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RESEARCH LETTER

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Right ventricular responses to CPAP therapy in obstructive sleep apnea: CMR analysis of the MOSAIC randomized trial

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Abstract

Effects of continuous positive airway pressure (CPAP) on right ventricular (RV) function in patients with untreated mild-to-moderate obstructive sleep apnea (OSA) are unclear. In this exploratory analysis of cardiac magnetic resonance (CMR)-derived indices of RV function in patients with minimally symptomatic OSA from the MOSAIC randomized control trial we found no effect of CPAP on RV CMR parameters. In those with lower RV ejection fraction and higher RV end-diastolic volume (EDV) at baseline, CPAP treatment appeared to improve RV function with a significant reduction in both RV EDV and RV end-systolic volume although between-group effects were not observed. These data suggest potential merit in a larger randomized study of CPAP in patients with mild-to-moderate OSA and a greater breadth of RV dysfunction.

KEYWORDS
CPAP, magnetic resonance scanning, myocardial function, obstructive sleep apnea, right ventricle

INTRODUCTION

Several mechanistic studies suggest a detrimental influence of obstructive sleep apnea (OSA) on the pulmonary vasculature, mediated by adverse effects of hypoxia and arousals.[1–3] However, current treatments for OSA including CPAP lack evidence of specific benefit on right ventricular (RV) function, especially in patients with untreated mild-to-moderate OSA.[4,5] The demonstration of benefits to RV function from CPAP outside of current OSA treatment indications could therefore have important implications for prioritizing OSA treatments with the potential for improved patient outcomes. We used randomized control trial data to conduct an exploratory analysis of responses in RV function

on cardiac magnetic resonance (CMR) in minimally symptomatic patients with mild-to-moderate OSA randomized to CPAP or standard of care for 6 months.

METHODS

The Multicentre Obstructive Sleep Apnoea Interventional Cardiovascular trial (MOSAIC trial) was conducted between May 2006 and February 2010: nine centers from the UK and one from Canada participated. Patients with minimally symptomatic OSA were randomized to either 6 months of CPAP therapy or standard care. The results of the trial and its full description have been published.[6] All patients were diagnosed with OSA using overnight respiratory polygraphy. Eligibility included an age range of 45–75 years old, proven OSA on sleep study with severity defined by >7.5 oxygen desaturations >4% per hour (oxygen desaturation index [ODI]), and insufficient daytime symptoms associated with OSA to warrant CPAP therapy.

This study analyzed a subset of patients who had a CMR scan at baseline and 6 months. All CMR scans were performed on a 1.5 Tesla MR system (40 mT/m; Siemens Healthcare). CMR scans were analyzed by experienced assessors, who were blinded to randomization status to reduce bias. Patients assigned to CPAP were instructed on the use of an auto-adjusting CPAP machine (Autoset S8, index ResMed) with detailed methods summarized elsewhere.[6]

Continuous variables were summarized as mean ± SD or median ± IQR. Pre and post-intervention comparisons were performed using paired sample Wilcoxon signed-rank test. Between groups, comparisons were performed with independent sample Kruskal–Wallis tests with post hoc pair-wise comparisons performed using the Mann–Whitney test. The treatment effect for outcomes was calculated by comparing the median change between groups. The primary outcome of this study was a change in RV ejection fraction (RVEF). Given a low level of clinically relevant RV dysfunction in the study population, RV variables were dichotomized by their median value and responses to CPAP were analyzed on an intention-to-treat analysis. Statistical analyses were performed using SPSS Statistics V27 (IBM Corp.). The trial was approved by the Oxford research ethics committee (REC 05/Q1604/159, and registered (ISRCTN 34164388).

RESULTS

Fifty-six patients had adequate quality CMR data for quantitative RV volume analysis. The CPAP intervention group included 31 patients (87.5% male, median age 59 years; IQR 12) and the standard-care group included 25 patients (87.5% male, median age 58 years; IQR 12). The total cohort had minimal day-time sleepiness with a mean Epworth Sleepiness Score (ESS) of 8.6 ± 3.6 and mild-to-moderate OSA on sleep study criteria at enrollment (ODI 16.2/h ± 13.5). Median CPAP usage in the interventional group was 3.16 h/night (IQR 1.65), 5 (16.1%) patients had 0.0 h/night usage having stopped CPAP and 12 (38.7%) patients had an average usage over 4 h.

Baseline and follow-up CMR data are summarized in Table 1 (intention-to-treat analysis). Due to significant variance in the average CPAP usage in the interventional group, treatment effects of CPAP were further assessed in patients with CPAP usage in whom average usage was over 4 h/night. In this group, significant correlations were observed between improvement in RVEF on CPAP with both improvements in ODI (mean 13.6/h to 0.8/h) on CPAP ($R^2 = 0.73$, $p = 0.012$) and improvement in mean SpO_2 (mean 94.7%–96.1%) on CPAP ($R^2 = 0.31$, $p = 0.011$).

DISCUSSION

This exploratory CMR study in minimally symptomatic patients with mild-moderate OSA evaluated a patient group who remain excluded from current OSA treatment guidelines that emphasize the requirement for daytime hypersomnolence. On an intention-to-treat basis, there was no effect of CPAP on right ventricular CMR parameters. However, in those with lower RVEF and higher EDVi at baseline, CPAP treatment of OSA appeared to improve RV function with a significant reduction in RV EDVi and ESVi although no between group-differences were observed. Despite minimally abnormal levels at baseline, serum BNP levels were also reduced in patients receiving CPAP therapy. In a patient population with predominant preservation in RV function, these results support the hypothesis that amelioration of nocturnal hypoxemia and intermittent respiratory events may contribute to improvement in RV function in minimally symptomatic patients with OSA. There may therefore be potential merit in a larger randomized study evaluating the effects of CPAP therapy not only in minimally symptomatic OSA but also in patients with a broader range of RV dysfunction at risk of progression to right heart failure.

