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Cardiac remodelling in patients with atrial fibrillation and obstructive sleep apnoea

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2024-002718).

To cite: Hunt TEF, Traaen GM, Aakerøy L, *et al*. Cardiac remodelling in patients with atrial fibrillation and obstructive sleep apnoea. *Open Heart* 2024;**11**:e002718. doi:10.1136/openhrt-2024-002718

Received 19 April 2024
Accepted 19 August 2024

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ABSTRACT

Background Obstructive sleep apnoea (OSA) can cause left atrial (LA) and left ventricular (LV) remodelling, which is linked to atrial fibrillation (AF). Whether continuous positive airway pressure (CPAP) can reverse LA and LV remodelling in patients with OSA and paroxysmal AF (PAF) has yet to be studied. We assessed the impact of CPAP treatment on LA and LV size and function in patients with OSA and PAF before and after catheter ablation.

Methods In a randomised controlled trial, we screened patients with PAF for OSA. We enrolled patients with an Apnoea–Hypopnoea Index ≥15/hour. The burden of AF was monitored by an implantable loop recorder in all patients. Patients were then randomised to CPAP treatment or standard care. Transthoracic echocardiography was performed at baseline and after 6 and 12 months to assess LV and LA function and remodelling with advanced echocardiographic imaging techniques.

Results We enrolled 109 patients (63±7 years, body mass index 29.6±4.3, 76% men). 83 patients were scheduled for pulmonary vein isolation (PVI) and 26 for clinical follow-up only. 55 patients were randomised to CPAP and 54 to standard care. The burden of AF decreased significantly in patients who underwent PVI irrespective of treatment with CPAP (p for difference ≤0.001). Patients in the study group had LV ejection fraction (LVEF) and LV global longitudinal strain (GLS) within the normal range, increased LA Volume Index (LAVI), LA volume (by speckle tracking) and decreased LA reservoir strain at baseline. We did not observe any improvement in LVEF, GLS, LAVI, LA volume or LA reservoir strain in either group during the 12 months of follow-up.

Conclusions In patients with PAF and OSA, treatment with CPAP was not associated with reverse LA remodelling within 12 months of follow-up.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Observational data suggest that sleep apnoea treatment may reduce the recurrence rate and total burden of atrial fibrillation (AF).

WHAT THIS STUDY ADDS

⇒ This study is part of the A3 study, a prospective controlled trial in patients with paroxysmal AF (PAF) and obstructive sleep apnoea (OSA) who were randomised to continuous positive airway pressure (CPAP) treatment or standard care, all with continuous AF monitoring by a loop recorder.

⇒ We found no significant difference in echocardiographic measurements of cardiac remodelling between patients with AF and OSA, treated with CPAP or not, in addition to standard AF treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The prevalence of AF and OSA is high, with consequences and costs for the individual patient and society.

⇒ We found that CPAP treatment effectively reduced Apnoea–Hypopnoea Index in patients with PAF and OSA. However, this was not reflected in the improvement of cardiac structure or function.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by upper airway obstruction and interrupted breathing during sleep. The pathophysiological disturbances of OSA, such as negative intrathoracic pressure, increased vagal and sympathetic activity, hypercapnia and hypoxaemia, may contribute to electrical and myocardial remodelling of the heart.[1 2] Patients with OSA often have diastolic dysfunction with left ventricular (LV), left atrial (LA) and right atrial (RA) remodelling.[2–4] Studies have shown that OSA is associated with the development of atrial fibrillation (AF), the burden of AF and complications of AF.[5–7] LA and RA dilatation are strongly associated with the maintenance of AF. In OSA, continuous positive airway pressure (CPAP) treatment may reduce the overall burden of AF by improving oxygen levels, reducing myocardial strain

during sleep and potentially reversing cardiac remodelling.[7]

The effectiveness of CPAP therapy in reducing cardiovascular events in patients with OSA remains a debated issue despite its well-documented efficacy in alleviating OSA symptoms and improving sleep quality.

While prior observational studies have demonstrated its benefits,[7 8] a recent randomised controlled trial[9] has yielded less optimistic outcomes, failing to show a significant reduction in cardiovascular events among CPAP users compared with standard care.

Noteworthy, observational studies have suggested that CPAP therapy might reverse LV, LA and RA remodelling in OSA patients.[3 10] Moreover, investigations in patients with AF have hinted at potential cardiac remodelling effects from antiarrhythmic treatment or pulmonary vein isolation (PVI).[11–13] These observations underscore the need for rigorous exploration and validation of treatment modalities in OSA and AF, elucidating their precise cardiovascular effects.

