The effect of atrial fibrillation intervention on nocturnal respiratory events in elderly patients with persistent AF

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Disclosures:

None of the authors have anything to disclose

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Keywords

• Atrial fibrillation • Sleep-disordered breathing • Rhythm control

Abstract

Background: Sleep-disordered breathing (SDB) and atrial fibrillation (AF) are associated. This study investigated the impact of AF intervention on 6 month home sleep testing data.

Methods: Sixty-seven patients (aged 66 to 86, 53% male) with persistent AF were randomized (1:1:1) to direct current cardioversion (DCCV) (22 patients), permanent pacemaker (PPM) + atrioventricular node ablation (AVNA) + DCCV (22 patients) or AF ablation (23 patients). Baseline and 6 month multichannel home sleep tests with the Watch-PAT200 (WP) (Itamar Medical Lts., Caesarea, Israel) were recorded. Implantable cardiac monitors (ICMs) (Medtronic Reveal XT (Minneapolis, MN, USA) in the DCCV and AF ablation groups, and PPM Holters in the 'pace and ablate' group were utilised to assess cardiac rhythm beat-to-beat throughout the study period.

Results: The prevalence of moderate-to-severe SDB (apnoea-hypopnoea index (AHI) ≥15/h) was 60%. At 6 months there was no change in AHI, Epworth sleepiness score (ESS), sleep time, %REM sleep, respiratory desaturation index (RDI) or central apnoeic events.

Twenty-five patients (15 AF ablation, 9 DCCV and 1 following DCCV post-AVNA) maintained SR at 6 months confirmed on ICMs in these patients. AHI fell from 29.8±26.6/h to 22.2±20.4/h; p=0.049.

Conclusions: SDB is highly prevalent in patients with persistent AF. Restoration of sinus rhythm, and the associated long-term recovery of haemodynamics, is associated with a significant reduction in AHI. This implicates reversal of fluid shift from the lower limbs to the neck region, a key mechanism in the pathogenesis of SDB.

Introduction

Sleep-disordered breathing (SDB) and atrial fibrillation (AF) are associated[1-3]. The prevalence of SDB in AF patients ranges from between 21% to over 90% and increases with age[4-6].

Risk factor management is critical in AF treatment[7, 8]. Patients with obstructive sleep apnoea (OSA) have >30% greater risk of AF recurrence after catheter ablation than patients without[9]. However, the efficacy of catheter ablation for AF is similar between patients without OSA and patients with OSA treated with continuous positive airway pressure (CPAP) treatment[9, 10]. Thus, detection of obstructive sleep apnoea (OSA) and appropriate treatment is a prime target for intervention to improve AF treatment outcomes[11].

Recent studies have demonstrated a reduction in nocturnal respiratory events (apnoeas and hypopnoeas) with successful DCCV and AF ablation procedures at short-term follow-up[12, 13]. The long-term effects of randomised AF intervention on sleep data was evaluated at baseline and at 6 months utilising the Watch-PAT200 (WP) (Itamar Medical Lts., Caesarea, Israel). This device has been shown to have high correlation with the gold-standard assessment of SDB, overnight polysomnography (PSG)[14-16]. Implantable cardiac monitors (ICMs) provided continuous beat-to-beat heart rhythm information for all patients.

Methods

Study design and participants

This study was performed at Eastbourne General Hospital, East Sussex Healthcare NHS Trust and was approved by the national ethics committee. It is an observational study based upon 67 participants with symptomatic persistent AF taking part in the CAPAPAF study (NCT02528604). The rationale and design of the CAPAPAF study have been described previously[17]. Inclusion criteria were patients aged over 65 years with a diagnosis of

symptomatic persistent AF made on the basis of medical history and physical examination. All patients gave written informed consent. The aims of the study were to determine the impact of randomised AF intervention on sleep data at 6 months. Post hoc analyses assessed the effect of successful restoration of SR on sleep data. Finally, within subject analyses were performed on a limb by limb basis. All patients underwent baseline and 6-month Watch-PAT200s (WPs). Twenty-two patients were randomized to DC cardioversion, 22 to PPM and atrioventricular node ablation (AVNA) and 23 underwent AF ablation according to the CAPAPAF study protocol[17].