Reports of CMR evaluation in minimally symptomatic patients with OSA are scarce, with previous studies focussing on patients with more severe OSA and obesity.[7,8] A previous sub-analysis from the MOSAIC study suggested CPAP carried minimal influence on the change in CMR-derived *left ventricular* parameters.[9] However, the effects of CPAP on RV function in patients with minimally symptomatic OSA remain unknown. Untreated OSA may potentially negatively influence

TABLE 1 Right ventricular CMR outcomes for study groups.

	Standard care					CPAP					
Outcome	***N***	**Baseline Mean (SD)**	**F/U Mean (SD)**	**% change**	***p***	***N***	**Baseline mean (SD)**	**F/U mean (SD)**	**% change**	***p***	**Overall treatment effect**
RVEF (%) total	25	55.6 (6.8)	57.6 (9.05)	2.2	0.124	31	58.7 (7.2)	60.4 (7.8)	4.1	0.313	1.5 (−3.0 to +6.7), $p = 0.85$
RVEF baseline category											
RVEF < median	12	50.2 (4.5)	55.2 (9.7)	9.4	0.065	15	52.8 (4.1)	59.4 (8.3)	12.9	**0.014**	
RVEF > median	13	60.5 (4.4)	58.9 (9.2)	− 2.9	0.504	16	64.2 (4.6)	61.3 (7.6)	−4.3	0.244	
RV EDVi/ml/m^2	25	68.8 (17.3)	68.1 (14.4)	−0.8	0.682	31	72.3 (16.6)	70.1 (13.6)	−2.1	0.405	−0.7 (−10.7 to +6.7), $p = 0.88$
RV EDVi baseline category											
RV EDVi < median	12	56.5 (9.0)	60.4 (8.5)	12.1	0.409	15	58.9 (9.8)	64.6 (11.5)	10.1	**0.043**	
RV EDVi > median	13	81.2 (13.4)	76.1 (14.6)	− 5.1	0.311	16	84.8 (8.9)	75.1 (13.8)	− 11.7	**0.007**	
RVESVi/ml/m^2	25	30.4 (8.6)	28.4 (7.3)	− 2.8	0.230	31	29.8 (8.5)	27.7 (7.3)	− 4.0	0.116	−2.2 (−6.7 to +2.5), $p = 0.79$
RVESVi baseline category											
RVESVi < median	12	24.3 (4.4)	24.0 (4.6)	2.3	0.593	15	22.7 (2.5)	24.7 (7.3)	7.8	0.244	
RVESVi > Median	13	37.2 (6.8)	33.1 (6.9)	− 8.2	0.230	16	36.4 (6.5)	30.7 (6.4)	−15.1	**0.004**	
BNP (pg/mL)	25	73.7 (85.9)	100.6 (184.5)	36.5	0.391	31	57.5 (58.9)	48.9 (35.4)	−14.8	**0.034**	− 5.3 (−16.7 to +12.2) $p = 0.39$
BNP baseline category											
BNP < median	12	32.2 (11.4)	45.2 (24.6)	40.4	0.060	15	27.2 (8.7)	31.7 (15.1)	16.2	0.173	
BNP > median	13	115.1 (107.5)	155.9 (257.3)	35.4	0.095	16	85.9 (71.5)	65.2 (41.4)	−24.1	0.098	

Abbreviations: BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance scan; F/U, follow-up; RV EDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; SD, standard deviation.

pulmonary vascular hemodynamics via several mechanisms. These include the upregulation of sympathetic nervous and renin-angiotensin-aldosterone axes following periods of overnight hypoxia acting as possible drivers of endothelial dysfunction,[10,11] exaggerated intrathoracic pressure rises generated during apnoeic episodes which generate large fluctuations in pulmonary artery pressure and chronic effects of intermittent hypoxia which predispose to hypoxic pulmonary vasoconstriction.[12–14] Conversely, the abolition of intermittent hypoxia in OSA using CPAP reduces both pulmonary vascular vasoreactivity to hypoxia and levels of soluble circulating selectins which correlate with OSA severity.[15,16] Put together, these findings suggest the RV may harbor raised susceptibility to the deleterious effects of OSA even in patients with less symptomatic disease.

Despite the suggested benefits of CPAP treatment on RV function, there are important limitations to these data. Patient numbers who completed CMR evaluation were low in a population with broadly preserved RV function at study entry with an unknown contribution from left ventricular diastolic disease. The study was also not powered to detect differences in RVEF with the potential introduction of bias through both participation bias and dichotomization of groups. Furthermore, extrapolation of our findings to patients with established RV dysfunction is also not possible. Additionally, the follow-up duration may not have been sufficient to detect significant changes in RV function with therapy. The CPAP machines used in this study did not utilize remote monitoring which may have impacted CPAP therapy usage,[17] and should be considered in future trials. Despite these limitations, this exploratory analysis supports consideration of further investigation of the effects of CPAP therapy in patients with mild-moderate OSA and RV dysfunction potentially within a randomized study where a longer follow-up duration may allow for observation of differences in the progression of RV remodeling with and without treatment.

AUTHOR CONTRIBUTIONS

All authors fulfilled the ICMJE criteria for authorship and approved the manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

The trial was approved by the Oxford research ethics committee (REC 05/Q1604/159, and registered (ISRCTN 34164388). No further local ethical approval was sought in undertaking this retrospective review.

DATA AVAILABILITY STATEMENT

Data is available on request due to privacy/ethical restrictions.

GUARANTORS

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