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Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial

Lindsay A. Smith[1]*, Marjorie Vennelle[2], Roy S. Gardner[3], Theresa A. McDonagh[4], Martin A. Denvir[1], Neil J. Douglas[2], and David E. Newby[1]

[1]*Cardiovascular Research, Centre for Cardiovascular Science, University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, UK;* [2]*Department of Sleep Medicine, University of Edinburgh, UK;* [3]*Western Infirmary, Glasgow, UK; and* [4]*Royal Brompton Hospital, London, UK*

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KEYWORDS
Congestive heart failure;
Obstructive sleep apnoea;
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Aims Obstructive sleep apnoea (OSA) is highly prevalent in patients with chronic heart failure (CHF) and may contribute to CHF progression. We aimed to determine whether treatment of OSA with continuous positive airway pressure (CPAP) would improve subjective and objective measures of heart failure severity in patients with CHF and OSA.

Methods and results Twenty-six patients with stable symptomatic CHF and OSA were randomized to nocturnal auto-titrating CPAP or sham CPAP for 6 weeks each in crossover design. Study co-primary endpoints were changes in peak VO_2 and 6 min walk distance. Secondary endpoints were changes in left ventricular ejection fraction, VE/VCO_2 slope, plasma neurohormonal markers, and quality-of-life measures. Twenty-three patients completed the study protocol. Mean CPAP and sham CPAP usage were 3.5 ± 2.5 and 3.3 ± 2.2 h/night, respectively ($P = 0.31$). CPAP treatment was associated with improvements in daytime sleepiness (Epworth Sleepiness Score 7 ± 4 vs. 8 ± 5, $P = 0.04$) but not in other quality-of-life measures. There were no changes in other study endpoints.

Conclusion In patients with CHF and OSA, auto-titrating CPAP improves daytime sleepiness but not other subjective or objective measures of CHF severity. These data suggest that the potential therapeutic benefits of CPAP in CHF are achieved by alleviation of OSA rather than by improvement in cardiac function.

Introduction

Chronic heart failure (CHF) is a major cause of morbidity and mortality in developed countries and its prevalence and incidence continue to rise.[1] The Sleep Heart Health Study has shown a cross-sectional association between obstructive sleep apnoea (OSA) and CHF.[2] Although often unrecognized, OSA is highly prevalent in patients with CHF: up to 37%, depending on diagnostic threshold and selection criteria chosen.[3,4] Furthermore, severe OSA is an independent risk factor for fatal and non-fatal cardiovascular events, and this risk may be reduced by the application of nocturnal continuous positive airways pressure (CPAP).[5]

OSA is characterized by intermittent partial or complete upper airway obstruction during sleep, disrupting normal ventilation and sleep architecture. OSA is associated with systemic hypertension,[6–8] vascular endothelial dysfunction,[9,10] increased sympathetic nervous activity,[11] and increased levels of inflammatory mediators.[12] In addition, inspiration against the occluded upper airway generates exaggerated negative intrathoracic pressure, which adversely affects cardiac performance.[13] These important factors are all implicated in the development and progression of CHF.

There have been only two previous randomized controlled trials to assess CPAP in patients with CHF and OSA.[14,15] These trials report improvements in left ventricular ejection fraction (LVEF), overnight urinary norepinephrine excretion, systolic blood pressure, and some quality-of-life measures. However, they employed parallel group comparisons with small numbers of patients ($n = 12$–19 per group) and, importantly, no appropriate placebo control.

The aim of this study therefore was to determine whether, using a double-blind randomized placebo-controlled

* Corresponding author. Tel: +44 131 242 6422; fax: +44 131 242 6422.
E-mail address: lindsay.smith@ed.ac.uk

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crossover trial, treatment of OSA by nocturnal auto-titrating CPAP would improve subjective and objective measures of CHF severity.

Methods

Participants

Patients were recruited from general cardiology clinics at two university hospitals in Edinburgh and from a specialist heart failure clinic in Glasgow. Consecutive patients with CHF aged between 18 and 80 years were enrolled into this prospective study if the following inclusion criteria were met: (i) symptomatic CHF [New York Heart Association (NYHA) classes II–IV], (ii) LVEF determined by echocardiography of $<45\%$, (iii) clinical stability for at least 1 month, (iv) optimal medical therapy, and (v) apnoea/hypopnoea index (AHI) ≥ 15 (predominantly obstructive) on polysomnography (PSG). Exclusion criteria were acute coronary syndrome within the preceding 3 months, primary valvular heart disease, sustained ventricular arrhythmias (but not atrial fibrillation), and stroke with residual neurological deficit. The study complied with the Declaration of Helsinki, the protocol had the approval of the local Ethics Committee, and all patients provided informed written consent.