To the best of our knowledge, the effect of CPAP on cardiac structure and function has not been assessed in a controlled setting in patients with OSA and AF. Therefore, we aimed to assess the effect of CPAP treatment on cardiac remodelling in patients with OSA and paroxysmal AF (PAF). We hypothesised that treating OSA with CPAP would reverse LV, LA and RA remodelling in addition to what might be achieved by catheter ablation.

METHODS

Study design and patient selection

The design of the AF, apnoea and airway pressure (A3) trial has been published previously.[14] Briefly, the A3 study was a randomised trial designed to evaluate the impact of CPAP treatment on the AF substrate before and after PVI. The trial was conducted at two cardiology centres in Norway: Oslo University Hospital and Trondheim University Hospital. The first part of the trial assessed the effect of 5 months of CPAP treatment compared with standard care on the burden of AF in patients with OSA and PAF.[14] The second part evaluated the impact of treatment with CPAP compared with standard care on the recurrence of AF in those patients proceeding to PVI.[15] In the present study, we report the effect of CPAP treatment on cardiac remodelling as assessed by advanced echocardiography.

Patients with PAF who were referred for PVI underwent a two-night respiratory polygraph test at baseline to diagnose OSA. Patients with an Apnoea–Hypopnoea Index (AHI) of ≥15 events/hour were eligible for this study, defined as moderate to severe sleep apnoea.[16] Exclusion criteria included previously diagnosed OSA, unstable coronary disease, transitory ischaemic attack, stroke, LV systolic dysfunction (ejection fraction (EF) <45%), severe obesity (body mass index >40 kg/m^2), severe excessive daytime sleepiness (EDS) (Epworth sleepiness scale score >15) or the present use of amiodarone. Eligible patients were assessed for 1 week for CPAP tolerance (Air Sense 10 Auto set, ResMed). The use of CPAP for at least 4 hours per night was regarded as adequate adherence. An implantable loop recorder (ILR) (Reveal LINQ, Medtronic) was implanted in patients who tolerated the CPAP and consented to randomisation. After 4 weeks of registration of AF burden, patients were randomised to CPAP, added to standard AF care or to standard care only. The ILR calculated the absolute time in AF. The study measured the percentage of time patients spent in AF per month for 18 months. For comparison, we also followed a reference group of patients with no OSA or mild OSA (AHI 0 to <15 events/hour, n=21) referred for PVI for PAF. The results are reported in accordance with the guidelines outlined in the Consolidated Standards of Reporting Trials statement. The trial is registered at ClinicalTrials.gov (NCT02727192) online supplemental file 2. For an overview of patient recruitment and study procedures, see online supplemental figures 1 and 2.

A significant strength of our study is the continuous monitoring of AF burden with an ILR. This method provides detailed insights into the temporal patterns and burden of AF, which were crucial for accurate assessment of the impact of CPAP treatment on AF.

Echocardiography, blood pressure and core laboratory analyses

Transthoracic echocardiography was used to assess cardiac remodelling at three different time points during the study. The first evaluation occurred 1 month after the study commenced as a baseline before randomisation for treatment with or without CPAP. The second assessment was conducted 6 months after the study began (5 months after randomisation and 1 day before PVI in patients undergoing catheter ablation). The final assessment was conducted 12 months after the study started (6 months after PVI in patients who underwent catheter ablation). The patients in the non-OSA reference group also had echocardiograms at baseline, 6 and 12 months after the study started.

Two-dimensional echocardiography, M-mode imaging and Doppler echocardiography were performed according to the European Society of Echocardiography's guidelines as stated in the A3 protocol. In addition to standard ultrasonic techniques, speckle-tracking imaging was obtained to assess LV and LA function and remodelling. Vivid e9 ultrasound scanners (GE-Vingmed Ultrasound, Horten, Norway) were combined with an M5s-d probe. All analyses were performed offline (EchoPAC 204, GE Vingmed Ultrasound) by one operator blinded to all clinical information except height, weight and heart rate.

We used traditional echo parameters and strain parameters to evaluate cardiac structure and function according to guidelines.[17] Measurements were indexed for body surface area when appropriate.

