



# The effects of continuous positive airway pressure therapy withdrawal on cardiac repolarization: data from a randomized controlled trial<sup>†</sup>

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## Aims

The preliminary evidence supports an association between obstructive sleep apnoea (OSA), disturbed cardiac repolarization, and consequent cardiac dysrhythmias. The aim of the current trial was to assess the effects of continuous positive airway pressure (CPAP) therapy withdrawal on the measures of cardiac repolarization in patients with OSA.

## Methods and results

Forty-one OSA patients established on CPAP treatment were randomized to either CPAP withdrawal (subtherapeutic CPAP) or continue therapeutic CPAP for 2 weeks. Polysomnography was performed, and indices of cardiac repolarization ( $QT_c$ ,  $TpTe_c$  intervals) and dispersion of repolarization ( $TpTe/QT$  ratio) were derived from 12-lead electrocardiography (ECG) at baseline and 2 weeks. Continuous positive airway pressure withdrawal led to a recurrence of OSA. Compared with therapeutic CPAP, subtherapeutic CPAP for 2 weeks was associated with a significant increase in the length of the  $QT_c$  and  $TpTe_c$  intervals (mean difference between groups 21.4 ms, 95% CI 11.3–1.6 ms,  $P < 0.001$  and 14.4 ms, 95% CI 7.2–21.5 ms,  $P < 0.001$ , respectively) and in the  $TpTe/QT$  ratio (mean difference between groups 0.02, 95% CI 0.00–0.03,  $P = 0.020$ ). There was a statistically significant correlation between the change in apnoea/hypopnoea index (AHI) from baseline, and both the change in the  $QT_c$  interval and the  $TpTe_c$  interval ( $r = 0.60$ , 95% CI 0.36–0.77,  $P < 0.001$  and  $r = 0.45$ , 95% CI 0.17–0.67,  $P = 0.003$ ,  $n = 41$ , respectively).

## Conclusion

Continuous positive airway pressure withdrawal is associated with the prolongation of the  $QT_c$  and  $TpTe_c$  intervals and  $TpTe/QT$  ratio, which may provide a possible mechanistic link between OSA, cardiac dysrhythmias, and thus sudden cardiac death.

## Keywords

Obstructive sleep apnoea • Continuous positive airway pressure • Cardiac dysrhythmias • Cardiac repolarization • Sudden cardiac death

## Introduction

Obstructive sleep apnoea (OSA) is a highly prevalent sleep-related breathing disorder affecting up to 30% of middle-aged adults.<sup>1,2</sup> Obstructive sleep apnoea is characterized by the repetitive interruption of ventilation during sleep caused by the collapse of the

upper airway, resulting in apnoeas and hypopnoeas associated with oxygen desaturations and arousals from sleep. As a consequence of the fragmented sleep, patients with OSA may suffer from increased daytime sleepiness leading to impaired quality of life and the increased risk of traffic accidents.<sup>3,4</sup>

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Symptomatic OSA has been implicated as an important factor in the pathogenesis of hypertension and cardiovascular disease.<sup>4–6</sup> Furthermore, the findings of observational studies suggest that OSA may be causally related with cardiac dysrhythmias, such as premature ventricular contractions, atrial fibrillation (AF), ventricular arrhythmias, atrioventricular block, and sinus arrest.<sup>7–12</sup> The observation that patients with OSA have an increased risk of sudden cardiac death (SCD) at night suggests an association between OSA and SCD.<sup>12</sup> The mechanistic link between OSA and SCD, however, has not yet been thoroughly established. An increase in the dispersion of cardiac repolarization has been suggested as a potential mechanism of ventricular arrhythmias and SCD.<sup>13–15</sup> The various markers derived from the surface electrocardiography (ECG) as well as from the electrophysiological studies provide information about the transmural dispersion of repolarization and the electrical inhomogeneity in the ventricles during repolarization.<sup>16–18</sup>

