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Intrathoracic pressure swings induced by simulated obstructive sleep apnoea promote arrhythmias in paroxysmal atrial fibrillation

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Aims There is preliminary evidence for a link between obstructive sleep apnoea (OSA) and arrhythmias such as paroxysmal atrial fibrillation (PAF) and sudden cardiac death but underlying mechanisms remain largely unknown.

Methods and results In this interventional crossover study, we evaluated whether intrathoracic pressure changes, induced by simulated OSA, trigger premature cardiac beats, and alter measures of ventricular repolarization [QT_c and T_{peak}-to-T_{end} ($TpTe_c$) intervals] in patients with PAF. 12-Lead-electrocardiograms were recorded continuously in 44 patients, while simulating obstructive apnoea (Mueller manoeuvre, MM), obstructive hypopnoea (inspiration through a threshold load, ITH), end-expiratory central apnoea (AP), and during normal breathing (NB) in randomized order. The prevalence of OSA in these 44 patients was assessed by a sleep study. Atrial premature beats (APBs) occurred more frequently during MM (55% of patients) and ITH (32%), but not during AP (14%), compared with NB (9%) ($P < 0.001$, $P = 0.006$ and $P = 0.688$, respectively). Mueller manoeuvre led to a significant prolongation of QT_c and $TpTe_c$ intervals (+17.3 ms, $P < 0.001$ and +4.3 ms, $P = 0.005$). Inspiration through a threshold load significantly increased QT_c (+9.6 ms, $P < 0.001$) but not $TpTe_c$. End-expiratory central apnoea did not alter QT_c and $TpTe_c$ intervals. According to the sleep study, 56% of patients had OSA (apnoea hypopnoea index ≥ 5).

Conclusion Simulated OSA induces APBs which may be important in patients with PAF, because the majority of episodes of PAF has been shown to be triggered by APBs. Simulated OSA leads to a significant prolongation of ventricular repolarization.

Keywords Atrial fibrillation • Obstructive sleep apnoea • Atrial premature complexes • Sudden cardiac death • Intrathoracic pressure changes

Introduction

Obstructive sleep apnoea (OSA) is a highly prevalent sleep-related breathing disorder affecting up to 30% of middle-aged male adults in Western countries.[1] Obstructive sleep apnoea is characterized by repetitive interruption of ventilation during sleep caused by a collapse of the upper airway resulting in apnoea and hypopnoea. Apnoea and hypopnoea lead to oxygen desaturations and frequent arousals from sleep leading to increased daytime sleepiness and increased sympathetic output. There is preliminary evidence from observational studies that OSA may be related to cardiac arrhythmias such as atrial premature beats (APBs) and ventricular premature beats (VPBs), second degree atrioventricular block, sinus arrest, as well as atrial fibrillation (AF). Quite how OSA might increase the susceptibility to cardiac arrhythmias, including AF, is not known. The increased sympathetic drive and impaired sympatho-vagal balance seen in patients with OSA may be important. Recent evidence from animal models and model studies in healthy humans suggests

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What's new?

- This study is the first to show that intrathoracic pressure changes induced by simulated OSA promote substantial rates of APBs and non-sustained atrial arrhythmias in patients with PAF.
- Simulated OSA was further associated with significant increases in QT_c and $TpTe_c$ interval times, thus potentially increasing the susceptibility to sudden cardiac death.
- In our sample of patients with PAF, 56% had OSA based on a sleep study.
- The severity of OSA (apnoea hypopnoea index) was independently associated with left atrial end-systolic diameter as assessed by echocardiography in multiple regression analysis.

that the considerable sub-atmospheric pressures generated within the thorax during obstructive apnoea may distend cardiac structures, such as the atria and may thereby alter electrophysiology.[2–4]

It is unknown if intrathoracic pressure changes occurring during obstructive apnoea and hypopnoea could trigger APBs in patients with paroxysmal atrial fibrillation (PAF) and may therefore be a risk factor for recurrent AF.[5] Therefore, we aimed to address this uncertainty by investigating the acute effects of intrathoracic pressure changes induced by simulated obstructive apnoea and hypopnoea on heart rhythm in patients with PAF, who are currently in sinus rhythm. We hypothesized that simulated obstructive apnoea and hypopnoea in patients with PAF would trigger APBs and alter measures of ventricular repolarization.