LA function was assessed using two-dimensional speckle tracking analysis, automated functional imaging of the LA (AFI LA) and EchoPAC 204 software. The software automatically obtained the LA maximal volume (LAVmax)

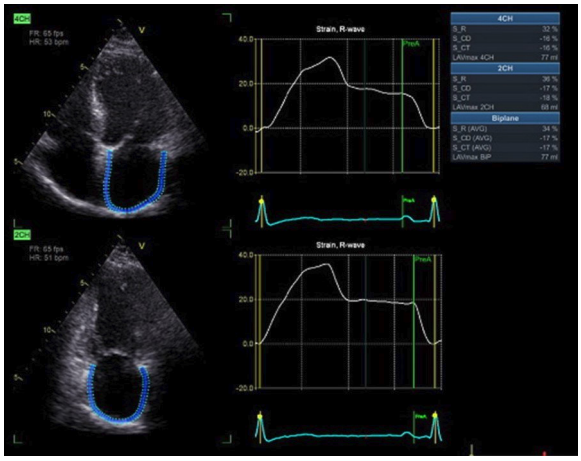

Figure 1 The image represents the analysis of left atrial (LA) strain and the LA maximal volume using specialised software, a two-dimensional speckle-tracking analysis of LA function (AFI LA, EchoPAC 204, GEVingmed, Horten, Norway). The left panel of the image displays the apical four-chamber and two-chamber views in biplane format. The middle section of the image shows the atrial strain curves, while the right section displays the LA strain and volume calculations. AFI, automated functional imaging.

and strain results by analysing the LA longitudinal strain in both four-chamber and two-chamber views. The frame before the mitral valve opening was used as a reference point to identify the end-systolic LA volume measurements[18–20] (figure 1).

Blood pressure was measured by the auscultatory method three times in the 'office' using a manual device. An appropriately sized cuff was positioned on the left upper arm while the patient was seated in a relaxing position. The two closest readings were averaged.

Blood samples were analysed by standard procedures. N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were determined by an electrochemiluminescence immunoassay (Roche proBNP II).

Sample size and statistical analysis

The A3 trial was powered to detect a 25% reduction in an assumed time in AF of 34%±12%.[21] After PVI, we expected AF to recur in 70% of the patients in the standard care group. We would need 28 patients in each group to identify a 50% reduction in the recurrence of AF in the CPAP group with a power of 80% and a significance level of 5%. The A3 trial was not explicitly designed to assess cardiac remodelling. The limited number of patients increases the risk of overlooking a true treatment effect. However, we assume that a reduction in the LA volume index of at least 5 mL/m^2 is required for a meaningful reverse remodelling to have occurred; this substudy comprising 104 patients had a reasonable 60% power to detect such a difference at an alpha of 5% given the observed data distribution.

Continuous variables are expressed as means±SD for normally distributed data or medians (IQR). Dichotomous variables are expressed as numbers and percentages. Using univariate and multivariate logistic regression analysis, we calculated ORs and 95% CIs for AF recurrence. Repeated measurements of continuous variables were compared by independent t-tests, one-way analysis of variance (ANOVA) or the Mann-Whitney U test as appropriate. Categorical variables were compared using χ^2 or Fisher's exact test. Repeated measures ANOVA was used to compare the results over time, and post hoc comparisons were performed using the Bonferroni correction. Results before and after PVI were analysed using paired t-tests or the paired Wilcoxon signed-rank test. Pretest and post-test analyses with analysis of covariance and repeated-measures ANOVA were used to find the change in the difference in two or more groups with two or more continuous variables.

RESULTS

Study population

We screened 579 patients referred for PVI for PAF. A two-night polygraph test revealed that 158 patients (42%) had moderate to severe OSA. However, 39 patients were excluded because they failed the CPAP tolerance test, and 10 patients were excluded for other reasons.

Of the 109 eligible patients, 55 were randomised to treatment with CPAP and 54 to standard care. One patient dropped out after being randomised, and 4 dropped out after 6 months of follow-up, leaving 108 patients in the full analysis set. The baseline clinical characteristics were not significantly different between the two groups (table 1).

Among the 55 patients randomised to CPAP and 54 randomised to standard care, 37 and 46, respectively, were scheduled for PVI (online supplemental figure 1).

Effect of CPAP treatment on sleep apnoea and blood pressure

In the CPAP treatment group, the AHI decreased from 26.7±12.7 events/hour at inclusion to 2.2±1.7 events/hour after 6 months (by the time of PVI) and 1.7±1.3 events/hour at 12 months (p<0.001), indicating good sleep apnoea control (measured by the CPAP machine at every visit, ResScan data). The overall mean duration of CPAP use was 3.9±1.5 hour/night during the first 5 months and 4.3±1.9 hour/night during the last 6 months. There were no significant differences between groups regarding the changes in systolic and diastolic blood pressure over time (p=0.41 and p=0.26) (table 2).