WatchPAT200 sleep monitor

The WP (Itamar Medical Ltd., Caesarea, Israel) is a class IIa, FDA-approved home sleep test correlating closely with the gold standard investigation of OSA, the overnight polysomnogram (PSG) [18], see Figure 1. There are 6-channels: (1) PAT (peripheral arterial tone), (2) pulse oximetry, (3) heart rate, (4) actigraphy, (5) body position and (6) snoring intensity (dB). All patients underwent a WP at baseline and 6 months following randomised AF intervention. Data included sleep time (minutes), % REM sleep, apnoea-hypopnoea index (AHI) and respiratory desaturation index (RDI).

An obstructive apnoea was defined as cessation of airflow for ≥ 10 seconds with continuing abdominal and thoracic movements [19]. A hypopnea was a reduction of breathing followed by desaturation of ≥ 3% and/or an arousal [19]. AHI was mean number of apnoeas and hypopneas per hour of sleep and ≥ 5/h was defined as OSA. RDI included respiratory-effort related arousals (RERAs); arousals from sleep that do not meet the definition of apnoeas or hypopnoeas, but do disrupt sleep. Thus,

RDI = (RERAs + hypopneas + apnoeas) x 60 / Total Sleep Time (in minutes)

A central apnoea was defined as a cessation of airflow for 10 seconds without respiratory movements. A WP test was performed and baseline and at 6 months with both the patient and investigator blinded to the results of the baseline test.

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) was used to determine daytime sleepiness at baseline and follow-up [20]. The ESS is a self-administered questionnaire with eight questions relating to the risk of falling asleep in different situations, with answers scoring from 0 to 3. Excessive daytime sleepiness was defined as an ESS of ≥11[21].

Statistical Analysis

Analyses were performed using SPSS statistical software (version 22, IBM Corp, New York, USA). Data are expressed as percentages for discrete variables and as mean ± standard deviation for continuous variables. Continuous variables were compared by ANOVA. Categorical comparisons were compared using Chi-square analysis and non-parametric inferential statistical analyses were performed using Mann-Whitney U and Wilcoxon signed-rank test. Multivariable analyses determined the effect of restoration of SR on key sleep data across the study cohort. A p-value of less than 0.05 was considered significant.

Results

Ninety-three patients with no prior history of OSA were screened and 25 patients were excluded: 10 patients were unable to commit to the duration of the study due to logistical difficulties, 6 patients refused consent and 9 patients were found to have long-standing persistent or permanent AF. Sixty-seven patients were included in a per-protocol analysis of

patients undergoing DCCV, PPM and AVNA or AF ablation for their persistent AF. Baseline demographics are displayed in Table 1.

Baseline Watch-PAT200 (Table 2a)

At baseline, the prevalence of SDB (defined as apnoea-hypopnoea index (AHI) ≥5/h) was 95%. Twenty-three patients (34%) had mild SDB (AHI 5-14/h), 18 (27%) had moderate SDB (AHI 15-29/h) and 22 (33%) had severe SDB (AHI >30/h). There was no difference in mean AHI score between different therapies.

6 month Watch-PAT200 (Table 2b)

There were no significant differences between the 3 groups for 6 month sleep data.

Change in sleep data for the overall study population (Table 3)

Change in principal sleep data for the overall population showed no significant differences in AHI, Epworth score, %REM sleep, RDI, total respiratory events (RDI) or central apnoeic events ($p>0.05$).

Patients with successful restoration of sinus rhythm at 6 months (Table 4a and Figure 2)

Twenty-five patients (15 AF ablation, 9 DCCV and 1 following DCCV post-AVNA) were in AF at baseline and SR at 6 months confirmed on ICM. There were no significant differences in sleep time, %REM sleep or central apnoeic events, ESS or RDI between groups. AHI fell from 29.8±26.6/h to 22.2±20.4/h; $p=0.05$.