Methods

Study population and design

Patients with an electrocardiogram (ECG)-documented history of PAF within the last 12 months were recruited in the outpatient clinic of the Cardiovascular Centre, University Hospital of Zurich, Switzerland. Subjects were eligible for the study if they were aged between 18 and 75 years, had sinus rhythm at the time of ECG recordings and did not meet the following exclusion criteria: therapy with amiodarone or dronedarone, severe structural heart disease, history of AF ablation, mental or physical disability precluding informed consent or compliance with the protocol. The trial was performed according to the Declaration of Helsinki, was approved by the University Hospital of Zurich Research Ethics Committee (KEK-ZH-Nr. 2012-0310) and registered (NCT01796080). All patients gave written informed consent.

Measurements

Breathing manoeuvres

Room temperature and lighting were set at the same level for all measurements. The patients were carefully instructed in the performance of the breathing manoeuvres, which were carried out in randomized order for 20 s each. A nose clip was placed before the manoeuvres. The Mueller manoeuvre (MM) was performed using an occluded mouthpiece with a small air leak to prevent complete closure of the glottis during inspiration. With this adjustment we ensured that there was negative pressure throughout the entire airway and not only in the upper respiratory tract. After expiration, forced inspiration was carried out against the mouthpiece generating a target negative intrathoracic pressure of −30 mmHg.[6] For the inspiratory threshold load manoeuvre (ITH), a device with an incorporated adjustable negative pressure threshold valve was used (Threshold® IMT, Respironics, Parsippany, NJ, USA) to generate an inspiratory threshold load (set at −30 mmHg; targeted negative intrathoracic pressure −20 mmHg[6]) that cannot be overcome unless the adjusted threshold pressure is generated during inspiration. For the end-expiratory central apnoea manoeuvre (AP), patients were instructed to withhold respiratory effort after expiration. We have previously shown that by using the same technique MM and ITH produced the targeted negative changes in intrathoracic pressure as measured with an oesophageal catheter.[6]

Electrocardiography

A commercially available 12-lead ECG (AT 104 PC, Schiller-Reomed AG, Zurich, Switzerland) was used for all electrocardiographic recordings. Leads V5 and II were recorded continuously throughout all manoeuvres (1 min pause between them), the beginning and the end of each manoeuvre were marked manually. All ECG recordings were analysed offline by the same investigator (C.S.) who was not aware of the randomization sequence. Atrial premature beats were defined as follows: coupling interval to the preceding QRS complex $\leq$80% of the mean RR interval of basic rhythm prior to the event, narrow QRS complex ($<$0.12 s) unless aberration was suspected and non-compensatory post-contraction pause. Ventricular premature beats were defined as follows: wide ($\geq$0.12 s) and deformed QRS complex, prematurity, compensatory post-contraction pause. Non-sustained atrial arrhythmias (nsAAs) were defined as follows: all atrial arrhythmias lasting $\geq$3 beats, but $<$30 s. Atrial fibrillation was defined as follows: the absence of any discernable P wave, absolute arrhythmia, lasting $\geq$30 s.

A dedicated software for analysis of intervals within the ECG recordings was used (DatInf Measure 2.1d, DatInf GmbH, Tubingen, Germany). Lead V5 was used for analysis and if unsuitable lead II. The QT interval was defined as the time from the onset of the QRS complex to the cutting point of the tangent to the downward slope of the T wave and the isoelectric line. The T_{peak}-to-T_{end} (TpTe) interval was defined as the time from the peak of the T wave to the cutting point of the tangent to the downward slope of the T wave and the isoelectric line. QT and TpTe intervals were corrected for heart rate using Bazett's formula. The mean value of the last three heart cycles of each of the following periods was used for analysis of ECG-interval times: 10 s preceding the manoeuvre (A), first (B) and second (C) 10 s of the manoeuvre, first (D) and second (E) 10 s after the manoeuvre.