There is preliminary evidence from uncontrolled studies suggesting that cardiac repolarization is prolonged and the transmural dispersion of repolarization is increased, in patients with OSA. These ECG abnormalities seem to reverse with continuous positive airway pressure (CPAP) treatment.<sup>19</sup> However, there is no data from randomized controlled interventional trials proving this association, and thus a controversy remains as to whether OSA is an independent aetiological risk factor for disturbed cardiac repolarization.<sup>11</sup>

To address this uncertainty, we have analysed the ECG data from a randomized controlled trial exploring the effects of a 2-week CPAP withdrawal vs. continuing CPAP in patients with previously treated OSA,<sup>20</sup> in order to investigate the effects of CPAP withdrawal and a return of OSA on ECG-derived measures of cardiac repolarization.

## Methods

### Patients, trial design, and sample calculation

Patients previously diagnosed with OSA, and treated with CPAP, who were registered in a database of the Sleep Disorders Centre and Pulmonary Division of the University Hospital of Zurich, Switzerland, were eligible for the trial if they were aged between 20 and 75 years, had an oxygen desaturation index (ODI,  $\geq 4\%$  dips) of  $>10/h$  during their initial sleep study, an ODI of  $>10/h$  during an ambulatory nocturnal pulse-oximetry performed on the last night of a four-night period without CPAP prior to the main study, and if they had been treated with CPAP for  $>12$  months with a average compliance of  $\geq 4$  h per night.

Patients with previous ventilatory failure, Cheyne–Stokes breathing, unstable and untreated coronary or peripheral artery disease, severe and inadequately controlled arterial hypertension, a history of any sleep-related accident, or with a heavy goods vehicle driver's licence, were excluded from the study. The trial was performed according to the Declaration of Helsinki, was approved by the University Hospital of Zurich research ethics committee (EK-1600) and registered (ISRCTN 93153804). Written informed consent was obtained from all participants. The primary outcomes of this trial [change in the ODI and apnoea/hypopnoea index (AHI)] are reported elsewhere in more detail.<sup>20</sup>

After confirming the persistence of OSA by home overnight pulse-oximetry at the end of a four-night period without CPAP, eligible patients returned to therapy with CPAP for  $\geq 7$  days. After baseline assessments, the patients were randomized to either continue with CPAP therapy or switch to subtherapeutic CPAP for 2 weeks by a series of presealed and numbered envelopes. The follow-up assessments of ECG were performed at 1 and 2 weeks. Patients remained blinded as to whether they were receiving therapeutic or subtherapeutic CPAP, as did the investigators. The member of the research team who randomized the patients did not take part in the outcome assessments.

A sample size estimation was performed based on the assumption that a clinically relevant difference in the ODI ( $\geq 4\%$  drop of oxygen saturation/h) between active treatment and placebo is 10/h (SD 10) and a clinically relevant difference in the QT<sub>c</sub> is 20 ms (SD 15).<sup>21</sup> Based on these assumptions, the power calculation indicated that 41 patients were required in total in order to not miss clinically relevant differences in the ODI (with a power of 90%) and in the QT<sub>c</sub> (with a power of 99%).

### Sleep studies and continuous positive airway pressure

At baseline and 2 weeks, attended polysomnographic sleep studies were performed and analysed according to the standard methods. Apnoeas were defined as a reduction in the amplitude of chest wall motion by  $>90\%$  from baseline over the previous 2 min for  $>10$  s, hypopnoeas were defined as a reduction in the amplitude of chest wall motion by  $>50\%$  from baseline over the previous 2 min for  $>10$  s, associated with a  $\geq 4\%$  drop in oxygen saturation.<sup>22</sup> The severity of sleep-disordered breathing was quantified as the number of apnoeas/hypopnoeas (AHI) and oxygen desaturations  $\geq 4\%$  per hour of study (ODI). In patients randomized to subtherapeutic CPAP, the subtherapeutic pressure was achieved by setting the CPAP machine to the lowest pressure, inserting a flow-restricting connector at the machine outlet, and inserting six extra holes in the collar of the main tubing at the end of the mask to allow air escape, thus preventing rebreathing of carbon dioxide, as previously described.<sup>23</sup> Sleepiness was assessed using the Epworth sleepiness score (ESS).<sup>24,25</sup>