Procedures

Sleep studies

Patients with 15 or more apnoeas/hypopnoeas per hour in bed on a limited sleep study performed at home were invited to attend for PSG at the Sleep Centre in Edinburgh. PSG was performed following our standard laboratory protocol[16] with a computerized recording system (Compumedics, Abbotsford, Australia) consisting of: (i) sleep monitoring through electro-encephalogram, electro-oculogram, and submental plus outer canthi electromyogram, (ii) bilateral tibial electromyogram and body position detector, (iii) nasal pressure using a nasal cannula/pressure transducer system, (iv) thoraco-abdominal movement from two inductance plethysmographic belts, (v) finger pulse oximetry, (vi) snoring detection by digital microphone, and (vii) three-lead electrocardiogram.

All sleep studies were scored according to standard criteria by the same experienced sleep technician.[17] Apnoeas were defined as a complete cessation in airflow lasting ≥ 10 s and hypopnoeas as a reduction in airflow or thoraco-abdominal movement by $\geq 50\%$ for ≥ 10 s. Apnoeas were classified as (i) obstructive if thoraco-abdominal movement was present during the apnoea; (ii) central if thoraco-abdominal movement was absent; and (iii) mixed if thoraco-abdominal movements were both present and absent during the period of airflow cessation.[18]

Study protocol

This was a double-blind randomized placebo-controlled crossover trial in patients with CHF and OSA. Patients were randomized to nocturnal auto-titrating CPAP (Autoset Spirit: ResMed, Sydney, Australia) and sham CPAP for 6 weeks each in a crossover design with a 1-week washout period. Randomization to treatment order was performed following baseline assessment using sealed envelopes and a balanced block design with six patients per block. Study co-primary endpoints were changes in peak VO_2 and 6 min walk distance. Secondary endpoints were changes in LVEF, VE/VCO_2 slope, plasma neurohormonal markers, and quality-of-life measures.

Auto-titrating CPAP automatically adjusts pressure according to upper airway obstruction, avoiding many of the disadvantages of titration and treatment with conventional CPAP. It is as effective as fixed pressure CPAP in reducing daytime sleepiness and AHI and also increases nightly use and provides better quality sleep and less discomfort.[19,20] Sham CPAP was chosen as the placebo in the present study because it was felt important to control for the discomfort and possible sleep disruption of wearing a mask overnight; it also makes observer blinding easier to maintain. The sham device was created by setting delivered airway pressure to a minimum, inserting a flow-restricting connector at the machine outlet, and creating an extra hole in the collar of the main tubing at the end of the mask.[21] The device delivered a CPAP pressure of $\sim$1 cm H_2O.

Patients underwent an initial daytime education session and were then supervised for their first night on each device in the Sleep Centre. They were asked to use the machine for a minimum of 6 h per night at home and provided with a contact telephone number in case of any problems. In addition, all patients were contacted by telephone by the Sleep Centre Research Nurse within 2 weeks of taking each device home. Compliance with therapy was assessed by interrogation of the CPAP unit to provide nightly usage data.

Study investigators performing assessments were blinded to treatment modality; they were not involved in randomization, device education, or follow-up; and study participants were instructed not to discuss their device with them. Study participants themselves were advised that two different types of breathing devices were being tested and that they would receive both in a random order.

Functional evaluation was performed at the coordinating centre at baseline, 6, and 13 weeks and included: (i) clinical assessment, (ii) transthoracic echocardiography, (iii) symptom-limited cardiopulmonary exercise testing, (iv) 6 min walk test, (v) neurohumoral markers, (vi) Oxford SLEep Resistance (OSLER) test,[22] and (vii) quality-of-life assessment. At baseline evaluation, two 6 min walk and two cardiopulmonary exercise tests were performed on separate days to minimize any potential bias due to a training effect; the second tests were taken as baseline data.