Sleep study

To determine the prevalence of OSA within this group of patients with PAF, participants underwent ambulatory sleep studies. Home sleep studies were performed using the ApneaLink plus® device (ResMed, MAP Medicine Technology, Martinsried, Germany). This device records the patients' nasal respiratory pressure, snoring sounds, thoracic movements, and finger oximetry during sleep. The nasal pressure signal was used to derive apnoea, hypopnoea, snoring, and flow limitation. Obstructive and central apnoea were discriminated by the thoracic belt. The device has been validated as an accurate instrument with which to detect snoring, apnoea–hypopnoea, and oxygen desaturations.[7] Results were scored automatically with dedicated software (ResMed, MAP Medicine Technology, Martinsried, Germany). Manual review of all sleep-study data was performed to ensure reliability of data. Apnoea was defined as cessation of airflow lasting $>$10 s and hypopnoea was defined as at least a 50% reduction in airflow for $>$10 s, associated with a $\geq$4% drop in oxygen saturation.

Left atrial end-systolic diameter

Echocardiography data, if obtained within the last 12 months, were used to assess the relationship between left atrial end-systolic diameter (LAESD) and the severity of OSA ($n = 33$).

Data analysis

The primary endpoint was the difference in the proportion of subjects developing premature cardiac beats during the breathing manoeuvres compared with normal breathing (NB). Secondary endpoints were changes in measures of ventricular repolarization (QT_c and $TpTe_c$). Values are presented as means (SD) unless otherwise stated. McNemar tests were used to assess the difference of the rate of premature cardiac beats between experimental conditions. Differences in the length of QT_c and $TpTe_c$ as well as differences in the number of APBs and differences in heart rate during the first and second 10 s of the MM were assessed by ANOVA for repeated measures with Fisher's *post hoc* tests. Univariate and multivariate regression analysis was used to assess the association between the severity of OSA [apnoea hypopnoea index (AHI)] and LAESD. All analyses were performed with STATA version 12 for windows (STATA Corporation, College Station, TX, USA). A two-sided *P*-value of <0.05 was considered to be of statistical significance.

Results

Figure 1 shows the trial profile. Subjects were screened for eligibility between October 2012 and December 2013. During that time more than 2000 patients were seen for heart rhythm disturbances in the outpatient clinic of the Cardiovascular Centre, University Hospital Zurich, Switzerland. Of these 263 patients were contacted. Forty-six patients attended for measurements. Two patients had to be excluded from further analysis as they were not in sinus rhythm at baseline. Forty-four patients were included for analysis of the primary endpoint. Patient characteristics are shown in *Table 1*.

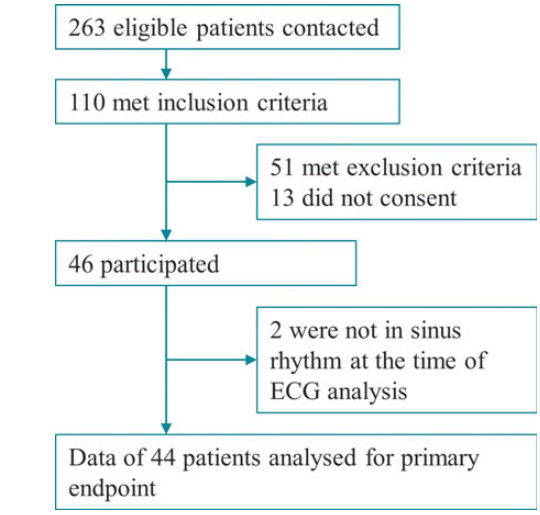

Figure 1 Study flow.