AF Ablation Sleep Data

There were no significant differences in AHI, ESS, sleep time, %REM sleep, or central apneic events 6 months post AF ablation ($p>0.05$).

Fifteen of 23 (65%) patients in the AF ablation limb were in SR at 6 months follow-up. There were no significant changes in AHI, sleep time, %REM sleep or central apnoeic events. There was a trend to reduction in RDI (31.2±19.6/h to 21.9±20.7/h; $p=0.06$). ESS reduced significantly (9.4±6.3 at baseline and 6.2±4.9 at 6 month follow-up; $p=0.03$), see Table 4b.

DCCV Sleep Data

There were no significant differences in AHI, ESS, %REM sleep, RDI or central apnoeic events at 6 months. There was a significant reduction in sleep time (361.5±98.1 minutes vs. 337.6±105.4 minutes; $p=0.004$).

Nine of 22 (41%) patients were in SR at 6 month follow-up. There were no significant change in AHI, or central apnoeic events. There was a trend to reduction in RDI (35.5±24.8/h to 24.6±13.5/h; $p=0.09$), see Table 4c.

PPM and AVNA + DCCV Sleep Data

There was a significant increase in AHI (24.0±15.9/h at baseline to 28.4±14.7/h; $p=0.004$), ESS (6.8±4.6 to 7.0±4.1; $p=0.005$), total respiratory events (RDI) (139.3±107.6 to 157.1±87.2; $p=0.0001$) and central apnoeic events (78.44±87.2 to 91.7±81.2; $p=0.0001$). There was no change in RDI. One out of 22 patients (5%) were in SR at 6 months.

Discussion

This is the first study to analyse the impact of standard AF intervention on sleep data utilising beat-to-beat cardiac rhythm monitoring with ICMs. A high prevalence of SDB in patients with persistent AF was found compared to the general population[22]. Successful restoration of SR resulted in a significant reduction in AHI at 6 months. These findings confirm previous studies which have demonstrated an immediate reduction in AHI 24h following DCCV and 1 week post AF ablation[12, 13] and provide insight into the pathophysiology of SDB and link with AF.

It is well established that OSA contributes to the development of AF and a number of potential mechanisms have been proposed to explain the association such as intermittent hypoxia, recurrent arousals and increased negative intrathoracic pressure[23]. This can result in increased sympathetic nerve activity and oxidative stress, and possible electrical and mechanical remodelling of both atrial and the left ventricle[23]. This is the first study to demonstrate improvement in AHI with long-term restoration of sinus rhythm confirmed with ICMs. Improving haemodynamic status and cardiac function with long-term restoration of SR could reduce fluid displacement from the lower limbs to the neck region of the body, a key mechanism in the pathogenesis of OSA[24-26]. This could, in turn, lead to decreased airway congestion, improving oxygen saturations and consequently provide and explanation for the decrease in AHI observed.

PPM and AVNA + DCCV resulted in an increase in AHI, central apnoeic events and ESS. Chronic ventricular pacing following AVNA can result in pacing-induced dyssynchrony and impairment of left ventricular function[27, 28] and has been shown to exacerbate fluid shift to the upper airway overnight[29, 30]. In addition, the majority of the PPM and AVNA + DCCV patients (21/22) remained in AF at 6 months follow-up and therefore did not experience the haemodynamic benefits of prolonged SR. The reduction in overnight oxygenation is the

likely explanation for the increase in ESS because increased desaturation overnight has been shown to correlate with ESS[31]. The increase in central apnoeic events is interesting and also implicates disruption of haemodynamics in patients chronically paced. Oscillation of $PaCO_2$ around the apnoeic threshold is the key component in CSA development and perpetuation seen in previous studies of heart failure patients.[32] It is possible that this was also the pathophysiological mechanism in the PPM and AVNA limb because data have shown that pacing the heart can accelerate progression of heart failure by inducing ventricular dyssynchrony [33] The resulting repeated episodes of apnoea, hypoxia, re-oxygenation, and arousal throughout the night are the factors leading to the pathophysiological consequences of CSA[32]. This mechanism is exacerbated by heart failure with reduced left ventricular function because stimulation of pulmonary vagal afferents by high cardiac filling pressures induces hyperventilation leading to hypocapnia[34] and this study suggests a similar pathogenesis in patients chronically paced following PPM and AVNA[32], a treatment known to increase cardiac filling pressures in animal models and to cause a degree of cardiac dyssynchrony[35].