### Electrocardiography

The participants were asked to abstain from alcohol, tobacco, or caffeine on the day the measurements were done. The room temperature and lighting were set at the same level for all measurements. The participants rested for 5 min in the supine position before measurements were done. For all electrocardiographic recordings a commercially available 12-lead ECG (AT 104 PC, Schiller-Reomed AG, Switzerland) was used and set at 25-mm/s paper speed and 10-mm/mV amplitude. The measurements of the ECG intervals were performed in duplicate with a dedicated ECG analysis software (DatInF® Measure 2.1d, DatInF GmbH, Tübingen, Germany) by two investigators who were blinded to the patient's group allocation. The mean of the measurements by the two investigators was used for statistical analysis. Lead V5 was used and when unsuitable, lead V4 or V6. The indices of cardiac repolarization were determined as follows: the QT interval was defined as the time from the earliest onset of the QRS complex to the point at which the downward slope of the T-wave returned to baseline and the Tpeak-to-Tend interval (TpTe) as the time from the peak of the T-wave to the end of the T-wave.<sup>26</sup> The end of the T-wave was defined as the cutting point of the tangent to the downward slope of the T-wave and the isoelectric line.<sup>18</sup> Both the QT and TpTe intervals were corrected for the heart rate as

described previously.<sup>27</sup> As a measure of dispersion of repolarization, TpTe/QT ratio was calculated.<sup>14</sup>

### Data analysis

All values are presented as mean (SD) unless otherwise stated. Statistical analysis was performed with Statistica V6.0 (StatSoft, Tulsa, OK, USA). Differences in baseline characteristics between the groups were assessed by independent *t*-tests and  $\chi^2$  tests as appropriate. Comparisons of changes between groups were assessed by independent *t*-tests and Mann–Whitney *U* tests as appropriate. The analyses were performed on an intention-to-treat basis with no change assumed for the missing follow-up data. Correlations between changes in the indices of OSA severity and the ECG measures of cardiac repolarization were assessed by Pearson correlation

coefficients. A two-sided *P* value of <0.05 was considered to be statistically significant.

## Results

### Trial profile and patient characteristics

Figure 1 shows the trial profile. The two groups were similar regarding all patients' characteristics at baseline (Table 1). Data on AHI downloaded from the patients' CPAP machines, as well as ESS values within the normal range, proved successful treatment of patients with CPAP prior to the study (Table 1). One patient in the subtherapeutic CPAP group withdrew from the study 4 days after randomization because of intolerable daytime symptoms.

