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Comparative Effectiveness Research in Complex Sleep Apnea

Commentary on Morgenthaler et al. The complex sleep apnea resolution study: a prospective randomized controlled trial of continuous positive airway pressure versus adaptive servoventilation therapy. SLEEP 2014;37:927-934.

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The area of complex sleep apnea has received considerable attention due to uncertainties in definition, lack of clarity regarding underlying mechanisms, emergence of new technology with potential benefits, and considerable costs associated with various therapeutic approaches. The new data provided by Morgenthaler and colleagues[1] in this issue of *SLEEP* shed some important light on these issues, although questions remain.

We use the term complex sleep apnea to be interchangeable with treatment-emergent central apnea, defined as the development of central apneas in patients with obstructive sleep apnea after the application of continuous positive airway pressure (CPAP). This phenomenon occurs in roughly 5% to 20% of CPAP titrations and has been recognized for some time, although the optimal management of complex sleep apnea has remained unclear.[2,3] Spontaneous resolution of these events over time in the majority of cases with ongoing CPAP therapy suggests that "expectant management" is reasonable.[4,5] On the other hand, the initial experience with CPAP may be a strong determinant of long-term CPAP adherence. As such, patients with considerable residual central apnea on CPAP may benefit from newer devices, if immediate improvement in apnea were to yield improved long-term adherence.

Morgenthaler et al. tested the hypothesis that newer devices may be superior to CPAP from the standpoint of residual apnea.[1] The authors randomized 66 OSA patients to receive either adaptive servo-ventilation (ASV) treatment (using ResMed VPAP Adapt SV) or standard CPAP, with a primary outcome of residual apnea hypopnea index (AHI) at 90 days. They found lower residual AHI among ASV treated patients compared to those on CPAP (4.7 ± 8.1 [central 1.1 ± 3.7] vs. 14.1 ± 20.7 [8.8 ± 16.3], $P < 0.001$). In the overall analyses, 89.7% of ASV treated patients achieved AHI < 10/h, whereas only 64.5% of CPAP treated patients fell below this threshold. The authors found a statistically significant improvement in AHI and therefore have presented findings supportive of their hypothesis. On the other hand, the data did not reveal a clinically meaningful difference in AHI (10 events per hour as *a priori* defined by the authors) and thus one could question the clinical relevance of the findings, based on the fact that secondary outcomes including PAP adherence, sleepiness, quality of life, and feeling refreshed were all the same in the ASV group as compared to CPAP. Thus, debate will ensue as to whether the new findings justify the use of new technology as compared to standard CPAP therapy.

What are some of the potential reasons for high residual AHI in the CPAP arm of the trial by Morganthaler? Although the authors matched the 2 groups of patients, there were more patients with heart failure (15.2% vs. 3%) in CPAP arm compared to ASV arm. As the authors note, central sleep apnea associated with heart failure may not be suppressed by CPAP in up to 50% of patients,[6] even with long-term use.[7] We also note that in most previous studies of complex sleep apnea, a residual central apnea index of 5 or greater during initial CPAP titration has been used as the threshold,[2,4] whereas the authors of this study used 10 or more. As a result, it is possible that patients were enrolled with increased ventilatory instability that would make them less likely to respond to CPAP.

The mechanism of treatment emergent central apnea remains unclear but could include several possibilities: CPAP-induced air leak washing out the anatomical dead space,[8] lowering of upper airway resistance which raises the chemoresponsiveness (i.e., controller gain), and possibly lung stretch reflexes induced by CPAP.[9] Reports of central apnea following oral appliance therapy given to patients with mild to moderate OSA are very rare, suggesting that more than lowering of upper airway resistance is at play. However, central apnea following tracheostomy is well described in severe OSA patients, perhaps suggesting that the mechanism underlying baseline OSA may be a critical variable.[10,11]

Recent data suggest that patients get OSA for variable reasons, with some having primarily an anatomical problem, whereas others may have dysfunction in pharyngeal dilator muscles and still others may have instability in ventilatory control as a major predisposing factor.[12,13] A concept of personalized medicine is thus emerging, such that therapies targeting underlying mechanism may be a method of treating apnea in carefully diagnosed patients.[14] Patients with multiple underlying abnormalities may require combinations of therapies to eliminate apnea. In theory, patients who develop central apneas on CPAP therapy may be those with unstable ventilatory control (elevated loop gain) and those with persistence of central apneas may be those with the highest loop gain values, as previously demonstrated in patients with Cheyne-Stokes breathing.[15,16]

Despite the new findings, a number of questions remain regarding the treatment of complex sleep apnea. First, can careful analyses of baseline demographic and polysomnographic data predict which patients are likely to benefit from

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ASV? For example, if baseline estimates of loop gain or patient-reported initial experience with CPAP-induced central apneas predict future CPAP failures, then ASV may be a reasonable alternative. Second, would a larger study with longer term clinical endpoints show benefit to ASV such that cost effectiveness research could be performed in a rigorous manner? Third, are pharmacological approaches viable in OSA at least for a subset of patients? Medications could be provided to selected patients to alter physiological traits to promote stable breathing or could be provided adjunctively for patients who experience a partial response to therapy. For example, an agent to modulate loop gain such as acetazolamide[17] could be given to CPAP treated patients with persistent central apneas. Similarly, an agent to raise the arousal threshold could be given to patients receiving hypoglossal nerve stimulation but with recurrent arousals.[14] Such approaches would also need to be subjected to randomized comparative effectiveness trials to compare outcomes versus other available treatments.[18] We applaud Morgenthaler and colleagues for the new findings and support further research into OSA pathophysiology and technology development.

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