The ESS is a measure of daytime sleepiness introduced in 1991[36]. The ESS was <10 at baseline and therefore within normal limits. The results of this study confirm previous data showing that typical SDB symptoms, such as daytime sleepiness, do not correlate with its presence in AF patients[21, 37]. The results highlight the importance of screening for SDB in patients with AF even in the absence of indicative symptoms because ESS cannot be relied upon to identify SDB within patients with AF[12]. Despite the normal range in ESS it is interesting that a significant reduction was observed after successful restoration in SR with AF ablation because this could be related to effective treatment of persistent AF. Persistent AF patients have been found to have more depressed mood with increased lethargy than those with paroxysmal or no AF[38]. Therefore, abolition of persistent AF with AF ablation

could offset the associated lethargy and fatigue associated with the condition. This is reflected in the lower ESS observed.

Conclusions

SDB is highly prevalent in patients with persistent AF more than 65 years of age yet these patients do not display typical features of daytime fatigue and elevated ESS. Correct diagnosis and treatment of SDB improves AF outcomes and medical professionals should consider screening all patients with persistent AF for this co-morbidity[6].

In patients who achieve SR a reduction in AHI is seen. These findings implicate the importance of the improvement in haemodynamic status in SR. The reduction in ESS is likely due to a reduction in RERAs which are closely associated with daytime somnolence. Successful AF ablation reduces ESS whereas PPM and AVNA results in an increase in AHI and ESS because of the detrimental effects of this treatment on haemodynamic and left ventricular function secondary to chronic pacing. PPM and AVNA also increases central apnoeic events probably because this treatment can lead to increased cardiac filling pressures, stimulating pulmonary vagal afferents leading to hypocapnoea, the key mechanism in CSA.

Study Limitations

1) The study implicates the mechanism behind the interaction between AF and SDB but further prospective studies analysing biochemical markers (for example measuring aldosterone levels pre- and post-AF intervention) could better reveal the pathophysiology behind the interaction.
2) There was a numerical reduction in RDI with successful DCCV and AF ablation (p values of 0.09 (95% CI -2.2 to 23.9) and 0.06 (95% CI -0.62 to 19.2) respectively. However, the confidence intervals were wide for these comparisons and a larger study

sample might show a significant difference in sleep data between these rhythm control treatments.

3) Two of 22 patients in the PPM and AVNA limb had CRT devices. Given the improvement in cardiac synchrony associated with CRT, it is possible that these devices could adversely affect sleep data to a lesser degree but a randomised prospective study with a larger patient population would be needed to test this hypothesis.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Table 1 Baseline demographics of per protocol study population. TIA: transient ischaemic attack; IQR: interquartile range

	DCCV	PPM and AVNA	AF ablation	Total
n	22	22	23	67
Mean age (years)	72	76.5	75	74.5
Gender (female)	10 (45%)	9 (41%)	12 (52%)	31 (46%)
CVA/TIA	2 (9%)	1 (5%)	3 (13%)	6 (9%)
Hypertension	18 (82%)	18 (82%)	16 (70%)	52 (78%)
Coronary artery disease	2 (9%)	7 (32%)	4 (17%)	13 (19%)
Diabetes	0 (0%)	2 (9%)	4 (17%)	6 (9%)
Mean CHA2DS2Vasc score	2.95	2.90	4.04	3
Vascular disease	4 (18%)	6 (29%)	5 (22%)	15 (22%)
COPD	3 (14%)	3 (14%)	2 (9%)	8 (12 %)
CKD	10 (45%)	11 (50%)	15 (65%)	36 (54%)
Valvular heart disease	3 (14%)	4 (18%)	5 (22%)	12 (18%)
LA Diameter (cm)	4.1±1.0cm	4.33±0.8cm	4.12±1.1cm	4.19cm
LA Area (cm^2)	23.2±7.0cm^2	25.0±5.9cm^2	22.35±6.5cm^2	23.66cm^2