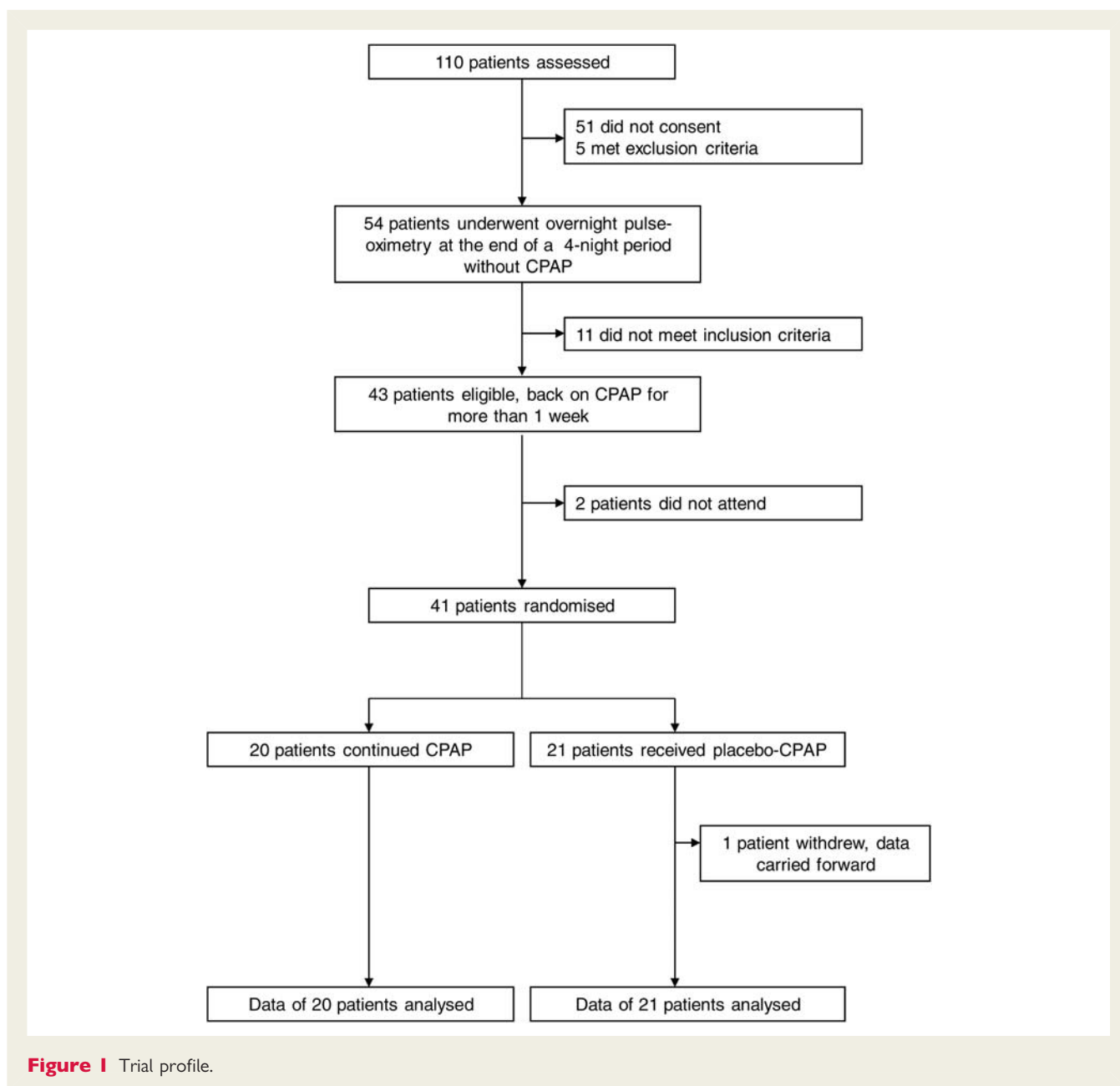


Figure 1 Trial profile.

**Table 1** Baseline characteristics

	Therapeutic CPAP (n = 20)	Subtherapeutic CPAP (n = 21)
Age (years)	63.6 (5.1)	61.8 (7.5)
Females (n)	1/20	0/21
Body mass index (kg/m <sup>2</sup> )	32.9 (6.5)	33.1 (4.4)
Waist/hip circumference ratio	1.0 (0.1)	1.0 (0.0)
Neck circumference (cm)	46.4 (3.7)	46.1 (4.2)
Current smokers (n)	1/20	4/21
Ex-smokers (n)	5/20	8/21
Hypertension (n)	14/20	17/21
Diabetes (n)	4/20	5/21
CAD (n)	2/20	1/21
Sokolow–Lyon index (mV)	21.1 (5.3)	21.1 (5.7)
Cardiac dysrhythmia <sup>a</sup> (n)	0/20	1/21
Antihypertensive medication (n)	13/20	16/21
Beta-blockers (n)	7/20	6/21
Diuretics (n)	5/20	8/21
Cholesterol-lowering medication (n)	7/20	7/21
Glucose-lowering medication (n)	3/20	2/21
Potassium (mmol/L)	3.9 (0.4)	3.9 (0.3)
AHI original sleep study	36.0 (17.3)	45.3 (22.3)
ODI original sleep study	26.6 (13.5)	37.3 (22.7)
ODI 4-day withdrawal	25.4 (8.6)	28.9 (16.2)
AHI on CPAP <sup>b</sup>	5.1 (2.7)	4.3 (2.3)
CPAP compliance (min)	373.1 (67.9)	362.8 (72.3)
CPAP use relative to time in bed (%) <sup>c</sup>	80.8 (14.5)	79.2 (20.0)
Duration of CPAP treatment (years)	5.6 (3.4)	7.4 (3.2)
ESS before therapy	7.4 (3.1)	6.6 (2.7)
Time from screening to randomization (days)	75.9 (29.0)	68.3 (29.9)

Values are mean (SD) where applicable.