Table 1 Patient characteristics

	Subjects ($n = 44$)
Age	60.1 (11.2)
Females, *n* (%)	6 (14)
Body mass index (kg/m^2)	26.6 (4.6)
Systolic blood pressure (mmHg)	134.8 (17.3)
Diastolic blood pressure (mmHg)	80.5 (8.7)
Heart rate (b.p.m.)	63.4 (13.9)
Arterial hypertension, *n* (%)	23 (52)
Coronary artery disease, *n* (%)	9 (20)
Diabetes mellitus, *n* (%)	8 (18)
β-Blocker medication, *n* (%)	35 (80)
QT interval (ms)	418.8 (48.5)
QT_c interval (ms)[a]	420.1 (33.4)
T_{peak}–to-T_{end} (ms)	81.1 (14.5)
T_{peak}-to-T_{endc} (ms)[a]	82.0 (16.4)

Values are mean (SD) where applicable.
[a]Corrected for heart rate.

Effect of simulated obstructive sleep apnoea on heart rhythm

Atrial premature beats

Atrial premature beats occurred more frequently during MM (55% of patients) and ITH (32%) but not during AP (14%) compared with NB (9%) ($P < 0.001$, $P = 0.006$, and $P = 0.688$, respectively, *Figure 2*). The total number of APBs was significantly higher during MM ($n = 61$) and ITH ($n = 28$) but not during AP ($n = 16$) compared with NB ($n = 8$) ($P < 0.001$, $P = 0.048$, and $P = 0.427$, respectively, *Figure 3*). The number of subjects developing APBs and the total number of APBs were significantly higher during MM than during ITH ($P = 0.013$ and $P = 0.001$, respectively). The number of APBs during the MM was significantly higher during the first 10 s of the MM when compared with the second 10 s of the MM (42 and 19, $P = 0.002$), whereas heart rate was significantly higher during the second 10 s of the MM when compared with the first 10 s of the MM (68.6 and 73.3 b.p.m., $P < 0.001$, *Figure 4*). Heart rate during the MM did not differ between subjects who developed APBs and subjects who did not ($P = 0.104$). P-wave morphology did differ between sinus rhythm and APBs.

Ventricular premature beats

The rate of subjects developing VPBs and the total number of VPBs did not differ significantly among MM, ITH, and AP compared with NB ($P > 0.05$ for all comparisons, *Figures 2 and 3*).

Atrial fibrillation and non-sustained atrial arrhythmias

Six patients developed nsAAs during MM ($P = 0.031$ vs. NB), three patients during ITH ($P = 0.25$ vs. NB, *Figure 2*). One patient developed AF during ITH and during AP (*Figure 2*). No other arrhythmias were recorded during breathing manoeuvres.

Effect of simulated obstructive sleep apnoea on ventricular repolarization

Mueller manoeuvre

Compared with prior to the MM, there was a significant increase in the QT_c interval [+15.2 ms (23.5), 95% CI 7.7–22.6 ms, $P < 0.001$] during the MM (C). The difference in QT_c further increased [+17.3 ms (20.9), 95% CI 10.7–23.9 ms, $P < 0.001$] after release of the MM (D)