There were no significant differences in baseline demographics between the three groups; $p>0.05$

Table 2a Baseline WP Sleep Data

	DCCV	**PPM and AVNA**	**AF Ablation**	**P Value**
Neck circumference (cm)	41.2±3.9	42.2±4.3	38.8±5.6	0.089
BMI	30.1±4.6	29.6±4.9	27.8±6.7	0.361
Epworth score	10.7±4.8	7.2±4.8	8.1±6.4	0.109
Sleep time (minutes)	361.5±98.1	357.7±106.0	383.7±110.2	0.668
% REM Sleep	19.3±7.1	16.7±9.6	19.0±8.0	0.562
AHI (/h)	29.4±21.5	24.0±16.0	27.3±25.9	0.726
Total number of respiratory events (RDI)	155.3±119.6	151.0±110.0	174.4±106.8	0.760
Total number of respiratory events (AHI)	144.2±119.3	139.3±107.6	137.9±109.3	0.981
Desaturation event number	129.2±204.5	91.1±86.9	78.5±84.5	0.444
Total desaturations	2468.8±2583.4	2816.1±2699.3	2194.6±2794.2	0.748
Mean desaturations	28.0±7.6	29.90±4.6	27.70±8.3	0.536
Central apnoeic events	79.0±124.3	78.4±87.2	39.1±54.4	0.599
No sleep disordered breathing (AHI<5/h) (%)	1/22 (4.5%)	1/22 (4.5%)	1/23 (4.3%)	0.995
Mild sleep disordered breathing (AHI 5-14/h) (%)	7/22 (31.8%)	5/22 (22.7%)	11/23 (47.8%)	0.168
Moderate sleep disordered breathing (15-29/h) (%)	3/22 (13.6%)	10/22 (45.5%)	5/23 (21.7%)	**0.022**
Severe sleep disordered breathing (AHI > 30/h) (%)	10/22 (45.5%)	6/22 (27.3%)	6/23 (26.1%)	0.277

Table 2b 6 Month WP Sleep Data

	DCCV	**PPM and AVNA**	**AF Ablation**	**P Value**
Neck circumference (cm)	40.76±4.535	40.48±3.371	39.65±6.293	0.468
BMI	29.32±6.432	29.77±5.080	28.65±7.604	0.968
Epworth score	9.00±4.461	7.33±4.258	6.87±5.337	0.174
Sleep time (minutes)	337.55±105.418	359.68±79.725	356.04±87.027	0.934
% REM Sleep	21.86±6.560	17.00±8.147	22.91±7.861	0.051
AHI	26.91±15.976	26.82±14.876	27.00±22.401	0.778
Respiratory events (RDI)	153.59±112.345	160.00±84.261	146.65±133.093	0.399
Respiratory events (AHI)	148.41±114.180	156.50±85.131	141.22±135.046	0.389
Desaturation event number	86.86±74.314	108.18±77.630	96.22±121.847	0.295
Total desaturations	2156.10±1867.678	3370.00±2712.759	2706.61±3531.737	0.148
Mean desaturations	26.29±8.026	30.27±6.288	27.00±6.755	0.111
Central apnoeic events	41.38±45.019	86.73±68.070	72.91±126.913	0.028
No sleep disordered breathing n (%)	1/22 (4.5%)	0/22 (0%)	2/23 (8.7%)	0.376
Mild disordered breathing n (%)	4/22 (18.2%)	4/22 (18.2%)	6/23 (26.1%)	0.755
Moderate sleep disordered breathing n (%)	8/22 (36.4%)	11/22 (50%)	10/23 (43.5%)	0.629
Severe sleep disordered breathing n (%)	9/22 (40.9%)	7/22 (31.8%)	5/23 (21.7%)	0.388

