COMMENTARY

Heart Failure, Central Sleep Apnea, CPAP, and Arousals: Another Piece of the Puzzle

A commentary on Ruttanaumpawan et al. Effect of Continuous Positive Airway Pressure on Sleep Structure in Heart Failure Patients with Central Sleep Apnea. Sleep 2009;32:91-98.

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THERE ARE MANY DIFFERENCES BETWEEN OBSTRUCTIVE AND CENTRAL SLEEP APNEA. MOST OBSTRUCTIVE EVENTS END IN AN AROUSAL WHICH IS regarded as a defense mechanism to terminate the apnea.[1] Obstructive sleep apnea (OSA) is characteristically responsive to an effective level of positive airway pressure maintaining upper airway patency thereby decreasing apneas and hypopneas and improving sleep quality. On the other hand, Cheyne-Stokes respiration and central sleep apnea (CSR-CSA) is often difficult to treat despite the application of multiple modalities including oxygen therapy, positive airway pressure, sedative-hypnotic medications, theophylline, and exogenous carbon dioxide.[2,3]

Both obstructive and central sleep apnea events occur commonly in patients with heart failure. In a prospective study of 100 male patients, Javaheri identified sleep-disordered breathing in 49% of patients: 37% with CSA and 12% with OSA.[4] The pathogenesis of CSR-CSA is complex and may involve multiple factors including hyperventilation secondary to stimulation of pulmonary irritant receptors, increased chemoreceptor responsiveness to carbon dioxide, reduced cerebrovascular blood flow, increased circulation time, and repeated arousal from sleep.[5] Hyperventilation is generally present in heart failure patients with CSR-CSA resulting in a narrow gap between the eupneic $PaCO_2$ and the apnea threshold. The $PaCO_2$ and the severity of CSR-CSA is related to pulmonary capillary wedge pressure.[6,7] Recently, Szollosi et al demonstrated that impaired diffusing capacity and hypoxemia are independently associated with CSA severity. Numerous studies have demonstrated that HF patients with CSR-CSA (and other populations with central apnea such as patients with renal failure) are hyper-responsive to carbon dioxide by a mechanism which is not well understood. Delayed circulation time appears to be more closely related to the duration of the hyperpnea phase than the duration of apnea.[5]

It appears that the presence of CSA in heart failure patients portends a poor outcome. Lanfranchi et al studied 62 patients with left ventricular ejection fractions ≤ 35% and found that an AHI ≥ 30/h was a powerful independent predictor of poor prognosis.[8] Similar findings have been reported by Javaheri et al.[9] Early studies suggested that correction of sleep-disordered breathing, particularly CSR-CSA, with CPAP could improve cardiac function and the combined mortality-transplantation rate in patients who complied with therapy.[10] These studies were the genesis of the ambitious CANPAP trial which was undertaken to elucidate these relationships.[11] Unfortunately, the CANPAP trial results produced a great deal of disappointment, criticism, and commentary. A total of 258 patients with heart failure and CSA were randomly assigned to receive CPAP or no CPAP. There was an early survival advantage in the control group but at the end of the study there was no difference in transplant-free survival between the CPAP-treated group and the control group. During this study, there were substantial improvements in the drug therapy of heart failure resulting in a much lower than anticipated mortality rate in the studied population. Consequently the study was not sufficiently large to arrive at definitive results. There has been criticism that the mode of introduction of positive airway pressure, which was not titrated, may have resulted in less than fully effective pressures.[12] A subsequent post hoc analysis of these data focused on 57 patients who responded promptly to CPAP compared to 43 patients in whom CSR-CSA was not suppressed by CPAP. This analysis suggested that CPAP might improve both left ventricular ejection fraction and transplant-free survival if it is successful in suppressing CSR-CSA soon after treatment is initiated.[13] Interestingly, a recent study demonstrated that both obstructive and central apnea remain prevalent despite advances in the medical management of heart failure.[14]

Ruttanaumpawan and colleagues in this issue of SLEEP introduce an ancillary finding from the CANPAP study that is of considerable interest to sleep medicine clinicians and researchers.[15] Two hundred five patients from the CANPAP cohort who demonstrated > 50% CSA were randomized to CPAP treatment or control. While CPAP significantly decreased the AHI, there was neither a corresponding decrease in arousal index nor changes in sleep structure. Clearly, the mechanism of CPAP correction of CSR-CSA in heart failure patients does not require suppression of arousals. These data suggest that cyclical arousals were not a consequence of CSA and that arousals were not necessary to terminate apneas as they seem to be in patients with OSA. Further separating arousals and CSR-CSA, Willson et al reported that the presence of EEG arousals did not augment the pressor response to CSR-CSA in patients with heart failure.[16] The improvement in AHI reported by Rut-

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tanaumpawan et al was less than many clinicians would accept as satisfactory. The baseline AHI of 38.9 ± 15.0 fell to 17.6 ± 16.3. Nevertheless, it is remarkable that most studies of positive airway pressure therapy of sleep apnea in heart failure patients have either paid little attention to improvements of sleep disruption and arousals or have demonstrated similar disproportionally modest decreases in arousal frequency. These studies have demonstrated substantial improvement in measures of frequency of CSA in response to oxygen therapy, elevation of $PaCO_2$ by addition of dead space, CPAP, or other more sophisticated methods of delivering positive airway pressure such as bilevel pressure and adaptive servoventilation. The decrease in arousal index is often much less dramatic than the decrease in apnea hypopnea index.[17-22] Of note, Bonnet et al demonstrated improvement in CSA in some patients in whom arousals were suppressed with benzodiazepines.[23]

It seems possible that arousals may exist more or less independently (for unknown reasons) and that this instability of sleep may underlie the generation of central apnea events since arousals result in abrupt increases in ventilation driving the $PaCO_2$ below the apnea threshold. Thus, it is reasonable to speculate that in many circumstances, CSR-CSA appears to be "arousal-driven." A number of interesting questions come to mind. Are sedative-hypnotic medications underutilized in the management of CSA? Do post-arousal respiratory pauses, which have historically been ignored, presage the development of central apnea during CPAP titration? Most importantly, when reviewing polysomnography tracings perhaps one should wonder if "disrupted breathing is causing unstable sleep (as appears to be true with OSA) or is unstable sleep producing disordered breathing?"

DISCLOSURE STATEMENT

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