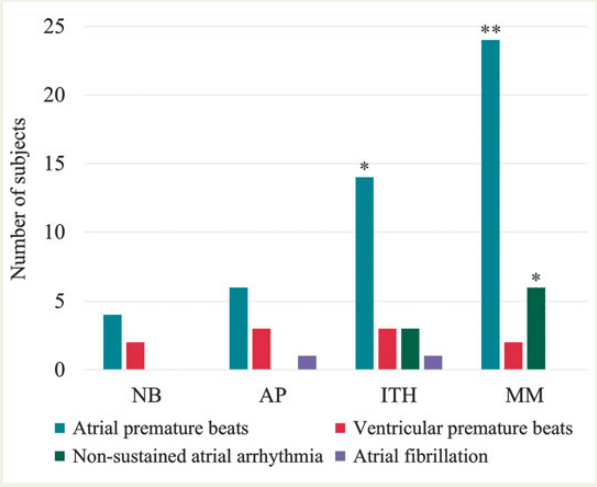

Figure 2 Number of subjects with heart rhythm disturbances during NB, AP, ITH, and during MM. $^{**}P < 0.001$ vs. NB. $^{*}P < 0.05$ vs. NB. NB, Normal breathing; AP, end-expiratory central apnoea; ITH, inspiration through a threshold load; MM, Mueller manoeuvre.

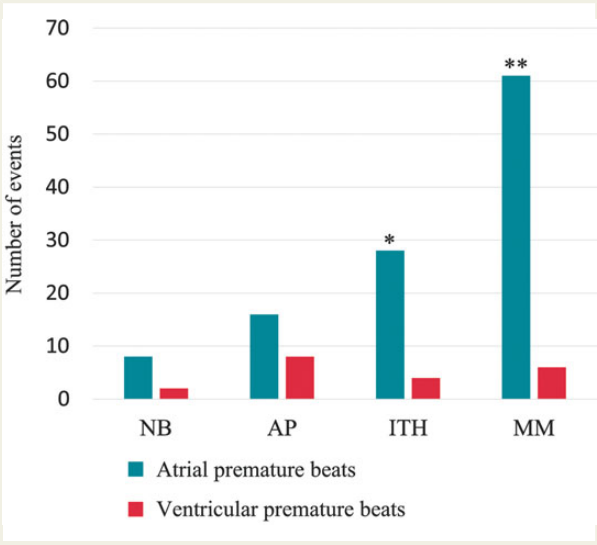

Figure 3 Number of events during NB, AP, ITH, and during MM. $^{**}P < 0.001$ vs. NB. $^{*}P < 0.05$ vs. NB. NB, Normal breathing; AP, end-expiratory central apnoea; ITH, inspiration through a threshold load; MM, Mueller manoeuvre.

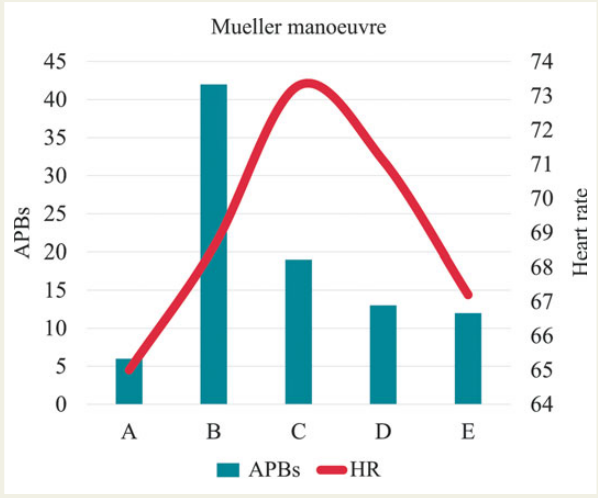

Figure 4 Number of APBs and heart rate 10 s prior to MM (*A*), during the first (*B*) and second (*C*) 10 s of MM, during the first (*D*) and second (*E*) 10 s after MM. Note that the majority of APBs occurred early in the manoeuvre prior to a marked increase in heart rate.