Echocardiographic measurements at 6 and 12 months

Baseline data were well balanced between intervention groups (table 2). LVEF and global longitudinal strain (GLS) were within the normal range. However, LA Volume Index (LAVI) was found to be moderately elevated in both the CPAP group and the standard care group at baseline, and the atrial strain was found to be decreased.

LVEF and GLS did not change in any group from baseline to 6 months or 12 months of follow-up (table 2).

Table 1 Baseline characteristics of OSA study participants

Characteristics	Total (n=108)	OSA-CPAP (n=54)	OSA-standard care (n=54)
Baseline			
Age (years)	63±7	63±7	62±8
Male sex	82 (76)	39 (72)	43 (80)
BMI (kg/m²)	29.6±4.3	29.5±4.5	29.4±4.0
CHA_2DS_2-VASc score	1.1±1.0	1.2±0.9	1.1±1.1
EHRA score	2.9±1.6	2.6±0.9	2.7±0.8
Haemoglobin 'g/L'	14.7±1.1	14.6±1.3	14.7±0.9
Creatinine (µmol/L)	79±15	77.1±13.0	80.3±6.1
Medical history			
Time in AF before PVI (years)	8.1 (1–38)	8.0 (1–38)	8.2 (1–38)
Hypertension	44 (41)	21 (39)	23 (43)
Diabetes mellitus	8 (7)	4 (7)	4 (7)
Myocardial infarction	8 (7)	4 (7)	4 (7)
Stroke/transient ischaemic attack	6 (6)	4 (7)	2 (4)
Sleep history			
Epworth total score	7.4±3.2	7.3±3.3	7.4±3.1
Apnoea–Hypopnoea Index	27 (15–86)	27 (15–86)	26 (15–60)
Oxygen Desaturation Index	27 (13–90)	27 (14–90)	26 (13–57)
Medication			
Beta-blocker	63 (58)	27 (50)	36 (67)
Calcium channel blocker	17 (16)	8 (15)	9 (17)
Flecainide	31 (29)	17 (32)	14 (30)
PVI			
PVI CRYO	54 (65)	20 (54)	34 (74)

Values are presented as mean±SD, median, IQR, n (%) or years.
AF, atrial fibrillation; BMI, body mass index; CHA_2DS_2-VASc score, Score for AF Stroke Risk; CRYO, cryoballoon; EHRA, European Heart Rhythm Association; PVI, pulmonary vein isolation.

However, LV end-diastolic volume and LV end-systolic volume decreased from baseline to 12 months follow-up. There was no between-group difference in the reduction of LV volumes.

LV diastolic function and LA indices did not change over time in either treatment arm (table 2). Across treatment arms, NT-proBNP increased from 140 (IQR, 205) ng/L at baseline to 170 (IQR, 226) ng/L at 6 months follow-up (PVI) (p=0.01). However, there was no between-group difference in the change (p=0.57). At 12 months follow-up, NT-proBNP had decreased significantly to 117 (IQR: 110) ng/L (p=0.01) irrespective of CPAP treatment allocation (p for between-group difference in change=0.56). The change across both treatment arms probably reflected the reduced AF burden after PVI.

LAVI or LAVmax by speckle tracking (AFI LA) did not change significantly by 6-month or 12-month follow-up in the two groups, and there were no between-group differences. There was no improvement in the LA reservoir strain at 6-month or 12-month follow-up or any difference between the groups (table 2 and figure 2).

After undergoing PVI, both the CPAP and standard care groups showed a significant decrease in AF burden. We have previously for these patients reported that the AF burden in patients with CPAP treatment before PVI was 6.4% and 0.6% 3–12 months after PVI. In the patients with standard care treatment, AF burden was 6% before PVI and 0.6% 3–12 months after PVI), (p<0.001 for both; p for between-group difference 0.94).[15] However, despite this reduction in AF, we observed no improvements in cardiac remodelling parameters (LVEF, GLS, LAVI, LA volume, LA reservoir strain) during the 12-month follow-up online supplemental file 5.