CAD, coronary heart disease; AHI, apnoea/hypopnoea index; ODI, oxygen desaturation index; AHI on CPAP, AHI downloaded from CPAP machine averaged from previous 6 months; ESS, Epworth sleepiness score.

<sup>a</sup>Atrial fibrillation.

<sup>b</sup>Derived from CPAP machine.

<sup>c</sup>Time in bed estimated by actimetry.

## Sleep-disordered breathing and sleepiness

Compared with therapeutic CPAP, AHI increased significantly with the subtherapeutic CPAP at 2 weeks (mean difference in the AHI change 30.2, 95% CI 18.8–41.7) and ODI (mean difference in the ODI change 24.0, 95% CI 13.5–34.4,  $P < 0.001$  for both comparisons). ESS increased significantly at 2 weeks in the subtherapeutic group compared with the therapeutic group (mean difference in ESS change 3.1, 95% CI 1.4–4.7,  $P < 0.001$ , Table 2).

## Effect of continuous positive airway pressure withdrawal on cardiac repolarization indices

ECG interval times at baseline, and changes from baseline, are shown in Table 3. There were no relevant differences between the two groups at baseline.

Compared with therapeutic CPAP, subtherapeutic CPAP for 2 weeks was associated with a significant increase in the length of the QT<sub>c</sub> and TpTe<sub>c</sub> intervals (mean difference 21.4 ms, 95% CI 11.3–31.6 ms,  $P < 0.001$  and 14.4 ms, 95% CI 7.2–21.5 ms,  $P < 0.001$ , respectively) (Figures 2 and 3) and in the TpTe/QT ratio (mean difference 0.02, 95% CI –0.00–0.03,  $P = 0.020$ ).

A statistically significant correlation was observed between the change in the AHI, and both the changes in the QT<sub>c</sub> and the TpTe<sub>c</sub> intervals ( $r = 0.60$ , 95% CI 0.36–0.77,  $P < 0.001$  and  $r = 0.45$ , 95% CI 0.17–0.67,  $P = 0.003$ , respectively,  $n = 41$ , Figures 4 and 5).

A statistically significant correlation was also found between the change in the ODI, and both the changes in the QT<sub>c</sub> and the TpTe<sub>c</sub> intervals ( $r = 0.44$ , 95% CI 0.16–0.66,  $P = 0.004$ , and  $r = 0.51$ , 95% CI 0.24–0.71,  $P < 0.001$ , respectively,  $n = 41$ ).

## Discussion

This is the first randomized controlled trial providing data on the effects of OSA on ECG measures of cardiac repolarization. We found that CPAP withdrawal was associated with a considerable prolongation and an increase in the dispersion of cardiac repolarization. These findings provide further evidence suggesting a possible link between OSA, cardiac dysrhythmias, and SCD.

The QT interval represents the electrocardiographic correlate of ventricular de- and repolarization, including the vulnerable period for reentry tachycardia. As such, numerous studies have

**Table 2** Effects of continuous positive airway pressure withdrawal on sleep-disordered breathing and sleepiness

	Baseline		Change from baseline		95% CI between groups	P-value
	Therapeutic CPAP (n = 20)	Subtherapeutic CPAP (n = 21)	Therapeutic CPAP (n = 20)	Subtherapeutic CPAP (n = 21)		
AHI (1/h)	1.7 (1.8)	2.2 (2.5)	0.4 (2.8)	30.6 (25.2)	18.8/41.7	<0.001
ODI (1/h)	0.5 (0.8)	0.9 (2.0)	–0.2 (1.0)	23.8 (23.1)	13.5/34.4	<0.001
ESS	7.4 (3.1)	6.6 (2.7)	–0.9 (2.2)	2.2 (2.9)	1.4/4.7	<0.001

Values are mean (SD). 95% CI = 95% confidence interval of the difference between groups in change from baseline.