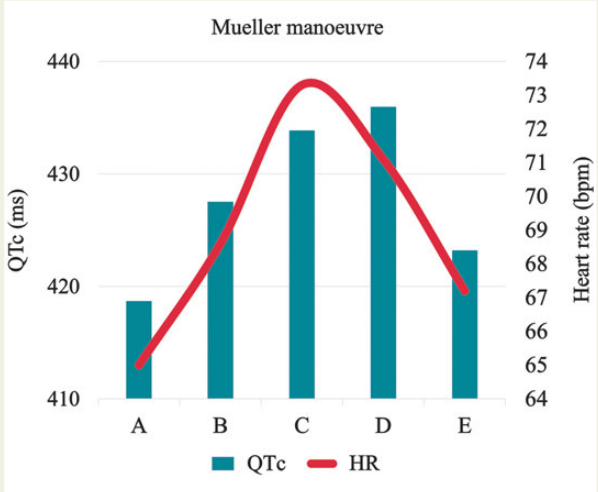

Figure 5 QT_c intervals and heart rate 10 s prior to MM (*A*), during the first (*B*) and second (*C*) 10 s of MM, during the first (*D*) and second (*E*) 10 s after MM. Note that the longest QT_c interval time was measured after the highest increase in heart rate.

compared with prior to the MM. There was a small statistically non-significant increase of the $TpTe_c$ interval during the MM (+0.08 and +0.04 ms during B and C, respectively), but a significant increase of $TpTe_c$ after release of the MM (D) [+4.3 ms (9.2), 95% CI 1.4–7.2 ms, $P = 0.005$], compared with prior to the MM. *Figure 5* shows the QT_c interval and heart rate prior, during and after release of the MM.

Inspiratory threshold manoeuvre

Compared with prior to ITH, there was a small non-significant increase of the QT_c interval during ITH [+1.3 and +0.4 ms during B and C, respectively]. The increase in QT_c reached statistical significance [+9.6 ms (15.5), 95% CI 4.7–14.4 ms, $P < 0.001$] after release of ITH (D). There were no significant changes in $TpTe_c$ during ITH or post-ITH when compared with prior to ITH.

End-expiratory central apnoea manoeuvre

There were no significant changes in QT_c and $TpTe_c$ during AP or post-AP compared with before the manoeuvre. More data on

repolarization times and heart rate are available online as Supplementary material online, *Table S1*.

Ambulatory sleep study and echocardiography

Of 41 patients with usable sleep-study data, 23 had OSA (AHI $\geq$ 5, 56%), 10 of them had moderate OSA (AHI $\geq$ 15, 24%) and 2 of them had severe OSA (AHI $\geq$ 30, 5%). Apnoea hypopnoea index and LAESD were significantly correlated (Pearson's $r = 0.539$, $P = 0.001$, $n = 33$, *Figure 6*). This association remained statistically significant in a multiple regression analysis controlling for age, gender, BMI, and arterial hypertension ($\beta = 0.412$, $P = 0.030$, 95% CI 0.04–0.78). The number of obstructive apnoea during the sleep study correlated significantly with the number of APBs observed during the MM (Pearson's $r = 0.39$, $P = 0.027$).

Discussion

This study is the first to show that intrathoracic pressure changes induced by simulated OSA promote substantial rates of APBs and nsAA in patients with PAF. This is of considerable clinical interest considering the findings of several Holter ECG studies showing that the majority of episodes of PAF is triggered by APBs, arising mostly from pulmonary veins.[5] Simulated OSA was further associated with significant increases in QT_c and $TpTe_c$ interval times, thus potentially increasing the susceptibility to SCD. According to the sleep study, 56% of patients had OSA.

Numerous studies have found an association between OSA and AF, but quite how apnoea and hypopnoea further the occurrence of AF, is not fully understood. A meta-analysis found an approximate 25% greater risk of AF recurrence after catheter ablation in those with, compared with those without, OSA.[8] Two non-randomized studies have compared patients with OSA who used their continuous positive airway pressure (CPAP) device, vs. those who did not use it, or were not prescribed it. Patel *et al.*[9] analysed 3000 patients having had pulmonary vein isolation therapy for AF, of the patients enrolled who also had sleep studies, 21% had OSA (AHI $> 15\ h^{-1}$). After an average follow-up period of 32 months, 79% of the CPAP users did not experience AF recurrence, compared with 68% in the CPAP non-user group. A smaller study by Kanagala *et al.*[10] included 39 OSA patients with AF/atrial flutter referred for direct current cardioversion. Twenty-seven of the 39 patients either were not, or poorly, treated with CPAP. Recurrence of AF 1 year after cardioversion was noted in 82% of these inadequately treated patients, whereas AF recurrence was only observed in 42% of patients adequately treated with CPAP.