Cardiopulmonary exercise testing

Symptom-limited exercise tests were performed under physician supervision using an electronically braked cycle ergometer. The incremental exercise protocol was individualized, aiming for exercise duration between 8 and 12 min.[23] Respiratory gas exchange measurements were obtained breath-by-breath using a computerized metabolic cart (MSX, Ferraris Group Plc, Birmingham, UK). Gas and flow calibrations were performed before each test.

Breath-by-breath data were formatted using a rolling eight breath average. Peak VO_2, VCO_2, and VE were recorded as the highest such values within the last 30 s of the test. Predicted peak VO_2 values were calculated using the standard formulae described by Wasserman *et al.*[24] The VE/VCO_2 slope was calculated as a linear regression function, excluding the non-linear part of the relationship after the onset of acidotic drive to ventilation.[23]

Six minute walk test

A standardized test procedure was followed.[25] Patients were asked to walk around a walking track, covering as much distance as possible for 6 min, and were allowed to rest if required.

Echocardiography

Transthoracic Doppler echocardiography was performed by a single, experienced research sonographer using an ATL HDI 5000 system (Philips Medical Systems Limited, Stevenage, UK). Left ventricular volumes and ejection fraction were calculated according to the modified Simpson's rule.

Clinical and quality-of-life assessment

Clinical assessment was performed at each study visit and NYHA class recorded. Standardized questionnaires (SF-36, Minnesota Living with Heart Failure and Epworth Sleepiness Scale[26]) were used to assess quality of life and symptoms.

Neurohumoral markers

N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and N-terminal pro-atrial natriuretic peptide (NT-pro-ANP) were measured using a chemiluminescent immunoassay (Roche Diagnostics Ltd, Lewes, UK) on an Elecsys 2010 analyser. Plasma norepinephrine concentrations were determined by an electrochemical method

after separation by reverse-phase high-performance liquid chromatography.[27]

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 10 software (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean values (±SD), or when not normally distributed, data as medians (interquartile range). Differences between CPAP and sham CPAP were assessed by two-tailed, paired *t*-tests. NT-pro-BNP and NT-pro-ANP data were normalized by logarithmic transformation prior to assessment. The study had 80% power, at 5% significance level, to detect absolute differences in the primary endpoints of 1.1 mL/min/kg in peak VO_2 and 33 m in 6 min walk distance, assuming standard deviation of expected changes of 1.9 mL/min/kg and 57 m, respectively. Statistical significance was taken at the 5% level.

Results

Of the 349 patients who potentially fulfilled the entry criteria, 114 consented to undergo study screening (*Figure 1*). Sleep studies were performed on 103, with 46 subsequently attending for in-laboratory PSG. Of the 29 patients fulfilling all trial entry criteria, two withdrew consent for personal reasons and one died prior to randomization (ruptured abdominal aortic aneurysm). Twenty-six patients were randomized and, of these, two withdrew immediately following the baseline assessment for personal reasons and one withdrew after completion of the first limb of the study because of mask claustrophobia. One patient was excluded from the final analysis because multiple changes to drug therapy, instituted by the patient's attending physician, were deemed likely to influence trial endpoints. No time-order effects were observed.

Patient characteristics and continuous positive airway pressure use

Study patients were predominantly late middle-aged men (*Table 1*) maintained on optimal drug therapy for LV systolic dysfunction. The study population demonstrated moderately severe OSA, although only eight patients (31%) complained excessive daytime sleepiness (*Table 2*). Mean nightly CPAP and sham CPAP use were similar: 3.5 ± 2.5 and 3.3 ± 2.2 h per night, respectively ($P = 0.31$). Mean CPAP pressure applied was 7 ± 2 cm H_2O.

