compared with the apneic period. 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." We contend that exactly the opposite occurs. As the study[4] showed, SV actually increased during the central apnea relative to that during hyperventilation, as we have already extensively discussed.[1] This is because the negative swings in pleural pressure occurring during hyperventilation, as depicted in the figures in our article,[1] increase left ventricle afterload and result in an overall reduction in SV, relative to that during the period of central apnea, when pleural pressure is constant. We therefore discard the contention that hyperventilation, as seen with CSA-HCSB, can assist cardiac output.

"The period of hyperventilation is associated with an increase in end-expiratory lung volume… This will increase oxygen stores…"

In this we are in agreement with Naughton. However, in a number of patients following hyperventilation, expiratory muscle activation deflates the lung below functional residual capacity,[5] thereby decreasing oxygen stores. In the accompanying editorial to this publication,[6] we hypothesized that an extremely high loop gain may be the underlying mechanism, as loop gain has a wide range in patients with HF and CSA.[7]

"Following the period of hyperventilation, there is a prolonged apnea… The upper airway may close…at which time the exhalation continues against a closed upper airway thereby creating a small amount of 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."

In his paper, Naughton lauds the creation of positive end-expiratory pressure when the upper airway closes part way through a central apnea, yet later is not willing to concede that the external application of positive end-expiratory pressure (CPAP, bilevel positive airway pressure, adaptive servoventilation) can provide similar benefits. He does not explain this seeming paradox.

"If CSA-HCSB is detrimental, one might expect to observe the severity of HF and CSA-HCSB to worsen across the night…"

Naughton cites a small study[8] that included 13 patients with CSA-HCSB in whom heart rate variability (HRV) was compared between two short segments of the electrocardiogram taken towards the beginning and the end of the night. We note that the same study included eight patients with obstructive sleep apnea (OSA). The measurement used did not demonstrate changes in HRV during the course of the night in either the CSA-HCSB or the OSA group. Therefore, if we were to accept that this study is sufficient to support the contention that CSA-HCSB carries with it no added risk in patients with HF, then we would be compelled to accept the same for OSA—an assertion that has been thoroughly disproved. Moreover, both types of sleep-disordered breathing increased the sympathetic band in HRV, whereas robust literature exists showing that increased sympathetic activity in HF is detrimental; hence the inclusion of beta-blocker therapy in all versions of guideline-directed management in HF. As reviewed in detail in our con paper, similar degrees of sympathetic activation occur in CSA and OSA in HF, and treatment of CSA-HCSB reverses sympathetic activity. Although not explicitly addressed in Naughton's pro article, we maintain that the findings of well-controlled small randomized trials showing that elimination of CSA-HCSB improves sympathetic activation and cardiac function in patients with HF should not be rejected outright.

"Is HCSB associated with poor prognosis? Small studies were ambiguous and clouded by multiple causes of death. Our data were unable to confirm. Three of the four recent longer term studies suggested increased mortality; however, all studies were not controlled for every pertinent factor and could well be explained by simply representing the known poor prognosis in end-stage HF."

We appreciate the observational nature of these mortality studies, and that they have not accounted for some confounding factors. Having said that, one of these studies, the largest in this area, used an inception cohort design to mitigate against referral bias.[9] In another study, we adjusted for 24 known predictors of mortality in HF.[10] In another large study of 937 patients with HF,[11] CSA was associated with excess mortality and there was a dose-dependent association between various desaturation thresholds and time to mortality. Authors adjusted for age, sex, New York Heart Association class, ischemic cardiomyopathy, diabetes, body mass index, heart rhythm, implanted cardioverter defibrillator or cardiac resynchronization therapy devices, and use of diuretics, beta blockers, and digitalis glycosides. In this context, significant oxyhemoglobin desaturation that persisted throughout the follow-up in patients on adaptive servoventilation in the SERVE-HF trial[12] might have been one of the factors contributing to the demonstration of excess cardiovascular mortality as a secondary endpoint.[13] We emphasize that in a study from Naughton' s laboratory[14] that concluded CSA was not proven to be associated with excess mortality, the number of patients with CSA was 33 and some were treated with CPAP!

"…should CSA-HCSB be suppressed by drugs that stimulate ventilation (eg, acetazolamide or theophylline)? "Should drugs that suppress ventilation be used?"

Here Naughton refers to our studies showing attenuation of CSA with both theophylline and acetazolamide. We agree with Naughton in that we do not routinely recommend these drugs, because long-term studies are lacking. Yes, there is a sustained rise in ventilation; however, if the repetitive episodes of intense hyperventilation consequent to repetitive central apneas are eliminated by these drugs, the overall level of ventilation could be less than that in untreated CSA-HCSB.

We agree with Naughton that benzodiazepines should not be prescribed for the long-term treatment of CSA-HCSB. However, we disagree that they can be used to treat insomnia. We avoid using these drugs in general and recommend treating the underlying cause of insomnia whether it be depression, insomnia diagnoses that respond to cognitive behavioral therapy, or insomnia that may respond to melatonin. We also note that some beta blockers inhibit melatonin synthesis and could potentially contribute to poor sleep in some patients with HF.[15]

"Thus, the role for supplemental oxygen is unproven and not recommended in HF guidelines."

Oxygen has been shown to attenuate or eliminate CSA-HCSB, but the mechanism is unlikely to be related to the alleviation of dyspnea as suggested by Naughton, although this may be a desirable epiphenomenon. Oxygen works by way of multiple mechanisms[15]: a decrease ventilatory drive; increase in PCO_2 reserve (the difference between eupneic PCO_2 and arterial PCO_2); and should also increase oxygen stores in the lung.

These factors dampen the tendency for a negative feedback control system to become unstable and oscillate. Randomized trials have shown that nocturnal oxygen therapy decreases sympathetic activity and improves exercise capacity (for review see Javaheri[15]). We believe in the absolute necessity of a long-term randomized controlled trial, adequately powered, to determine the effects of treatment of CSA-HCSB with low-flow nocturnal oxygen. Following the results of SERVE-HF, such a trial should be placebo controlled (room air from a concentrator), and with well-defined primary endpoint(s). A pragmatic trial of low-flow oxygen in HF is currently under consideration by the National Institutes of Health. Naughton mentions that "… two well-performed studies have shown oxygen at super normal amounts further impair cardiac function." These studies were performed during the daytime and in normoxic subjects, and both showed that administration of high oxygen concentrations had adverse cardiac effects. However, we contend that these data are not pertinent to the current debate: the purpose of administering oxygen is to treat apnea-related hypoxemia during sleep, and not to cause hyperoxia!

In summary, as concluded in our con paper, our message to readers of the *Journal of Clinical Sleep Medicine* is twofold: Naughton's hypotheses are riddled with contradictions and lack of a firm base with respect to known physiology; and the SERVE-HF study, imperfect as it is, does not supply added credibility to Naughton's message.

CITATION

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DISCLOSURE STATEMENT

The authors report no conflicts of interest.