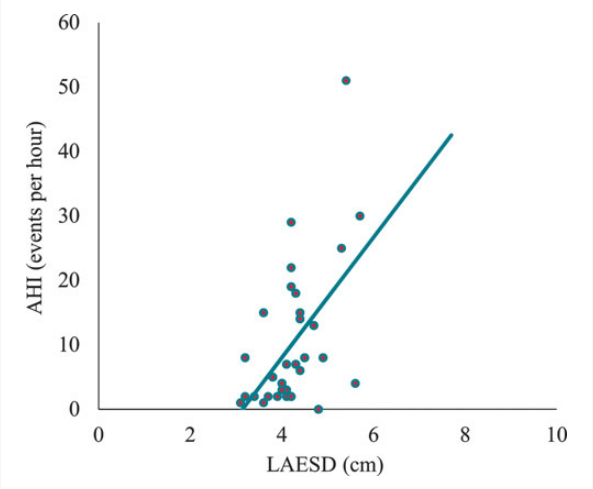

Figure 6 Correlation (Pearson's $r = 0.54$, $P = 0.001$) between LAESD and severity of OSA (AHI).

The main pathophysiological consequences of OSA are intermittent hypoxia, intrathoracic pressure swings, and arousals from sleep, all leading to increased sympathetic activation.[11] While it is usually difficult to disentangle these mechanisms, an advantage of the current study is the possibility to assess direct physiological consequences of intrathoracic pressure changes without the confounding effects of prominent intermittent hypoxaemia and arousals from sleep.

The number of APBs during the MM was significantly higher early in the manoeuvre, whereas heart rate increased later in the MM (*Figure 4*). Thus, our findings imply that atrial distortion through intrathoracic pressure changes is the actual cause of APBs. This is reinforced by the observation we made in the first four patients of the study in whom no change in SpO2 during the manoeuvre was found (Supplementary material online, *Table S2*). Moreover, as the majority of APBs occurred in the initial seconds of the manoeuvre, falls in oxygen saturation are even more unlikely to play a causal role.

Studies in healthy human subjects and in an animal model have previously confirmed a causal role of negative intrathoracic pressure changes in the development of APBs, shortened atrial effective refractory period (AERP) and AF inducibility.[2–4] Linz *et al.* demonstrated in a pig-model that the enhanced inducibility of APBs and AF through application of negative tracheal pressure is inhibited by vagotomy or atropine on the one hand[3] and by renal denervation or combined blockade of the renin-angiotensin-aldosterone system and beta-adrenoreceptors on the other hand.[4] It is therefore conceivable that altered autonomic activity plays an important role in the genesis of APBs.

Simulated obstructive sleep apnoea and atrial remodelling

Mechanisms leading to the onset, the acute initiation of episodes of PAF, maintenance and ultimately deterioration of PAF to chronic AF are complex, and once episodes begin they seem to increase their propensity ('AF begets AF'). Acute atrial distortion and chronic atrial enlargement are believed to play central roles in this circuit.[12] The forced inspiratory effort against an occluded pharynx, as seen during the MM as well as repeatedly in patients with OSA during sleep, causes large sub-atmospheric falls in intrathoracic pressure.[6] Acute distortion of the wall of the LA, when repeated over and over during the course of a night as seen in patients with OSA, may elicit high rates of APBs during obstructive apnoea and hypopnoea, providing an electrical trigger. Although changes in sympatho-vagal balance play a critical role in the dispersion of AERP and other atrial electrical properties, the exact

