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Journal search and commentary

Role of cardiac pacing in sleep apnea uncertain
Article reviewed: S. Garrigue, P. Bordier, P. Jais, et al., Benefit of atrial pacing in sleep apnea syndrome, N Engl J Med, 346 (2002) 404–412

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Abstract

Objectives: To determine the effect of atrial overdrive pacing on sleep apnea severity in patients with sinus node dysfunction.

Study design: Unblinded, cross-over study of the effect of atrial pacing on sleep apnea–hypopnea, with randomized order of study conditions (paced versus unpaced).

Study population: Fifteen patients (11 men, 4 women), mean age 69 (SD 9) years, with sinus node dysfunction and permanent dual-chamber pacemakers, with polysomnographic evidence of either central or obstructive sleep apnea–hypopnea (mean apnea–hypopnea index (AHI) 27 (SD 16)). None had symptomatic heart failure, but 11 (73%) had mildly reduced left ventricular ejection fraction (40–56%).

Methods: One hundred and fifty-two patients with pacemakers implanted at least one year previously for symptomatic sinus node dysfunction (including tachycardia–bradycardia syndrome) were screened for symptoms of sleep apnea. Of 47 patients identified, 26 underwent polysomnography and 15 had an apnea index >5/h and an AHI >15/h. Following the baseline polysomnogram, subjects underwent polysomnography on the subsequent two nights under the following conditions, in random order: (1) pacemaker set at a rate 15 beats/min higher than the mean heart rate of the diagnostic study (overdrive pacing phase); and (2) pacemaker rate reduced to 40 beats/min (no-pacing phase). The main outcome measure was the difference in AHI between the two pacing modes.

Results: Mean nocturnal heart rate during the pacing phase was 72/min, versus 51/min during the no-pacing phase. During the no-pacing phase, AHI was unchanged from the baseline night at 28/h (SD 22). During overdrive pacing, however, the AHI was 61% lower at 11/h (SD 14). The AHI was lower on the pacing than the no-pacing night in all 15 subjects, regardless of whether the predominant type of apnea was central or obstructive. The mean central apnea index fell from 13 (SD 17) to 6 (SD 7), and the obstructive apnea index from 6 (SD 4) to 3 (SD 1). Both lowest oxyhemoglobin saturation and the percent time at saturation below 90% also improved on the pacing night. There was little difference in total sleep time between pacing and no-pacing nights; other measures of sleep quality were not reported.

Conclusions: The authors conclude that atrial overdrive pacing at a relatively modest rate causes a substantial improvement in both central and obstructive sleep apnea, by mechanisms that are uncertain.

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Keywords:

1. Discussion

Sleep apnea associated with hypersomnolence is conservatively estimated to affect 2–4% of the middle-aged US population [1]. The number with polysomnographic evidence of sleep apnea is at least five times as great, and even these less symptomatic individuals may be at increased risk of hypertension and cardiovascular disease. In most sleep laboratories, greater than 90% of sleep apnea patients have obstructive sleep apnea (OSA), which is generally treated mechanically: positive airway pressure, oral appliances, or surgical enlargement of the airway. As these therapies are often poorly tolerated or unacceptable to patients, and pharmacotherapy has generally proven ineffective, an efficacious non-mechanical therapy for OSA would be welcome. The study by Garrigue, et al. conducted in response to their clinical observation that some patients had an improvement in sleep symptoms following pacing, is thus quite intriguing. The study is well designed and executed, and demonstrates that atrial overdrive pacing caused a 60% reduction in the apnea–hypopnea frequency during sleep in a small group of patients with sinus node dysfunction and sleep apnea. While the reduction in AHI was less than that typically produced by continuous positive airway pressure (CPAP) (if adhered to!), and only the acute physiologic benefits of pacing were assessed, a sustained improvement

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in AHI of this magnitude might well lead to therapeutic benefit. The major limitation of this study is that the subjects are quite dissimilar to the typical sleep apnea patient, making generalization of the results problematic.

It is particularly interesting that pacing caused similar improvements in both central and obstructive sleep apnea (OSP). While OSA is often considered a predominantly anatomic disorder, a strictly dichotomous view of central versus OSP is overly simplistic. Dilator muscles of the upper airway, such as the genioglossus, are under central nervous system control. Cyclic decreases in the activity of both diaphragm and genioglossus muscles have been demonstrated not only in central sleep apnea but in OSA as well [2]. Whether individuals with such cyclic decreases in respiratory effort develop central or obstructive apnea likely depends on the anatomic propensity of the airway to collapse. Approximately half of the patients in this study had predominantly central sleep apnea, but even among those with OSA the proportion of central apneas was unusually high. This suggests that central mechanisms may have played an important role even in those subjects with a preponderance of obstructive apneas.

As atrial pacing clearly does not directly influence airway patency, a central mechanism affecting both respiratory rhythm generation and pharyngeal motoneuron activity offers the most likely explanation for the reported equivalent improvement in central and obstructive apneas during overdrive pacing. A change in sleep architecture with pacing is neither expected nor reported, so it is unlikely that pacing mitigated the sleep-related loss of the wakefulness drive to breathe. The authors suggest that vagolytic effects of pacing underlie the observed improvement. Although it has not been demonstrated that pacing is vagolytic, nor that such a vagolytic effect would ameliorate sleep apnea, it is plausible that atrial pacing exerts its effect by influencing signaling from cardiac vagal or sympathetic afferents. Although their impact on respiration is unknown, cardiac vagal afferents synapse in the nucleus of the tractus solitarius [3], an important component of the medullary respiratory control center. Cardiac sympathetic afferents may also be relevant, as norepinephrine is excitatory to respiratory motoneurons, including those innervating the pharyngeal muscles.

The most cogent explanation of the observed findings has been offered by Wellman et al. [4], who point to the effects of cardiac output on ventilatory loop gain. Loop gain is the ratio of response to stimulus in a negative-feedback control system; when the response is greater than the stimulus the system is prone to oscillation. Low cardiac output increases ventilatory loop gain by prolonging the lung-to-chemoreceptor delay [5]. Although hemodynamic measures are not presented in this study, atrial overdrive pacing may well increase cardiac output, thereby reducing ventilatory loop gain and stabilizing the respiratory pattern. This explanation is consistent with the apparent importance of central mechanisms even in those subjects with predominantly obstructive apnea, and also with the observation of mild cardiac dysfunction in most of the patients studied.

It is not yet time to add atrial overdrive pacing to the limited armamentarium for treatment of OSA. Although theophylline increases heart rate and cardiac output, and would thereby be expected to reduce ventilatory loop gain, it has met with little success in treating OSA. While ventilatory loop gain may be high in OSA, the relative importance of respiratory motoneuron activity versus upper airway anatomy in OSA will clearly influence the extent to which manipulation of loop gain or other ventilatory control factors may be useful in its treatment. Identification of subsets of OSA patients in which disordered control of ventilation is particularly important may allow the targeted testing of non-mechanical interventions such as pacing. Although it is entirely speculative, the age-related decline in the association of sleep apnea with obesity suggests that the elderly, in whom sleep apnea is common, could be one such group.

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