Cardiac remodelling in patients with and without OSA

The study showed no significant differences in cardiac structure and function changes between patients with or without OSA (table 3). However, patients without OSA had higher GLS scores, smaller LA volume and lower LA

Table 2 Cardiac structure and function by treatment

	OSA-CPAP (n=54)					OSA-standard care (n=54)					Intergroup difference	
	Baseline	6 months FU	P value*	12 months FU	P value†	Baseline	6 months FU	P value*	12 months FU	P value†	P value‡	P value§
LVEF (%)	58±5	59±5	0.55	59±5	0.90	57±6	57±5	0.81	57±6	0.94	0.43	0.70
GLS avg. (%)	−18.0±−3.0	−18.5±3	0.93	−19.3±2.3	0.92	−18.0±3.4	−18.9±3.3	0.77	−18.5±1.1	0.62	0.35	0.65
LV EDV index (ml/m^2)	136±36	133±34	0.75	120±27	0.03	136±38	128±37	0.31	120±33	0.08	0.54	0.23
LV ESV index (mL/m^2)	60±17	61±18	0.70	58±19	0.06	62±20	60±18	0.70	55±17	0.12	0.48	0.91
HR (sec)	65±22	66±18	0.98	66±15	0.78	59±11	60±18	0.66	62±13	0.49	0.60	0.75
LVCO (L/min)	6.5±1.8	6.4±2.2	0.91	6.8±2.1	0.12	5.7±1.5	5.7±1.4	0.46	5.9±1.7	0.60	0.13	0.44
E/A ratio	1.2±0.5	1.1±0.3	0.05	1.1±0.4	0.60	1.2±0.5	1.2±0.4	0.18	1.3±0 .9	0.92	0.52	0.50
E/e'	8.2±1.9	8.6±1.8	0.93	8.1±2.5	0.82	8.7±2.5	9.0±2.7	0.83	7.4±2.5	0.11	0.95	0.77
DecT (ms)	203±46	199±57	0.62	197±67	0.69	189±43	206±52	0.09	207±30	0.20	0.59	0.23
LA diameter (mm)	37±4	39±7	0.15	37±10	0.66	38±5	36±4	0.90	37±7	0.97	0.81	0.76
LAVI (mL/m^2)	38±8	36±10	0.16	38±12	0.37	39±12	37±11	0.20	38±12	0.32	0.69	0.62
LAVMax by ST (mL)	49±14	49±17	0.93	48±14	0.81	52±17	49±16	0.10	48±18	0.10	0.39	0.93
LA reservoir strain (%)	30±8	31±9	0.78	32±9	0.15	28±7	30±7	0.09	30±6	0.11	0.12	0.41
TRMax PG	22±6	24±6	0.07	22±5	0.31	23±5	21±7	0.66	22±6	0.02	0.93	0.37
RVDd focused (mm)	44±4.5	44±11	0.68	46±6	0.11	46±6	43±12	0.42	45±5	0.24	0.27	0.85
TAPSE (cm)	2.4±0.4	2.2±0.4	0.76	2.3±0.4	0.35	2.3±0.3	2.2±0.4	0.74	2.2±0.5	1.0	0.68	0.67
RA Areal (cm^2)	20.2±5.4	21.8±7	0.27	20±6.0	0.49	19.2±4.4	20.2±2.8	0.04	19±3.7	0.54	0.65	0.40
Systolic BP (mm Hg)	134±15	142±20	0.05	135±15	0.98	135±19	134±14	0.55	136±16	0.68	0.78	0.41
Diastolic BP (mm Hg)	78±9	80±11	0.87	77±10	0.54	79±11	79±10	0.90	80±12	0.62	0.44	0.26

Values are given as mean±SD.
*P value for within-group change from baseline to 6 months follow-up.
†P value for within-group change from baseline to 12 months follow-up.
‡Represents the average difference between CPAP and standard care at baseline and 6 months follow-up.
§Represents the average difference between CPAP and standard care at baseline, 6 and 12 months follow-up.
BP, blood pressure; CPAP, continuous positive airway pressure; E/A ratio, E: early transmitral flow velocity, A:atrial transmitral filling velocity; ESV, End Systolic Volume; FU, follow-up; GLS, global longitudinal strain; LA, left atrium; LAVI, Left Atrial Volume Index; LAVMAX by ST, left atrial maximal volume by speckle tracking; LVCO, Left Ventricular Cardiac Output; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnoea; RA, right atrium; RVD, right ventricular diameter; TAPSE, Tricuspid annular plane systolic excursion.