Outcome data

There were subjective but no objective improvements in daytime sleepiness with auto-titrating CPAP therapy (*Table 3*). No differences were demonstrated in other quality-of-life measures such as the SF-36 and Minnesota Living with Heart Failure questionnaire scores (*Table 3*;

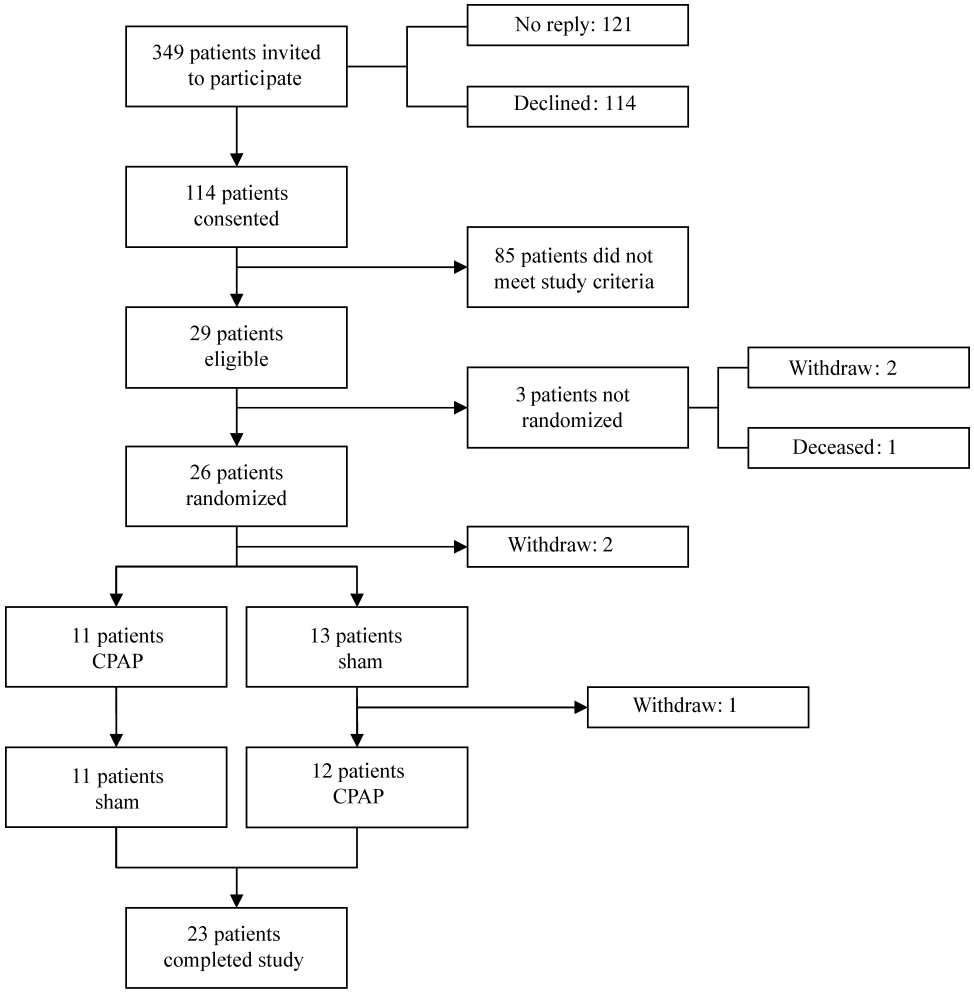

Figure 1 CONSORT diagram of trial recruitment.

Table 1 Patient characteristics ($n = 26$)

Age (years)	61 ± 8
Sex (male:female)	23:3
Body mass index (kg/m^2)	31 ± 4
Hypertension	11 (42%)
Diabetes mellitus	7 (27%)
Hyperlipidaemia	16 (62%)
Smoking history	18 (69%)
Aetiology of CHF	
Ischaemic heart disease	12
Dilated cardiomyopathy	12
Other	2
Atrial fibrillation	8 (31%)
Drug treatment	
ACE/ARB	25 (96%)
Beta-blockers	21 (81%)
Digoxin	11 (42%)
Diuretics	20 (77%)
Spironolactone	9 (35%)
NYHA class—II/III/IV	20/5/1

Mean ± SD or number (%). ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association.

Table 2 Sleep assessment

Epworth Sleepiness Score	10 ± 5
OSLER time (min)	29 ± 15
Obstructive apnoeas (per hour)	11 ± 15
Central apnoeas[a] (per hour)	1 (4)
Mixed apnoeas[a] (per hour)	0 (1)
Hypopnoeas (per hour)	22 ± 17
Apnoea/hypopnoea index (AHI)	36 ± 23
Total sleep time (h)	4.6 ± 1.5
Sleep efficiency (%)	61 ± 17
Oxygen saturation (%)	93 ± 2
Oxygen desaturations ≥4% (per hour)	22 ± 26

[a]Mean ± SD except median (interquartile range).

