

# Obstructive sleep apnea: can the downward spiral be reversed—a summary of John Stradling’s ATS keynote speech

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In a gripping ATS keynote speech Professor John Stradling from Oxford argued his view of obstructive sleep apnea (OSA) as a self-perpetuating disease, and the potential of continuous positive airway pressure (CPAP) to reverse some of the pathophysiological changes that are both caused by and contribute to OSA. In his view, CPAP use may allow patients to enter a “remission phase” of sleep apnea, or that reversal of these changes may also allow for successful treatment with non-CPAP therapies in selected individuals that would otherwise not work as initial therapy.

Professor Stradling first started with evidence that the upper airway (UA) of individuals with OSA undergoes pathologic changes and that some of these changes can be reversed with CPAP therapy. Tongue size has been found to be one of the most predictive factors for OSA (1). One study measured pharyngeal cross sectional area and tongue size by MRI before and after CPAP therapy. A significant improvement in pharyngeal volume, decreased tongue size and water content of the oropharynx was observed following four weeks of CPAP therapy. These improvements were attributed to CPAP’s protection from the trauma of repeated UA closure and resulting edema (2). A similar study used lateral cephalometry rather than MRI to measure posterior airway space and again found significant improvement in this space after 3 months of CPAP use (3). Mucosal damage and loss of the pharyngeal protective reflex may be another mechanism by which OSA perpetuates and exacerbates itself. In early studies by Horner, the UA of individuals without OSA were subjected to sudden negative pressures and a subsequent increase in genioglossus dilator electromyogram (EMG) tone was observed, now known as the genioglossus negative pressure reflex. This reflex

could be abolished in subjects whose UAs were anesthetized suggesting superficial receptors in the pharynx have a pivotal role in the genioglossus reflex (4). This finding is pertinent to understanding OSA pathophysiology as resected uvula samples from snorers demonstrate vibration induced injury including degeneration of myelinated nerve fibers and axons (5). Another study that evaluated resected uvulas of patients with OSA versus those of healthy controls found an increase in inflammatory markers and denervation of both the UA mucosa and muscles (6). Others have found remodeling of the hypoglossal nerve that innervates the genioglossus muscle through EMG techniques (7). These changes likely lead to the observed decrease in UA sensation of patients with OSA when compared to controls. Importantly these changes could be reversed following a period of CPAP therapy (8). These studies support the idea of trauma induced injury to the UA in patients with OSA with the consequence of perpetuating and exacerbating the disease.

Sleep deprivation caused by OSA may also in turn contribute to the disease. Prof Stradling hypothesized that patients with OSA more commonly fail to arouse sufficiently from apneic events to shift position from supine to lateral sleep. This “postural defense” may fail with increasing pressure to sleep. Although there is no definitive study to date, CPAP may restore the postural defense by decreasing sleep pressure. Evidence to support this claim comes from a study measuring the respiratory arousal, both before and after CPAP use, and found subjects with OSA wake up more easily from respiratory stimuli after three months of CPAP therapy compared to prior to therapy (9). Sleep deprivation may also contribute to OSA through effects on genioglossus

activity. Patients without OSA, but subjected to sleep deprivation, had reduced EMG genioglossus activity during CO<sub>2</sub> stimulation studies compared to non-sleep deprived controls. Furthermore, genioglossus function returned to normal after the subjects were allowed to sleep (10).

OSA may not always be due to fixed anatomical factors alone. The initial onset of OSA may occur during an upper respiratory tract infection, a time of sleep deprivation, increased alcohol intake, untreated GERD causing UA edema, or a night of forced supine sleeping position and then may be perpetuated and exacerbated through mechanisms previously discussed. If true, then attenuation of exacerbating factors—UA edema, muscle and neuronal damage, increased sleep pressure—following CPAP therapy may prime the UA for successful application of alternative OSA treatments that may not have worked without prior CPAP use. Such therapies could include positional therapies, mandibular advancement devices (MADs), reduction of nasopharyngeal edema, or combinations of these interventions. Positional OSA is defined as an AHI while sleeping supine two times higher than while sleeping in a non-supine position and has been observed between 5–50% of patients with OSA in different studies. Positional therapy has been shown to be as effective as CPAP in small selected groups of patients (11). MADs have variable efficacy but in one study half of patients with OSA previously treated with CPAP, who were able to tolerate the MAD, no longer had clinically significant OSA for up to a month after CPAP cessation (12).

Are there other treatments that might influence the UA to make it less collapsible? Hoffstein *et al.* introduced the idea that topical agents could be used therapeutically in snoring, specifically with topical administration of the surfactant phosphocholinamin in snorers and found a small but statistically significant reduction in snoring (13). Newer agents may be more applicable to those suffering from OSA and include AVE0118 which is a selective potassium channel blocker that works on potassium subtype receptor found on mucosal receptors in the pharynx. In a pig model this drug was shown to create significant increases in genioglossus activity. Pigs were subjected to increasing negative pressures from -50 to -150 mbar and were able to resist UA collapse when drug was applied compared to controls whose UA collapsed at -50 mbar or less (14).