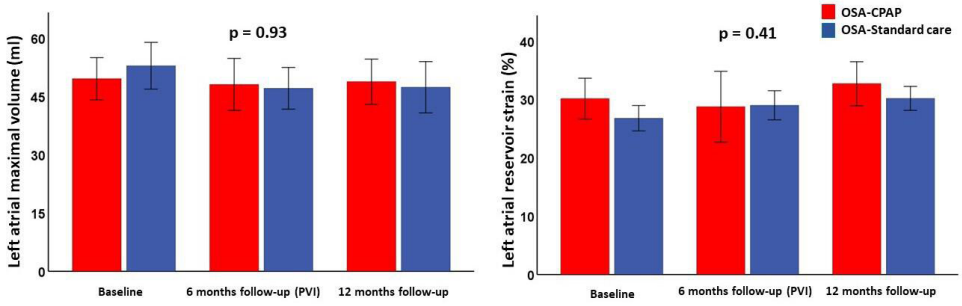

Figure 2 The figure shows the results of the study on the effect of continuous positive airway pressure (CPAP) treatment on left atrium (LA) function in patients with obstructive sleep apnoea (OSA) and PAF. The study used left atrial maximal volume by speckle tracking and LA reservoir strain (%) measured in a biplane with the AFI LA method at baseline 6 and 12 months follow-up to compare the outcomes of patients who received CPAP treatment and those who received standard care. The results were presented in a bar chart model, and it was found that CPAP treatment did not have a significant effect on the CPAP group compared with the OSA standard care group. The p value represents the average intergroup difference between CPAP versus standard care at baseline, 6 and 12 months follow-up after inclusion. The error bars represent ±2 SE. AFI, automated functional imaging; PAF, paroxysmal atrial fibrillation; PVI, pulmonary vein isolation.

reservoir strain at baseline (table 3), probably reflecting that the non-OSA reference patients had less atrial disease and less atrial remodelling than the OSA patients at the time they were referred for catheter ablation.

DISCUSSION

In this study, we performed a comprehensive echocardiographic evaluation of cardiac remodelling in a randomised trial that focused on the effect of CPAP on patients with PAF and OSA. We hypothesised that treatment for OSA would improve structural and functional parameters. However, treatment with CPAP did not reverse cardiac remodelling in patients in spite of a significant reduction in AF burden postablation.

These results are concordant with previous results of the A3 trial; however, they are contrary to some other studies. We have previously reported that treatment with CPAP did not affect the burden of AF in these patients.[14] Moreover, allocation to CPAP treatment did not affect outcomes at 12 months follow-up after PVI and did not reduce the burden of AF beyond PVI and standard care,[15] despite good adherence to CPAP therapy.

The absence of significant differences in blood pressure and NT-proBNP levels between the groups (table 2) supports these findings. Pengo *et al*[22] conducted a meta-analysis on patients with OSA, demonstrating that CPAP treatment resulted in a modest average reduction in office systolic and diastolic arterial blood pressure of approximately 2 mm Hg when compared with controls. Our results are numerically in concordance with these findings.

Echocardiography is the primary method used to evaluate the structure and function of the LA. The LA volume index (LAVI) has been the preferred measurement in the past, but it has limitations as it is based on a static volumetric measurement and does not reflect dynamic LA aspects. A novel LA strain method has been introduced to assess LA function to address these limitations. Additionally, new software has been developed (AFI LA), which is simpler, has good repeatability and has fewer image quality issues.[18 20]

Several studies have demonstrated that OSA is associated with atrial remodelling, suggesting a role for OSA management in AF. Thus, previous observational studies,[3 4 10] as well as a randomised trial,[23] have demonstrated reverse remodelling after treatment with CPAP, in contrast to our results. This can be due to several factors, including differences between the study populations regarding age, sex, obesity, duration of OSA, comorbidities, alcohol consumption, as well as the severity of OSA.[7] Moreover, Colish *et al*[24] and Kim *et al*[23] included patients with more severe OSA (an AHI of 63/hour and 55/hour, respectively). They observed a significant improvement in remodelling indexes following 3 months of CPAP therapy. Similarly, Vural *et al*[10] noted a correlation between OSA severity and improvement in LA function after 12 and 24 weeks of CPAP therapy. Their findings suggest that better CPAP adherence among severe OSA patients could significantly mitigate cardiovascular consequences associated with severe OSA.

The severity of OSA, as indicated by AHI, could also play a role in future research.

Our findings also contrast the CANPAP trial,[25] which found improved LV EF with CPAP therapy in patients with central sleep apnoea and heart failure. However, our results concord with the substudy of the SAVE trial,[26] which investigated CPAP therapy in patients with OSA and cardiovascular disease.