Figure 2). Similarly, there were no differences in cardiac function, exercise capacity, or neurohormonal activation between CPAP and sham placebo (*Table 3*; *Figure 3*).

Discussion

We have conducted the first randomized double-blind placebo-controlled crossover trial of auto-titrating nocturnal CPAP therapy in patients with CHF and OSA. In contrast to smaller previous trials, CPAP improves daytime sleepiness but not other subjective or objective measures of CHF severity. These data suggest that the potential therapeutic benefits of CPAP in CHF are achieved by alleviation of OSA rather than by improvement in cardiac function. However, the efficacy of CPAP as a treatment for patients with CHF and OSA may be limited in part by poor patient tolerability and compliance.

Important advances have been made in the management of patients with CHF in the last two decades. A range of therapeutic options that are known to impact on symptoms, quality of life, and prognosis are now available to the physician. However, the prevalence of CHF continues to rise, associated morbidity and mortality rates remain high, and the financial burden to healthcare systems is great.[1] The identification of potential exacerbating factors and possible therapeutic targets therefore remains extremely important. OSA is one such factor that commonly co-exists with CHF, may contribute to disease progression, and can be potentially targeted by CPAP therapy.

Two recently published randomized controlled trials in patients with CHF and OSA are encouraging.[14,28] These trials reported that CPAP therapy improved LVEF, systolic blood pressure, and symptoms. However, these studies had important limitations including the single-blind design and the small numbers of patients ($n = 12$–19 per intervention group) completing study protocols. Some of the study findings were not entirely consistent given that there were no changes in peak VO_2 or NYHA class, despite improvements in LVEF.

Previous trials of CPAP have used non-intervention control groups raising concerns regarding potential placebo effects and adequate blinding. This is a particular problem when using device interventions that require training, supervision, and close liaison with healthcare professionals. Prior work with CPAP in patients with OSAHS has revealed a powerful placebo effect, reducing ESS score by 2 points and improving other quality-of-life measures.[29,30] Failure to control for a placebo effect could therefore overestimate differences in endpoints between intervention and non-intervention groups. We therefore used sham CPAP as a placebo control and, in our study, there were no differences in compliance or dropout rates between sham and active CPAP limbs, suggesting that patient blinding was maintained and that an effective placebo was indeed employed.

Results of parallel group studies involving small numbers of patients are susceptible to bias introduced by baseline differences between control and treatment groups as well as by outliers. For example, the control group in the Kaneko *et al.*[14] trial had significantly worse OSA than the treatment group at baseline and this may have led to worsening of cardiovascular variables over the conduct of the trial. Decisions whether to include or exclude outliers in statistical analysis, or inadequate matching of outcome variables at study entry, such as LVEF and AHI thresholds, may markedly alter statistical results and reported outcomes. Indeed, the impact of outliers and the methods of statistical analysis on the results of the study by Mansfield *et al.* have been discussed elsewhere.[31]

Determining the effects of CPAP on cardiovascular outcomes in patients with CHF and OSA remains an extremely important clinical question. The present study utilized a robust randomized double-blind placebo-controlled crossover trial design that enables patients to act as their own control, thus reducing between-subject variability, avoiding the need for matched control subjects, and increasing statistical power. Indeed, our analysis of 23 patients yields a power two to four times greater than that of the previously published parallel group studies.[20,21] The entry criteria and endpoints for the current study were well defined and clinically relevant. Robust symptomatic and quality-of-life assessments are vital when considering CPAP as a potential treatment, as the patient's perception of benefit is a major determinant of future compliance with therapy. Peak VO_2, VE/VCO_2 slope, and NT-pro-BNP all provide

Table 3 Effect of continuous positive airway pressure and sham continuous positive airway pressure on quality of life and cardiac function