Table 3 Key sleep data at baseline and 6 months post AF intervention

	Baseline	**6 Months Post Intervention**	**P value**
AHI (/h)	27.0±21.5	26.9±18.0	0.470
RDI (/h)	29.6±18.6	26.8±15.7	0.421
Epworth score	8.7±5.5	7.7±4.7	0.121
Sleep time (mins)	368.0±104.0	351.2±90.4	0.283
%REM Sleep	18.4±8.2	20.6±7.9	0.140
Total RDI respiratory events	160.6±111.0	153.±110.5	0.434
Total AHI respiratory events	140.4±110.5	148.6±112.1	**0.0001**
Total central apnoeic events	69.2±97.6	71.9±90.1	0.864

Table 4b Baseline and 6 month WP data for 15 patients with successful restoration of sinus rhythm following AF ablation

	Baseline (in AF)	**6 Months Post Intervention (in SR)**	**P value**
AHI (/h)	29.53±29.022	23.93±23.747	0.278
Epworth score	9.43±6.297	6.21±4.870	0.029
Sleep time (mins)	383.13±102.284	369.27±64.116	0.503
%REM Sleep	19.36±7.365	21.93±8.748	0.292
RDI (/h)	31.2±19.6	21.9±20.7	0.06
Central apnoeic events	27.60±32.837	34.00±51.971	0.619

Table 4a Baseline and 6 month WP data for 25 patients with successful restoration of sinus rhythm

	Baseline (in AF)	**6 Months Post Intervention (in SR)**	**P value**
AHI (/h)	29.8± 26.6	22.2± 20.4	**0.049**
RDI (/h)	32.8±21.2	22.9±18.1	**0.010**
Epworth score	9.1± 5.4	6.5± 4.4	**0.007**
Sleep time (mins)	372.2± 91.1	349.5± 83.2	0.824
%REM Sleep	19.9± 7.0	21.1± 8.9	0.824
Total RDI respiratory events	189.6± 25.4	125.7± 118.7	**0.006**
Total AHI respiratory events	156.7± 132.6	118.5± 121.2	0.081
Total central apnoeic events	72.4± 132.6	38.0± 17.7	0.268

Table 4c Baseline and 6 month WP data for 9 patients with successful restoration of sinus rhythm following DCCV

	Baseline (in AF)	**6 Months Post Intervention (in SR)**	**P value**
AHI (/h)	29.78±25.366	20.44±15.379	0.079
Epworth score	8.86±3.848	7.14±3.976	0.143
Sleep time (mins)	353.67±77.311	321.33±108.291	0.246
%REM Sleep	21.00±7.464	19.88±7.661	0.719
RDI (/h)	35.5±24.8	24.6±13.5	0.09
Central apnoeic events	117.20±182.994	42.00±65.742	0.233

Table 6 Baseline and 6 month WP data for 9 patients with successful restoration of sinus rhythm following DCCV

	Baseline (in AF)	**6 Months Post Intervention (in SR)**	**P value**
AHI (/h)	29.78±25.366	20.44±15.379	0.079
Epworth score	8.86±3.848	7.14±3.976	0.143
Sleep time (mins)	353.67±77.311	321.33±108.291	0.246
%REM Sleep	21.00±7.464	19.88±7.661	0.719
RDI (/h)	35.5±24.8	24.6±13.5	0.09
Central apnoeic events	117.20±182.994	42.00±65.742	0.233

Table 5 Baseline and 6 month WP data for 15 patients with successful restoration of sinus rhythm following AF ablation

	Baseline (in AF)	**6 Months Post Intervention (in SR)**	**P value**
AHI (/h)	29.53±29.022	23.93±23.747	0.278
Epworth score	9.43±6.297	6.21±4.870	0.029
Sleep time (mins)	383.13±102.284	369.27±64.116	0.503
%REM Sleep	19.36±7.365	21.93±8.748	0.292
RDI (/h)	31.2±19.6	21.9±20.7	0.06
Central apnoeic events	27.60±32.837	34.00±51.971	0.619