CPAP treatment for obstructive sleep apnoea in heart failure: expectations unmet

Sean M. Caples and Virend K. Somers*

Division of Pulmonary and Critical Care Medicine (SMC) and Division of Cardiovascular Diseases and Internal Medicine (VKS), Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA

Online publish-ahead-of-print 30 April 2007

This editorial refers to 'Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo controlled trial† by L.A. Smith et al., on page 1221

Heart failure (HF) is an epidemic, increasing in prevalence as the population ages. The Rotterdam Study shows that persons who live to age 55 have a one in three chance of eventually developing HF.1 The staggering prevalence estimate of more than five million currently living with HF in the United States may underestimate the overall problem, since population-based studies find that a substantial proportion of those with systolic dysfunction are asymptomatic, although still at increased mortality risk.2,3 Despite advances in treatment with drugs, lifestyle modifications, and therapeutic devices, mortality from HF continues to rise, fuelling interest in alternative methods of treatment. One such target of therapy has been obstructive sleep apnoea (OSA).

HF and OSA are closely linked by their strong associations with ageing and obesity, and frequently co-exist, with the prevalence of OSA approaching 40% in HF patients referred to a clinical sleep laboratory.4 This relationship may extend beyond that of simple co-morbidity, as mounting data suggest that the cascade of physiological responses to repetitive upper airway closure in OSA may exert deleterious effects on cardiac function, particularly in the already compromised heart. These acute, repetitive stressors include, among others, hypoxemia,5 surges in sympathetic neural output,6 inflammation,7,8 and swings in intrathoracic pressure with respiratory efforts against a collapsed upper airway.9 These effects may conceivably be summative over time, and contribute to the development of myocardial dysfunction. Recent data provide further evidence linking OSA to HF. The Framingham study showed that increasing body mass index (BMI) is directly correlated with incident HF.10

The mainstay of therapy for OSA is continuous positive airway pressure (CPAP), which, when titrated properly, effectively maintains upper airway patency and prevents the acute physiological perturbations described above. In those who suffer from the classic, though not universal clinical symptom of excessive daytime sleepiness, CPAP is an effective countermeasure.

Two controlled, interventional trials of CPAP for OSA in the setting of HF have been performed, both yielding various positive results.13,14 Utilizing a randomized, parallel comparative design, the control groups were comprised of subjects optimally medically managed, though not subjected to placebo. The intervention was applied after a full, second night in-lab polysomnographic titration of CPAP. Kaneko and colleagues reported an approximately 9% increase in left ventricular ejection fraction (LVEF) and significant reductions in blood pressure after just 1 month of CPAP therapy.13,14 Mansfield et al.13 studying a group of subjects with somewhat less severe degrees of both HF and OSA than did Kaneko, applied CPAP therapy for 3 months and showed significant improvements in LVEF and reductions in urinary catecholamines, but no changes in blood pressure (BP).

Smith et al.15 elevate the methodology of OSA trials in HF to a rigorous new level, with a randomized, placebo-controlled, cross-over CPAP treatment design. In this protocol, subjects were randomly assigned to 6 weeks of either CPAP treatment utilizing an auto-titrating device or an identical placebo CPAP hardware set-up that delivered sub-therapeutic (approximately 1 cm H2O) pressure. Following a 1 week washout period, the subjects were crossed over to the other arm for another 6 weeks. In contrast to the two previous trials,13,14 Smith et al. could...
show no significant changes in any cardiovascular parameter with the use of CPAP.

How do we reconcile these disparate results? First, it is helpful to examine the methodological differences between the previous and current studies. One argument in favour of cross-over designs is that, using a subject as his or her own control, variations (both overt and hidden) between ‘matched’ groups are minimized, if not eliminated, thereby augmenting statistical power.16 For example, it is possible that baseline between group differences in the severity of both OSA and LV systolic dysfunction in the Kaneko study may have influenced treatment outcomes. In the Mansfield paper, the control group had higher BP at baseline than did the CPAP group. There are, however, also potential drawbacks to the cross-over design, most notably the carryover of treatment effect beyond the washout period, thereby influencing the placebo interval.

Does the use of a placebo control help explain the differences between the studies? The finding in the current study of reduced sleepiness in both groups is supported by a number of prior treatment trials in OSA demonstrating significant placebo effects on validated measurements of sleepiness and quality of life associated with the use of a mask device delivering sub-therapeutic levels of pressure.17,18 Furthermore, the concern that wearing a non-therapeutic mask could worsen sleep quality and oxygenation has been refuted by a clinical trial utilizing a partial cross-over design.19 Notwithstanding arguments for or against the relative importance of sleepiness and quality of life on cardiovascular measures, the lack of a placebo control could overestimate the pure effects of eliminating repetitive upper airway collapse in HF. On the other hand, the use of sub-therapeutic CPAP in the cross-over design of the current study may be a cause for concern. While it is reassuring that there were no significant differences in nightly duration of use between CPAP and placebo, it is possible that the group initially randomized to therapeutic CPAP took note of the reduction in delivered pressure after cross-over, thereby potentially unblinding them.