	Baseline	Sham	CPAP	Treatment effect	*P*-value
Echocardiography					
LVESD (mm)	50 ± 11	51 ± 13	51 ± 14	−0.1 (−0.4 to 0.3)	0.79
LVEDD (mm)	61 ± 10	63 ± 12	63 ± 12	0.0 (−0.4 to 0.3)	0.83
FS (%)	18 ± 7	20 ± 8	19 ± 6	0.1 (−3.3 to 3.6)	0.95
LVEF (%)	29 ± 10	30 ± 10	30 ± 10	0.7 (−1.8 to 3.2)	0.56
Exercise capacity					
6 MW (m)	550 ± 121	552 ± 121	546 ± 124	0 (−14 to 14)	0.98
Exercise time (min)	10.0 ± 2.3	9.7 ± 3.0	9.8 ± 3.1	0.2 (−0.3 to 0.7)	0.44
Peak VO_2 (mL/kg/min)	14.8 ± 4.2	14.7 ± 4.6	14.5 ± 4.2	−0.2 (−0.9 to 0.4)	0.48
VE/VCO_2 slope	32 ± 5	33 ± 7	33 ± 8	−0.3 (−1.9 to 1.4)	0.73
Quality of life					
Minnesota	38 ± 27	34 ± 28	36 ± 29	1.0 (−4.3 to 6.4)	0.70
SF-36—physical	34 ± 16	35 ± 14	34 ± 14	−1.0 (−3.6 to 1.6)	0.43
SF-36—mental	51 ± 10	50 ± 11	49 ± 12	−0.5 (−4.2 to 3.2)	0.79
Daytime sleepiness					
ESS	10 ± 5	8 ± 5	7 ± 4	−1 (−1.9 to 0.0)	0.04
OSLER (min)	27 ± 15	29 ± 13	30 ± 14	0.7 (−2.2 to 3.6)	0.63

Mean ± SD except treatment effect (95% confidence interval).
ESS, Epworth Sleepiness Scale; FS, fractional shortening; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; OSLER, Oxford SLEep Resistance test; 6 MW, 6 min walk test.

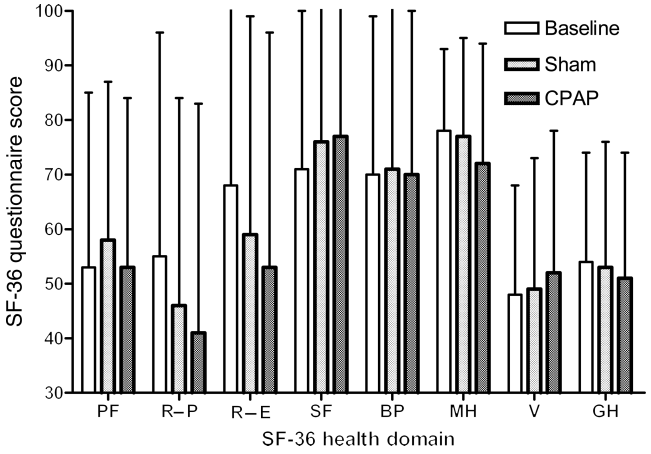

Figure 2 Effect of continuous positive airway pressure and sham continuous positive airway pressure on quality-of-life measures (SF-36). PF, physical function; R–P, role–physical; R–E, role–emotional; SF, social function; BP, bodily pain; MH, mental health; V, vitality; GH, general health.

important prognostic information in CHF.[32–34] LVEF also provides useful information but correlates poorly with symptoms and functional limitation in CHF.[35] Major treatment advances in the management of CHF patients, such as the introduction of ACE inhibitors, beta-blockers, and, more recently, biventricular pacing, have been shown to improve these parameters and subsequently, in large randomized controlled trials, to reduce hospitalization rates and mortality.[36–39]

We have shown small and clinically modest improvements in subjective, but not objective, measures of daytime sleepiness with CPAP that are not due to a placebo effect. This is perhaps not surprising as the aetiology of sleepiness in patients with CHF is clearly multifactorial. In contrast to previous work, no improvements in quality-of-life measures, functional capacity, or other markers of CHF severity were identified with CPAP therapy in this patient group. This is despite the greater severity of both CHF and OSA in our study population when compared with that of Mansfield *et al.*[15]

Compliance with CPAP therapy in this study was reasonable, particularly when the reduced total sleep time is considered, but was poorer than that achieved in other studies.[14,15] This was despite careful education, initiation of treatment in-laboratory, and the provision of ongoing support, suggesting that CPAP may not be acceptable to a proportion of patients with CHF and OSA. Previous work in patients with OSAHS has shown that there is a need to derive symptomatic benefit from CPAP in order to accept the associated discomfort and inconvenience. Accordingly, compliance and long-term usage in patients with mild OSAHS are poor.[29] Similarly, patients with CHF and OSA who do not have excessive daytime sleepiness, or whose sleepiness is due to factors other than OSA, may not comply with CPAP therapy. We did not find the ESS and OSLER tests to be helpful in identifying which patients with CHF and OSA would derive symptomatic benefit from CPAP.

