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The impact of continuous positive airway pressure treatment on the recurrence of atrial fibrillation post cardioversion: A randomized controlled trial

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ABSTRACT

Background: Observational data suggest that positive airway pressure (PAP) treatment of obstructive sleep apnea (OSA) can reduce the risk of recurrent atrial fibrillation (AF) post-direct current cardioversion (DCCV) or catheter ablation.
Methods: We conducted a study of adult patients with AF and sleep apnea, stratified by age and gender, who underwent successful DCCV to sinus rhythm, and who were randomized to receive PAP or usual care. Those with sleepiness, significant cardiac or respiratory disease were excluded. Patients were followed for ≤1 year. Primary outcome assessed was time to AF recurrence. Secondary outcomes included sleepiness and quality of life measured using the Epworth Sleepiness Scale (ESS) and Functional Outcome of Sleep Questionnaire (FOSQ) respectively.
Results: Of 1757 patients that were screened, 34 underwent polysomnography for this study, 25 of whom had an apnea-hypopnea index (AHI) >5/h. Twelve were randomized to PAP therapy and 13 to usual care. All eligible patients were found to have OSA. There were no differences in body mass index, blood pressure, ejection fraction, AHI, or nocturnal oxygen parameters between intervention and control groups (all $p > 0.05$). AF recurred in 25% of patients in the PAP and control groups, at 129.0 ± 166.5 versus 109.3 ± 73.2 days respectively, $p = 0.98$; there were no differences in ESS (5.8 ± 2.6 versus 5.7 ± 2.3; $p = 0.17$) or FOSQ (18.3 ± 1.5 versus 17.5 ± 1.9; $p = 0.26$) at follow-up.
Conclusions: This is the first randomized controlled trial assessing the impact of treatment of OSA on recurrence of AF post-DCCV, and did not detect a difference between those treated with PAP versus usual care.
Clinical trial registration: Clinicaltrials.gov, identifier number: NCT00263757.

1. Introduction

Obstructive sleep apnea (OSA) and atrial fibrillation (AF) are both highly prevalent conditions that are associated with adverse cardiovascular outcomes [1–3]. OSA and AF are common co-morbidities [4,5], and OSA may lead to the development of AF. Multiple potential pathophysiologic mechanisms have been described in this context, including intermittent hypoxemia/hypercapnia, negative intrathoracic pressure swings leading to left atrial stretch, autonomic activation, and blood pressure surges acutely, and systemic inflammation, vascular dysfunction and oxidative stress in the longer term [6,7]. Furthermore, there are epidemiologic and polysomnographic data supporting a possible temporal association between OSA and AF [8,9].

There is a growing body of literature suggesting that treatment of OSA with positive airway pressure (CPAP) may decrease the risk of recurrence of AF after direct current cardioversion (DCCV) and pulmonary vein isolation [10–12], although not all studies are consistent [13–16]. Notably, all of these studies are observational or retrospective in nature [17]. Furthermore, the distinction between OSA and central sleep apnea (CSA) is not always clear, and objective adherence to positive airway pressure (PAP) is often not determined or specified. To date, there are no prospective longitudinal randomized controlled trials reporting the effect of treatment of OSA on the development or recurrence of AF. Thus, the importance of screening and treatment for OSA in patients with AF remains a highly debated topic and recommendations from major cardiac societies are inconsistent [18,19].

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In this study, we sought to examine the impact of PAP treatment of sleep disordered breathing on the recurrence of AF post-DCCV in a randomized controlled trial.

2. Methods

This was a single-center randomized, parallel group study. Patients were randomized with the use of a computer program that stratified by gender and age to PAP therapy or to usual cardiovascular care including structured risk factor modification and observed for as long as one year. The primary outcome was time to recurrence of AF. Secondary outcomes included daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS) and quality of life as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ).