role of vagal tone is still controversial. It remains speculative whether intrathoracic pressure changes induce heterogeneities of atrial conduction via disruption of electrical interconnections between muscles due to atrial distortion or via sympatho-vagal imbalances or both at the same time. Because OSA may also lead to structural remodelling of the atria, over time APBs will fire on an atrial substrate already predisposed to AF.[12] This hypothesis is supported by the findings based on an animal model, which suggest that chronically repeated OSA episodes lead to atrial fibrosis.[13] Obstructive sleep apnoea has also been linked to left ventricular systolic and diastolic dysfunction. Orban *et al.*[14] argued that in OSA the LV has to pump blood from the lower pressure thorax to the higher pressure extrathoracic compartment, which poses a chronic afterload burden on the LV, ultimately leading to chronic left atrial stretch.[15] In the current study, the severity of OSA (AHI) was independently associated with LAESD as assessed by echocardiography in multiple regression analysis. This is in line with previous studies[15] also showing that OSA was associated with left atrial enlargement. The current study further supports the 'OSA substrate' hypothesis, as we found a correlation between the number of obstructive apnoeas during sleep and the number of APBs observed during the MM.

Simulated obstructive sleep apnoea and ventricular repolarization

In this study, simulated apnoea and hypopnoea were both associated with a significant increase in the QT_c interval. Contrary to the association of simulated OSA and APBs, which was pronounced at an early stage of the manoeuvres, the QT_c interval increased more at the end and even further after release of the MM (*Figure 5*). An extensive body of evidence exists on the association between prolonged QT intervals and malignant ventricular arrhythmias, including torsade de pointes and SCD. Sudden death from cardiac causes has been shown to peak during the sleeping hours in patients with OSA, while patients without OSA and the general population were least likely to die from sudden death from cardiac causes during the sleeping hours.[16] Obstructive sleep apnoea predicted incident SCD in a large study including more than 10 000 adults referred for polysomnography, nocturnal hypoxaemia and AHI strongly predicting SCD independent of well-established risk factors.[17]

Obstructive sleep apnoea seems to be causally related to length and transmural dispersion of repolarization, as we previously found that in 41 patients with moderate to severe OSA, a 2-week withdrawal from effective CPAP therapy led to significant increases in QT_c and $TpTe_c$.[18] In the current study, the MM was also associated with an increase in the $TpTe_c$ interval, a measure of transmural dispersion of ventricular repolarization, which represents a gradient of action potential duration from endocardial cells to epicardial cells. A prolonged $TpTe_c$ interval has been linked to an increased risk of ventricular tachycardia and SCD through enhanced susceptibility to early and late after-depolarizations.[19] In the current study, the increase in $TpTe_c$ was only significant after release of the MM, but not during the manoeuvre. Due to this time course one could hypothesize from our findings that changes in QT_c and $TpTe_c$ are primarily the effect of enhanced sympathetic tone. Alternatively, the changes in QT_c and $TpTe_c$ may be the result of intrathoracic pressure swings and associated acute cardiac volume changes. Accordingly, Orban *et al.*[14] described reduced parameters of LV systolic performance during the MM, but immediately after termination of the MM, there was an increase exceeding the baseline values.

Limitations

We did not directly measure sympathetic activity. However, although changes in heart rate are an indirect surrogate of sympathetic tone, our findings are in line with those reported by Somers *et al.*[20] who found that sympathetic activity was inhibited during the initial period of the MM and augmented during the last 10 s of the MM.

Conclusions

In our sample of patients with PAF, 56% had OSA based on the sleep study. Intrathoracic pressure swings through simulated OSA promoted substantial rates of APBs which are considered crucial in the onset of episodes of AF in this population. Patients with PAF should possibly be screened for OSA to prevent deterioration of PAF into chronic AF. This holds true especially for patients with PAF undergoing catheter ablation therapy given the findings of significantly decreased success rates in patients with OSA.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: J.R.S. reports personal fees from ResMed UK, outside the submitted work. M.K. reports grants from University of Zurich during the conduct of the study.

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