Phenotyping the underlying pathophysiology of a patient's OSA once they have been on CPAP for a while will be important to identify appropriate targeted therapies in selected patients. Obesity and anatomical factors clearly increase pharyngeal critical pressure (Pcrit), the pressure

at which the UA will collapse, leading to OSA, however not every patient with OSA follows this pattern. There is much interest in further defining these non-anatomical factors that contribute to or cause OSA. A number of such factors have already been described including dilator muscle responsiveness, arousal threshold, and loop gain. Eckert *et al.* developed a protocol to measure these physiological traits by repetitively dropping CPAP level to induce partial UA obstruction and monitoring the changes in muscle activity and ventilation (using patients already on CPAP). These data can then be used to calculate loop gain, pharyngeal muscle responsiveness, Pcrit, and arousal threshold (15). Individuals who have OSA but have only modestly collapsible airways can then be identified. While many patients have a collapsible airway that can only be stented open by CPAP or other therapies, a substantial minority of patients might be improved by attention to the non-anatomical traits. Identifying these abnormalities is important so that tailored alternative therapies, especially following a period on CPAP, can be implemented. For instance AVE0118 could be applied to patients with decreased genioglossus response. Trazodone and eszopiclone have been shown to increase the arousal threshold and could be used in patients with low arousal threshold (16). In patients with high loop gain, oxygen therapy or acetazolamide have shown to have a modest effect in reducing AHI and may be tried after a period of CPAP therapy. Despite the excitement of targeted therapies success has been limited. However, this finding may be because most studies were performed on patients who had not had a period on CPAP first. Different results may be observed if these studies were repeated following attenuation of OSA induced UA pathology with a period of CPAP therapy.

In conclusion, Prof Stradling argued that some patients develop OSA due to transient changes (e.g., alcohol induced) but that OSA then becomes self-perpetuating. Such patients may not need permanent CPAP therapy, but may require it intermittently if a precipitating factor re-occurs. In order to identify treatable underlying phenotypes properly, patients may need to undergo a period of CPAP therapy first, and once recognized these patients may benefit from alternative targeted therapies. Such a concept of intermittent CPAP usage, and identification of alternative therapies requires rigorous testing.

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## Footnote

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## References

1. Kim AM, Keenan BT, Jackson N, et al. Tongue fat and its relationship to obstructive sleep apnea. *Sleep* 2014;37:1639-48.
2. Ryan CF, Lowe AA, Li D, et al. Magnetic resonance imaging of the upper airway in obstructive sleep apnea before and after chronic nasal continuous positive airway pressure therapy. *Am Rev Respir Dis* 1991;144:939-44.
3. Mortimore IL, Kochhar P, Douglas NJ. Effect of chronic continuous positive airway pressure (CPAP) therapy on upper airway size in patients with sleep apnoea/hypopnoea syndrome. *Thorax* 1996;51:190-2.
4. Horner RL, Innes JA, Murphy K, et al. Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. *J Physiol* 1991;436:15-29.
5. Woodson BT, Garancis JC, Toohill RJ. Histopathologic changes in snoring and obstructive sleep apnea syndrome. *Laryngoscope* 1991;101:1318-22.
6. Boyd JH, Petrof BJ, Hamid Q, et al. Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;170:541-6.
7. Saboisky JP, Butler JE, Luu BL, et al. Neurogenic changes in the upper airway of obstructive sleep apnoea. *Curr Neurol Neurosci Rep* 2015;15:12.
8. Kimoff RJ, Sforza E, Champagne V, et al. Upper airway sensation in snoring and obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;164:250-5.
9. Haba-Rubio J, Sforza E, Weiss T, et al. Effect of CPAP treatment on inspiratory arousal threshold during NREM sleep in OSAS. *Sleep Breath* 2005;9:12-9.
10. Leiter JC, Knuth SL, Bartlett D Jr. The effect of sleep deprivation on activity of the genioglossus muscle. *Am Rev Respir Dis* 1985;132:1242-5.
11. Permut I, Diaz-Abad M, Chatila W, et al. Comparison of positional therapy to CPAP in patients with positional obstructive sleep apnea. *J Clin Sleep Med* 2010;6:238-43.
12. Smith DM, Stradling JR. Can mandibular advancement devices be a satisfactory substitute for short term use in patients on nasal continuous positive airway pressure? *Thorax* 2002;57:305-8.
13. Hoffstein V, Mateiko S, Halko S, et al. Reduction in snoring with phosphocholinamin, a long-acting tissue-lubricating agent. *Am J Otolaryngol* 1987;8:236-40.
14. Wirth KJ, Steinmeyer K, Ruetten H. Sensitization of upper airway mechanoreceptors as a new pharmacologic principle to treat obstructive sleep apnea: investigations with AVE0118 in anesthetized pigs. *Sleep* 2013;36:699-708.
15. Eckert DJ, White DP, Jordan AS, et al. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188:996-1004.
16. Eckert DJ, Malhotra A, Wellman A, et al. Trazodone increases the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold. *Sleep* 2014;37:811-9.

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