This study was approved by the Mayo Clinic Institutional Review Board (protocol number: 1254-05) and all participants gave written informed consent for this research. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Author S.M.C. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

2.1. Study subjects

Patients at least 18 years of age with AF who recently underwent DCCV to sinus rhythm within the last 30 days, documented by 12-lead electrocardiogram, were eligible for study participation. If no exclusion criteria were met (see Table 1), consented patients underwent attended, in-laboratory split-night polysomnography. At least 2 h of a diagnostic study determined the presence and severity of OSA and/or CSA, defined by an apnea-hypopnea index (AHI) of ≥5 per hour per current American Academy of Sleep Medicine guidelines [20–22]. Apneas were defined as a decrease in oronasal thermistor or alternate sensor amplitude by ≥90% from baseline for ≥10 s and hypopneas were defined as a decrease in nasal pressure transducer or alternate sensor signal by ≥30% from baseline for ≥10 s with a ≥4% oxygen desaturation from pre-event baseline [23]. The second half of the night was a therapeutic titration with PAP therapy, using either CPAP (for primarily obstructive events) or adaptive servoventilation (for primarily central and/or CPAP-emergent central events) sufficient to suppress disordered breathing events (AHI <5 per hour). A single device (Resmed™ VPAP Adapt SV), which could be programmed in either mode, was provided to patients randomized to PAP therapy at the settings determined during the in-laboratory titration. A trained polysomnogram technologist fitted the patients with a preferred interface and provided instructions on the device, the heated humidifier and to use the device every night, all night.

2.2. Follow-up

Patients were seen in the clinic setting within two weeks of randomization, then every 3 months for up to one year or until AF recurrence. PAP devices were downloaded at each visit and a 12-lead electrocardiogram was performed at each visit to assess for recurrence of AF.

2.3. Statistical methods

A power calculation was performed. Assuming a 1:1 treatment:control ratio, with 60% recurrence in controls, 40% recurrence in the treated group, 2 years accrual duration, minimum 1 year of follow-up per patient, a test significance level of $\alpha = 0.05$, and 90% power (to account for possible loss at follow-up), a total of 90 patients in each group would be required. AF-free survival was estimated using the Kaplan-Meier method. The univariate and multivariate associations of clinical factors with incident AF (such as AHI at baseline, age, body mass index) were estimated using the Cox proportional-hazards framework. Continuous variables were compared within groups using the paired *t*-test, and between groups using the unpaired *t*-test.

Table 1
Exclusion criteria.

	Exclusion criteria
1	Moderate to severe pulmonary disease (e.g. asthma, chronic obstructive pulmonary disease, pulmonary fibrosis)
2	Moderate to severe cardiac valvular disease
3	Congestive heart failure (LVEF <40%)
4	Previous diagnosis of sleep apnea or PAP treatment
5	Neuromuscular disease or residual neurologic impairment following stroke
6	Previous pulmonary vein ablation procedure
7	Pacemaker in situ
8	Uncontrolled hypertension (despite use of ≥3 antihypertensive medications)
9	Sleepiness, defined as an ESS score >10

Abbreviations: ESS, Epworth Sleepiness Scale; LVEF, left ventricular ejection fraction; PAP, positive airway pressure.

3. Results

A total of 1757 patients were screened; the most common reason for exclusion was current PAP therapy ($n = 293$, 17%), followed by implanted pacemaker ($n = 244$, 14%) and previous ablation procedure ($n = 236$, 14%). Thirty-four subjects consented to the study and underwent polysomnography, nine of whom had an AHI of <5 per hour and were therefore excluded, leaving 25 who were randomized, 12 to the PAP group and 13 to usual care.

There were no significant differences in baseline characteristics between the PAP group and the control group other than ESS and FOSQ scores (see Table 2). The ESS and FOSQ scores were statistically different between groups; by design neither group comprised of patients who were sleepy and the high FOSQ scores indicated that there was no significant sleep-related quality of life impairment at baseline. All ethnic backgrounds were recruited but only Caucasians were represented in the studied sample.