Study limitations

The study protocol did not include follow-up PSG. Our aim was to investigate whether auto-titrating CPAP was a tolerable and effective treatment for patients with CHF and OSA rather than whether auto-titrating CPAP reduced AHI. Although not routinely performed in the clinical setting, we accept that a follow-up PSG would have been helpful to ensure efficacy of the treatment intervention.

Inadequate reduction in AHI, due to limited subject compliance, would be a possible explanation for the lack of efficacy of CPAP therapy for cardiovascular endpoints. However, it is important to note the low total sleep times observed in this study: in itself an interesting and important finding in patients with CHF. Moreover, CPAP use was greater than that observed in our previous studies of patients with OSAHS where we have shown that CPAP therapy produced

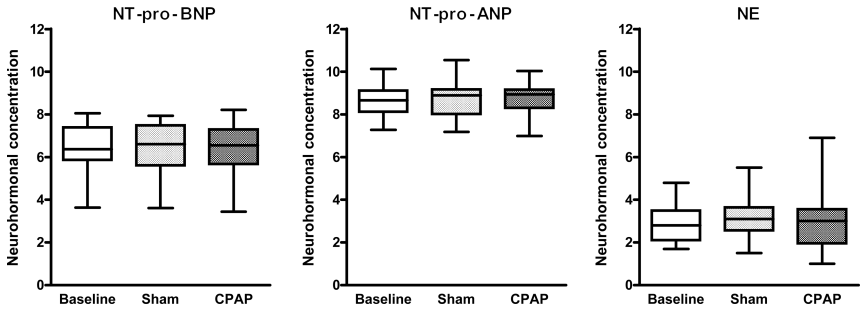

Figure 3 Effect of continuous positive airway pressure and sham continuous positive airway pressure on plasma neurohumoral measures of cardiac function NT-pro-BNP, N-terminal pro-brain natriuretic peptide; NT-pro-ANP, N-terminal pro-atrial natriuretic peptide; NE, norepinephrine. NT-pro-BNP and NT-pro-ANP are logarithmically transformed and data are presented as mean, interquartile ranges, and 95% confidence intervals.

significant improvements in both quality-of-life and cardiovascular endpoints.[8,29] Moreover, Bradley *et al.*[40] demonstrated sustained improvements in LVEF and plasma norepinephrine concentrations with comparable nightly CPAP use (3.6 h at 12 months), albeit in CHF patients with central sleep apnoea rather than OSA. We also accept that the duration of treatment in the present study may have been insufficient to demonstrate effects on cardiovascular endpoints, although previous work has shown benefits after only 4 weeks of treatment.[8,14,41,42]

We used the American Academy of Sleep Medicine definition of significant respiratory events which does not require oxygen desaturation when flow is measured by nasal pressure rather than thermal signal.[18] Our system recorded flow by nasal pressure in addition to thoracoabdominal movement and these signals were used to identify hypopnoeas. Hypopnoeas cannot be differentiated with certainty between central and obstructive from surface techniques and therefore we report events per hour rather than central and obstructive events separately. The study cohort showed a moderate degree of OSA with the majority of respiratory events being hypopnoeas, a proportion of which may have been central in nature. On the basis of these results, it is not possible to exclude benefit from auto-titrating CPAP in patients with concomitant severe OSA and CHF.

Conclusion

Auto-titrating nocturnal CPAP improves subjective daytime sleepiness but not other quality-of-life measures or markers of CHF severity in patients with CHF and OSA. These data suggest that symptomatic benefit in this patient group is achieved by alleviation of OSA rather than by improvement in cardiac function. The efficacy of CPAP as a treatment for patients with CHF and OSA may in part be limited by poor patient tolerability and compliance. On the basis of our findings, we believe that this approach is unlikely to provide a major therapeutic impact on the morbidity and mortality associated with CHF.

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Conflict of interest: N.J.D. was on the Medical Advisory Board of ResMed until May 2006 and is a stockholder of ResMed. All other authors declare no competing interests.

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