This substudy did not observe an improvement in EF after 6 months of CPAP treatment. Whereas our study patients did not have heart failure, all had AF, which was absent in the CANPAP as well as in the SAVE trial substudy. Although CPAP treatment effectively improves AHI in patients with OSA, its impact on cardiac remodelling may be more diverse. Where the SAVE trial included patients in secondary prevention, only a few had a previous myocardial infarction or stroke in the present study. These observations challenge the presumed

Table 3 Cardiac remodelling in patients with and without OSA

	OSA (n=108)					Non-OSA (n=21)					Intergroup difference	
	Baseline	6 months FU	P value*	12 months FU	P value†	Baseline	6 months FU	P value*	12 months FU	P value†	P value‡	P value§
LVEF (%)	58±5	58±5	0.83	58±6	0.57	56±4	57±4	0.92	58±6	0.94	0.43	0.88
GLS avg (%)	−18.2±1.5	−18.8±2.3	0.74	−20.3±1.8	0.42	−21.1±2.2	−21.2±1.7	0.57	−22.1±1.8	0.62	0.35	0.28
LV EDV index (ml/m^2)	137±35	130±33	0.60	122±30	0.01	143±21	137±23	0.10	122±21	0.08	0.54	0.85
LV ESV index (mL/m^2)	61±18	62±16	0.59	56±18	0.02	67±10	64±10	0.02	58±12	0.12	0.48	0.80
HR (s)	62±17	63±18	0.73	63±13	0.48	61±13	58±11	0.82	64±10	0.49	0.60	0.89
LVCO (L/min)	6.2±1.8	6.0±1.9	0.67	6.4±1.9	0.33	5.9±1.4	5.7±0.9	0.39	6.1±1	0.60	0.52	0.73
E/A ratio	1.2±0.5	1.1±0.4	0.03	1.2±0.7	0.58	1.2±0.4	1.3±0.5	0.11	1.1±0.2	0.92	0.56	0.56
E/e'	8.3±2.4	8.8±2.3	0.88	7.7±2.5	0.23	7.3±2.2	8.0±2.0	0.80	6.8±1.9	0.11	0.95	0.56
DecT (ms)	196±44	202±55	0.43	202±75	0.23	230±68	202±51	0.91	219±47	0.20	0.59	0.39
LA diameter (mm)	39±5	38±0.6	0.30	37±9	0.52	41±5	41±5	0.74	40±5	0.97	0.69	0.73
LAVI (mL/m^2)	38±10	37±10	0.06	37±10	0.74	39±10	38±13	0.81	38±14	0.32	0.74	0.96
LA volume by ST (mL)	51±16	49±16	0.14	48±16	0.08	64±16	66±18	0.07	63±16	0.50	0.06	0.14
LA strain (%)	28±7	30±9	0.48	31±8	0.03	31±7	31±8	0.47	33±6	0.11	0.74	0.39
DecT (ms)	196±44	202±55	0.43	202±75	0.23	230±68	202±51	0.10	219±47	0.20	0.59	0.39
TRMax PG	22±6	23±7	0.39	22±5	0.30	19±8	21±7	0.56	21±5	0.02	0.65	0.36
RVDd Focused (mm)	46±5	44±11	0.38	40±15	0.60	46±5	43±12	0.35	45±5	0.24	0.27	0.70
RA Areal (cm^2)	20.7±4.9	21.0±4.0	0.02	19.1±5.0	0.13	22.3±4.2	22.5±5.3	0.62	19.5±4.0	0.54	0.65	0.48

Values are given as mean±SD.
*P value for within-group change from baseline to 6 months follow-up.
†P value for within-group change from baseline to 12 months follow-up.
‡Represents the average difference between OSA and non-OSA at baseline and 6 months follow-up.
§Represents the average difference between OSA and non-OSA at baseline, 6 and 12 months follow-up.
E/A ratio, E: early transmitral flow velocity, A:atrial transmitral filling velocity; ESV, End Systolic Volume; FU, follow-up; GLS, global longitudinal strain; LAVI, left atrial volume index; LVCO, Left Ventricular Cardiac Output; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnoea; RA, right atrium; RVD, right ventricular diameter.

cardiovascular advantages of CPAP therapy, underscoring the need for further research.

Excessive daytime sleepiness (EDS) is considered a contributing factor to the complications of OSA. In the study of Xie *et al*,[27] patients with moderate to severe sleep-disordered breathing and EDS had a higher risk of major adverse cardiac events compared with those without EDS. Our patients did not exhibit EDS, which may partly explain the lack of effect on cardiac remodelling. More pronounced daytime sleepiness in the Xie *et al* study might explain why an effect was observed there.