Although CSA was not an exclusion criterion, all of the eligible patients had predominant OSA. Twenty five percent had mild, 42% had moderate and 33% had severe OSA in the control group; 31% had mild, 31% had moderate and 38% had severe OSA in the PAP group. All patients randomized to PAP were managed in the CPAP mode, with a mean pressure of 8.0 cm water pressure (range 6.0–10.0). None of the patients received adaptive servoventilation as prescribed therapy. At 3 month follow-up, mean PAP use was 6 h and 16 min (60.1% of nights >4 h), and at 12 months, mean PAP use was 6 h and 11 min (71.8% of nights >4 h).

Of the 12 patients randomized to PAP therapy, 3 (25%) had recurrence of AF while on treatment (mean 129 ± 166.5 days) (see Fig. 1). Four (33%) patients completed one year of follow-up without AF recurrence. Five (42%) were lost to follow-up or withdrew. In the usual care group, 3 (25%) also had AF recurrence during follow-up (mean 109.3 ± 73.2 days). Five (38%) patients completed the one year of follow-up without AF recurrence. Two withdrew to seek PAP treatment and two were lost to follow-up. One developed an ESS score of >11 at month 6 and was therefore excluded from further observation and offered PAP therapy.

There were no significant differences in ESS scores in either group at follow-up. In the PAP group, the mean ESS score at baseline was 4.8 ± 2.1 and at follow-up was 5.8 ± 2.6 ($p = 0.31$). In the usual care group, the baseline ESS score was 7.3 ± 3.3 and at follow-up was 5.7 ± 2.3 ($p = 0.16$). There was no significant difference between ESS scores in the PAP and control groups at follow-up ($p = 0.17$). There

Table 2
Baseline patient characteristics.

Characteristic	Control ($N = 13$) Mean (SD)	PAP ($N = 12$) Mean (SD)	*p* value
Age, in years	64.6 (10.1)	63.5 (7.9)	0.76
Male gender no. (%)	7 (54)	7 (58)	–
BMI, kg/m^2	35.8 (7.0)	36.0 (8.4)	0.95
LVEF, %	57.3 (7.1)	58.1 (7.5)	0.78
LAVI, ml/m^2	35.6 (6.5)	40.6 (6.8)	0.10
AHI, events per hour	29.8 (21)	30.3 (19.5)	0.95
AHI range, events per hour	13.1–71.7	10.0–60.8	–
Obstructive apnea index, events per hour	13.8 (16.0)	13.7 (16.1)	0.98
Central apnea index, events per hour	0.6 (2.3)	0.8 (2.3)	0.83
Minimum SpO_2, %	80.1 (8.2)	80.2 (8.1)	0.97
Time with SpO_2 >90%, %	90.2 (14.1)	90.1 (14.2)	0.98
Baseline ESS score	7.3 (3.3)	4.8 (2.1)	0.04
Baseline FOSQ score	17.6 (1.6)	19.1 (0.7)	0.01

Abbreviations: AHI, apnea-hypopnea index; BP, blood pressure; BMI, body mass index; ESS, Epworth sleepiness scale; FOSQ, functional outcome of sleep questionnaire; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; PAP, positive airway pressure; SpO_2, oxyhemoglobin saturation.

was minimal impairment of sleep-related quality of life as measured by the FOSQ, although there was a statistical difference in the baseline values (mean score 19.1 ± 0.7 in the PAP group; 17.6 ± 1.6 in the usual care group, $p = 0.01$). There were no significant changes (18.3 ± 1.5 versus 17.5 ± 1.9 in PAP versus control groups respectively, $p = 0.26$) measured at follow-up.

There were no serious adverse events necessitating withdrawal of any patients from the trial.