What can be said about the use of auto-titrating CPAP in the current trial, the first to use such a device in the setting of HF? Auto-titrating CPAP is designed to deliver variable pressures throughout a night of sleep, according to upper airway mechanics that may change in response to sleeping position or sleep stage. Systematic reviews have shown auto-titrating CPAP to be a viable alternative to lab-based titration of positive airway pressures in populations without overt cardiovascular disease.20 Volume overload and variations in central venous pressure, characteristic of HF, particularly with recumbency, have been shown to acutely alter upper airway mechanics and luminal diameter.21 While auto-titrating CPAP may be expected to be reasonably effective under such circumstances, its validity in this setting is not firmly established. Furthermore, unlike the two previous studies which had polysomnographic confirmation of CPAP efficacy, the current study does not, opening the door to possible undertreatment of OSA.

Second, methodological variations notwithstanding, the usual limitations of patient-based research on cardiovascular outcomes in OSA remain in all of these studies. Are several weeks of CPAP therapy adequate to measure functional outcomes in HF, particularly when adhered to <4 h per night? What is the significance of the relative lack of sleepiness in HF patients with severe OSA and how does that influence the response to treatment?

Finally, even though clinicians caring for HF patients with OSA have many anecdotal cases of improvement of HF with OSA treatment, we need to recognize the less attractive, but real possibility that CPAP treatment of OSA may simply have no independent effect on cardiovascular measures in HF.

The important work done by Smith and colleagues clearly underscores the urgent need for large and robust clinical trials to help answer the greater and more fundamental question of whether or not CPAP treatment of OSA prevents cardiovascular events and/or death.

Acknowledgements

The authors are supported by NIH grants HL-65176, HL-70302, HL-73211 and M01-R000585, and the Mayo Clinic, and a grant from the Res Med Foundation. The authors gratefully acknowledge the assistance of Debra Pfeifer and Ann Peterson in preparing this manuscript.

Conflict of interest: S.M.C. is supported by a grant from the ResMed Foundation. V.K.S. is a consultant for Respirionics and Cardiac Concepts.

References

Clinical vignette

doi:10.1093/eurheartj/ehl395
Online publish-ahead-of-print 22 November 2006

Value of cardiovascular magnetic resonance for determining cardiac involvement in systemic amyloidosis

Chiara Bucciarelli-Ducci, Didier Locca, Gerald Barbeau, and Sanjay K. Prasad*

Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

*Corresponding author. Tel: +44 20 7351 8812; fax: +44 20 7351 8816. E-mail address: s.prasad@rbht.nhs.uk

A 66-year-old woman presented with atypical chest pain, symptoms of heart failure (NYHA class III), and loss of appetite. Her past medical history was notable for previous episode of decompensated heart failure and two transient cerebral ischaemic attacks. Physical examination revealed a raised jugular venous pressure, marked peripheral oedema, hepatomegaly, and bilateral rales. An adjunct S4 heart sound was heard suggesting a stiff left ventricle. Electrocardiogram documented right bundle branch block and Q-waves in the inferior leads. Chest X-ray confirmed bilateral pleural effusions\(^\text{13}^\). Echocardiogram showed asymmetric left ventricular hypertrophy (LVH), diastolic dysfunction, and pulmonary hypertension. Right and left cardiac catheterization showed unobstructed coronary arteries, pulmonary arterial pressure of 44/15 mmHg, mean 24 mmHg, and a wedge pressure of 20 mmHg.

Cardiovascular magnetic resonance (CMR) was performed to characterize her underlying cardiomyopathy. Her scan showed severely impaired biventricular systolic and diastolic function, concentric LVH (maximal wall thickness 18 mm), a small pericardial effusion, and bilateral pleural effusions (Panels A and B). In the cine images, the presence of a large mobile thrombus was seen in the left atrial appendage (Panel C) and confirmed by the early inversion-recovery imaging following gadolinium-DTPA contrast administration (Panel D). On the delayed enhancement images, the blood pool was characteristically dark and there was circumferential late enhancement of the endocardial and mid-wall layers suggestive of an extensive infiltrative process and in particular cardiac amyloidosis (Panels E and F). Subsequently, a serum amyloid P component (SAP) scan was performed showing amyloid deposition in the spleen and bone marrow (Panel G). Serum blood tests showed an IgG lambda serum paraproteinaemia and serum-free light chain assay confirmed an excess of lambda light chains. Primary systemic AL amyloidosis with severe cardiac involvement was diagnosed.

Cardiac involvement is the cause of death in approximately 50% of patients with AL amyloidosis and is associated with overt congestive heart failure. SAP scintigraphy is an effective non-invasive tool for diagnosis of systemic AL amyloidosis but it is considered inadequate for evaluating the heart. In cardiac amyloidosis, CMR presents a characteristic pattern of circumferential subendocardial late enhancement that is related to the histological distribution of amyloid protein. The potential of CMR in detecting cardiac amyloid load may suggest diagnostic value of this innovative non-invasive imaging technique and may yield an opportunity to assess therapeutic response.