Sleep apnoea: a therapeutic target in congestive heart failure

See pages 922-928 for the article to which this Editorial refers

The timely article by Staniforth et al.[1] in this issue addresses sleep apnoea as a potential therapeutic target in congestive heart failure. Despite its fundamental importance, this area has received scant attention in the heart failure literature. Sleep-related breathing disorders, including obstructive and central sleep apnoea associated with Cheyne-Stokes respiration (obstructive sleep apnoea and central sleep apnoea, respectively), are present in approximately 40–50% of patients with congestive heart failure[2,3]. Because these breathing disorders place upon the failing myocardium intense mechanical and adrenergic loads that may not be reversed by conventional pharmacological therapy, their diagnosis and specific treatment should be considered part of the optimum management of congestive heart failure[3].

In healthy humans, sleep is a period of relative cardiovascular and autonomic neural quiescence. By contrast, sleep in patients with obstructive sleep apnoea or central sleep apnoea is characterized by repetitive cycles of apnoea, hypoxia, sympathetic nervous system excitation and arousals from sleep leading to surges in blood pressure. For the failing myocardium, exquisitely sensitive to increases in afterload, and for the heart failure patient, whose prognosis is inversely related to the degree of sympathetic activation, this is ominous pathophysiology. Moreover, current drug therapy of congestive heart failure appears to have little impact on these nocturnal events. In contrast, within a month of treatment, abolition of obstructive sleep apnoea by nocturnal nasal continuous positive airway pressure causes significant improvements in left ventricular ejection fraction and heart failure symptoms. These observations underscore the importance of identifying and treating obstructive sleep apnoea when present in congestive heart failure[3].

How may we benefit patients with central sleep apnoea, which is an independent marker for increased mortality in congestive heart failure? Nocturnal administration of supplemental oxygen is one potential intervention. Andreas et al.[4] reported that 2 weeks of nocturnal oxygen caused a modest decrease in the frequency of central apnoeas and a slight, but significant increase in peak oxygen consumption during maximal exercise, but had no effect on symptoms or markers of cardiac function. The present paper by Staniforth et al.[1] describes a double-blind cross-over study of 4 weeks of treatment with overnight oxygen, or air, administered by nasal cannulae at a rate of 2 l. min⁻¹. These investigators compared the effect of these two interventions on sleep architecture, breathing patterns, cognitive function, patient symptoms, catecholamines, and natriuretic peptides. The study was well designed, and the number of variables studied sufficiently broad as to provide these authors a reasonably balanced assessment of the potential benefits and limitations of this intervention in congestive heart failure patients with central sleep apnoea.

Nocturnal oxygen caused a modest but significant increase in minimum oxyhaemoglobin saturation (from 82 to 91%), and a slight but significant reduction in the frequency of central apnoeas and hypopnoeas (38 to 25 events/hour of sleep). Perhaps the most remarkable effect of nocturnal oxygen was that it caused a significant reduction in nocturnal urinary noradrenaline, but not adrenaline, excretion. Nocturnal noradrenaline excretion in central sleep apnoea correlates with two potent stimuli to sympathetic nervous system activation: the frequency of arousal from sleep and the degree of nocturnal hypoxia[5]. Because the frequency of arousals in the patients described by Staniforth et al.[1] was unusually low for central sleep apnoea, and not suppressed by oxygen, the improvement in nocturnal oxygenation is the more likely mechanism for this reduction. The magnitude of this effect (a fall in overnight noradrenaline excretion of approximately 50%) is greater than observed over a similar time period when comparable patients are given new drug therapy, and is particularly striking when one considers that these patients were optimally treated with angiotensin converting enzyme inhibitors and diuretics. However, there was no effect on daytime plasma noradrenaline...
concentration, and the functional importance of this observation with respect to heart rate and blood pressure was not described.

Despite these encouraging findings, oxygen did not fulfill the investigators' other expectations in that sleep quality, day-time symptoms, and cognitive function did not improve, and plasma or urinary concentrations of the natriuretic peptides were unchanged. Left ventricular ejection fractions and cardiac dimensions were not assessed. Some of these negative findings may reflect insufficient statistical power because the number of patients studied was small (n=11), but on balance, these observations suggest that nocturnal oxygen therapy has only a limited, albeit beneficial, role to play in the management of congestive heart failure patients with central sleep apnoea.

These investigators did not address the fundamental question as to why oxygen should benefit patients, such as those studied, who are not hypoxic while awake, and have only mild hypoxic dips during sleep. Hypoxia is the result rather than the cause of central sleep apnoea[9]. Central sleep apnoea in congestive heart failure arises from hypocapnia during sleep. Because Paco2 lies close to the apnoeic threshold, only slight increases in ventilation, as occur in response to an arousal, are required to drive Paco2 below the apnoeic threshold and trigger central apneas. These in turn precipitate hypoxic dips. Unless these dips are quite pronounced it is unlikely that the relief of hypoxia would depress CO2 drive sufficiently to allow Paco2 to rise above the apnoeic threshold.

The most thoroughly tested treatment for central sleep apnoea in the setting of congestive heart failure, and the one thus far shown to have the greatest clinical benefit is continuous positive airway pressure. How does experience with nocturnal continuous positive airway pressure extend beyond those demonstrated for nocturnal oxygen, and include beneficial 'reverse remodelling' of ventricular architecture. We propose that this is because continuous positive airway pressure also lowers preload and afterload by raising intrathoracic pressure. Despite these benefits, some patients with congestive heart failure and central sleep apnoea will not accept this device.

Although improvements in objective measures of the severity of heart failure due to continuous positive airway pressure or oxygen therapy have not been shown, as yet, to translate into reduced mortality, taken together, these observations argue strongly for an independent benefit of specific treatment of central sleep apnoea when present in congestive heart failure. Whereas our preferred therapy is continuous positive airway pressure, nocturnal oxygen could be administered to patients intolerant of this device. However, it must be emphasized that the worldwide experience with either intervention, thus far, is small, and the clinical question addressed exceedingly common and important. It is therefore an opportune time for larger scale outcome trials of these non-pharmacological therapies of central sleep apnoea in congestive heart failure.

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References