4. Discussion

This is the first randomized controlled trial seeking to assess the impact of PAP therapy on the recurrence of AF after successful DCCV in patients with sleep disordered breathing. In this small but well-matched sample of non-sleepy patients with mostly moderate to severe OSA, we found no impact of PAP therapy on the primary outcome, namely time to AF recurrence following DCCV.

In order to best isolate the impact of sleep apnea on AF, we excluded patients with significant cardiopulmonary disease, including those with heart failure and chronic respiratory disorders. Patients had an overwhelming predominance of OSA as compared to CSA, despite a previous report of an increased incidence of CSA in those with AF and normal left ventricular systolic function [24]. All patients were treated with a CPAP mode of therapy, which controlled sleep apnea with suppression of the AHI to <5 per hour.

Since most would consider PAP to be standard therapy in sleepy patients with OSA, we limited recruitment to patients without excessive daytime sleepiness as defined by an ESS score of <11. We have previously shown that a large proportion of patients with AF and moderate to severe sleep apnea do not report excessive daytime sleepiness [25]. While this may partially explain why some patients withdrew from the PAP arm of the study, those that remained on treatment were remarkably adherent to therapy.

A large number of eligible patients were excluded from or did not consent to this study. More patients were excluded from enrollment because of current or previous PAP therapy for sleep disordered breathing ($n = 293$) than for any other criterion. This is probably a reflection of limitations in equipoise at our institution, where many patients with AF are referred for a sleep apnea evaluation, with a bias towards treatment.

In this small, highly selected sample of patients, firm conclusions about efficacy of PAP therapy in modifying AF outcomes cannot be drawn; arrhythmia recurrence was similar in each group. We have, however, demonstrated that reasonable adherence to PAP therapy is feasible in a minimally symptomatic cohort of cardioverted AF patients. Whether such success can be replicated in typical practice settings, particularly where resources to support PAP adherence may be more limited, is not known. It is also worth mentioning that we encountered no serious safety issues with randomization of patients.

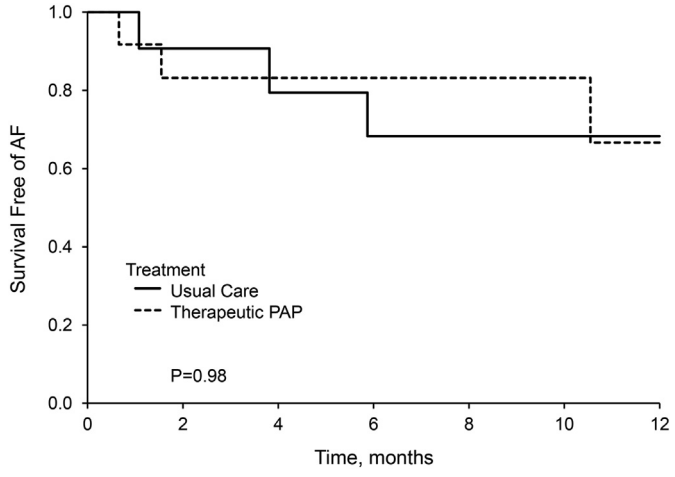

Fig. 1. Survival free of AF after direct current cardioversion in subjects on PAP versus those receiving usual care. Abbreviations: AF, atrial fibrillation; PAP, positive airway pressure.

The absence of sleepiness in the treated group merits discussion. Like other recently published trials of PAP therapy in OSA patients with cardiovascular disease [26,27], patients in this study were devoid of daytime sleepiness, arguably the most established indication for treatment of sleep apnea. In light of published trial results showing no significant cardiovascular benefit of PAP therapy in non-sleepy patients with OSA, selection of such patients by design raises serious questions about the utility of conducting further large, resource intensive trials that exclude OSA patients with daytime sleepiness. Indeed, in a prospective follow-up of patients with untreated OSA after myocardial infarction, only those with ESS score of ≥11 showed evidence of marked increase in risk of major adverse cardiovascular events [28]. Furthermore, in non-sleepy (ESS score <11) post-myocardial infarction patients with untreated moderate to severe OSA (AHI >15 per hour), the likelihood of a major cardiovascular event after 3 years was very similar to the major cardiovascular event risk in those without OSA (AHI <5 per hour).