Kim *et al* reported that LV function by GLS improves with CPAP treatment.[23] In addition to a more severe OSA in this study, patients with arrhythmia were excluded. Moreover, this study is limited by the relatively small sample size and the short duration of follow-up, which may have influenced the results. Also, daytime sleepiness was not reported. Our larger study included patients with AF only. AF affects cardiac mechanics and could, therefore, potentially influence GLS and thus mask a positive effect of CPAP on LV function. These findings challenge the presumed cardiovascular advantages of CPAP therapy, underscoring the need for further research on this topic.

The well-known association between AF and OSA may also influence the results. OSA is a known risk factor for AF, and observational studies have found that treating OSA with CPAP can help maintain sinus rhythm. However, these studies used intermittent rhythm monitoring and only self-reported use of CPAP.[28 29] The study by Eysenck *et al*[30] in patients with persistent AF and sleep-disordered breathing with an AHI ≥15 provides valuable insight into this area, highlighting the potential for AF interventions with cardioversion or PVI to restore sinus rhythm and reduce nocturnal respiratory events with a significant reduction in the AHI. In contrast, we have previously, in a larger study, observed that PVI had no additional effect on patients with moderate to severe OSA who were randomised to CPAP compared with standard care.[15]

In previous studies, researchers have primarily relied on methods developed to evaluate the left ventricle to measure LA remodelling. However, these methods may be quite challenging due to the thinness of the LA wall and the complex muscle fibre pathways, the oval foramen and the pulmonary vein ostia, which can all affect the accuracy of measurements. To overcome these limitations, we used a new atrial software to evaluate LA remodelling (AFI LA, EchoPAC 204). This approach has not been used before in patients with OSA and AF.

OSA and AF are associated with obesity, hypertension, diabetes and a sedentary lifestyle. These risk factors synergistically promote cardiac remodelling and may confound the effect of a treatment that targets sleep apnoea only. Larger randomised trials of longer duration may be necessary to characterise the complex relationship between OSA and AF and to clarify the clinical relevance of CPAP treatment.

Limitations of the study

The strengths of our study are the randomised controlled design, continuous rhythm monitoring and continuous CPAP therapy monitoring, comprehensive echocardiographic assessments and the relatively homogeneous patient population with PAF and sleep apnoea. However, our study also has some limitations. The sample size was relatively small, and the study groups ended up slightly skewed in numbers between the OSA-CPAP and OSA-standard care groups due to the exclusion of more patients randomised to the CPAP group who did not proceed to PVI.

We cannot exclude the possibility that a larger study might have yielded different results. We made many comparisons, which increases the risk of finding differences by chance. The participants in our trial were exclusively of white European origin and predominantly male, limiting the generalisability of our results. The trial had an open-label design, which may have introduced bias, but all echocardiograms were analysed by an expert echocardiographer blinded to other patient data. Our results may not be representative of the entire population of AF and sleep apnoea, particularly not for those with predominantly central sleep apnoea, low LV EF, EDS or significant cardiopulmonary comorbidities.

CONCLUSION

In patients with OSA and PAF, treatment with CPAP did not reverse LV, LA or RA remodelling within 12 months, neither before nor after PVI. These results suggest that CPAP is unlikely to improve LV and LA structure and function in patients with AF and OSA.

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Acknowledgements We acknowledge our patients' time, commitment, and contributions to this study. Additionally, we thank Senior Consultant Per-Kristian Svardal from the Department of Hospital-specific clinical solutions for valuable assistance with installing echo programs and addressing all technical issues.

Contributors All authors have conformed to the ICMJE requirements for manuscripts. All authors fulfil all criteria for authors. LG: principal investigator of the A3 study and guarantor. TEFH and SA had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. TEFH, GMT, BØ, SA, SS, O-GA, HA, JPL and LG contributed to the conception or design of the work. TEFH, GMT, LA, RJM, CB, BØ, HA, SS, JPL, KB, ØHL, TH-V, AKA, LG, O-GA, LG and SA contributed to the acquisition, analysis or interpretation of data for the work. TEFH, KB and SA completed the statistical analysis. TEFH and SA drafted the manuscript. All authors critically revised the

manuscript, gave final approval to the version to be published and agree to be accountable for all aspects of the work, ensuring integrity and accuracy.

Funding This research was performed at the Department of Cardiology, Oslo University Hospital, Norway. It was supported by a public research grant from the Research Council: The South-Eastern Norway Health Authority and the Norwegian Research Council (#257888 SysAfib and #309762 Precision Health Center for optimised Cardiac Care (ProCardio)).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Norwegian South-East Regional Ethics Committee (REK, ID: 2015/436). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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