4.1. Study limitations

As noted previously, this was a small and highly selected group of patients, with a significant number lost to follow-up. There are several other limitations to this trial. First, the best outcome measure to determine PAP efficacy in AF is unknown. Our selection of time to AF recurrence following cardioversion is straightforward but vulnerable to imprecision; furthermore, we only assessed for recurrence on periodic EKGs performed at the follow-up visits, thus, runs of asymptomatic AF may have been missed [29,30]. Time to AF recurrence may be too crude an indicator of disease activity and burden to capture more subtle potential effects of PAP therapy at the electrical, mechanical and structural levels [31]. It is possible that different results may have been seen if patients with paroxysmal AF determined by more intensive monitoring had been included. Second, this trial did not account or adjust for hypertension or the myriad of medications used for the management of AF. How such drugs interact with effects of PAP therapy in influencing the primary outcome is yet to be determined, but is likely important. Third, we need to consider efficacy of PAP therapy in prevention of AF. The triggers for AF are incompletely understood, and may consist of very brief episodes of neural and/or circulatory stressors, such as simultaneous vagal and sympathetic activation. Thus even though PAP use in the present study was longer than seen in other randomized trials, even brief but sudden cessation of PAP in the setting of obstructive apneas with significant hypoxemia, with reflex cardiac vagal and vascular sympathetic activation [32], may be adequate to trigger the onset of AF notwithstanding the use of PAP for much of the night.

In this regard, PAP use presumably begins around onset of sleep, and discontinuation likely occurs towards the latter part of sleep, when REM sleep, and hence obstructive apneas are most profound. Moreover, it is arguable whether sudden exposure to severe apneas and hypoxemia after hours of effective PAP therapy, is better or worse than no therapy (which may conceivably enable "preconditioning" of the cardiovascular system to hypoxemia). This may be especially important for an outcome such as AF, which could be abruptly triggered by an acute constellation of autonomic, hypoxemic, and mechanical stressors, despite preceding hours of normoxia enabled by adequate PAP therapy. All treated patients in this study utilized CPAP and not adaptive servoventilation; thus, the differing effects of these positive airway pressure devices on outcomes could not be assessed.

Finally, our study focused on a very select group of subjects. Our sample represented a very small proportion of the screened patients and those who had not been pre-selected for diagnosis and treatment of OSA. In addition, these findings cannot be extrapolated to the overall

population of AF patients with sleep apnea, especially not to those with predominant CSA, or low ejection fraction, or significant cardiopulmonary co-morbidities.

5. Conclusion

In conclusion, this is the first randomized controlled study of post-cardioversion recurrence of AF in treated versus untreated OSA patients, and shows no clear benefit of CPAP therapy. Our study shows limitations in equipoise with recruitment constrained by the high prevalence of already treated OSA in this patient population. Lack of benefit of PAP may be explained by suboptimal detection of AF recurrence, or by the absence of sleepiness in our patient population, or by the possible inadequacy of CPAP as a therapeutic strategy for prevention of AF. Finally, it may be that despite the extensive observational data implicating OSA as a cause of AF and its recurrence, it may be that treatment of OSA is simply unable to prevent AF recurrence after cardioversion.

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Disclosures

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Dr. Somers is supported by research grants from the National Institutes of Health (HL65176) and Philips Respironics Foundation (gift to Mayo Foundation). Dr. Somers is a Consultant for Respicardia, ResMed, U-Health, GlaxoSmithKline, Itamar and Bayer. He is an investigator on the SERVE-HF Steering Committee and is working with Mayo Health Solutions and their industry partners on intellectual property related to sleep and cardiovascular disease.

Dr. Caples and Dr. Friedman have no conflicts of interest to disclose.

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