AHI, apnoea/hypopnoea index; ODI, oxygen desaturation index; ESS, Epworth sleepiness score.

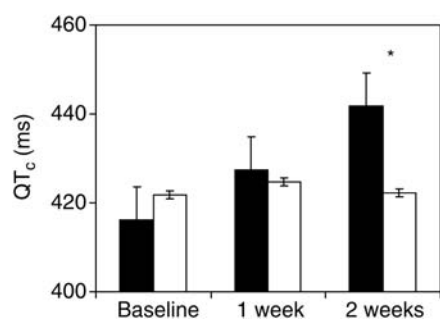
**Table 3** Effect of continuous positive airway pressure withdrawal on the electrocardiographic intervals and urinary norepinephrine

	Baseline		Change from baseline		95% CI between groups	P-value
	Therapeutic CPAP (n = 20)	Subtherapeutic CPAP (n = 21)	Therapeutic CPAP (n = 20)	Subtherapeutic CPAP (n = 21)		
RR (ms)	962.2 (180.2)	892.8 (205.4)	-46.9 (111.5)	-54.7 (195.7)	-92.2/108	0.875
P (ms)	108.5 (15.3)	110.6 (16.2)	-3.3 (34.7)	8.1 (46.2)	-14.5/37.3	0.379
PQ (ms)	196.7 (25.2)	181.1 (26.3)	-1.8 (18.4)	-2.9 (11.7)	-10.8/8.6	0.824
QRS (ms)	106.4 (25.6)	101.0 (13.7)	0.9 (15.9)	1.1 (11.2)	-8.4/8.9	0.960
QT (ms)	416.8 (38.5)	389.1 (39.2)	-11.5 (38.6)	9.0 (18.7)	1.5/39.5	0.035
QT <sub>c</sub> (ms) <sup>a</sup>	421.9 (16.0)	416.1 (28.0)	-0.1 (9.3)	21.3 (20.4)	11.3/31.6	<0.001
TpTe (ms)	108.8 (14.4)	104.3 (12.6)	-2.4 (10.7)	9.6 (10.9)	7.0/16.9	0.001
TpTe <sub>c</sub> (ms) <sup>a</sup>	111.8 (14.5)	114.7 (14.6)	0.5 (11.3)	14.9 (11.3)	7.2/21.5	<0.001
TpTe/QT	0.26 (0.03)	0.27 (0.04)	0.00 (0.03)	0.02 (0.03)	-0.00/0.03	0.020
Norepinephrine (nmol/mmol)	22.1 (11.5)	26.3 (10.2)	0.9 (5.4)	11.5 (15.5)	2.5/18.7	0.012

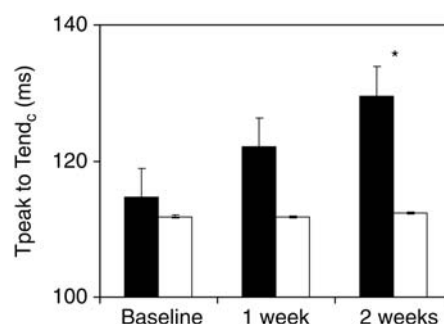
Values are mean (SD).

95% CI = 95% confidence interval of the difference between groups in change from baseline. N = 17 and 18 for urinary norepinephrine (nmol/mmol of creatinine) in the therapeutic and subtherapeutic CPAP group, respectively.

<sup>a</sup>Heart-rate corrected.



**Figure 2** Data are presented as mean and standard error. Black bars represent the subtherapeutic continuous positive airway pressure group and white bars represent the therapeutic continuous positive airway pressure group. There was a significant increase in the length of the QT<sub>c</sub> at 2 weeks in the subtherapeutic continuous positive airway pressure group compared with the therapeutic continuous positive airway pressure group. \**P* < 0.001 for comparisons of changes from baseline between groups.



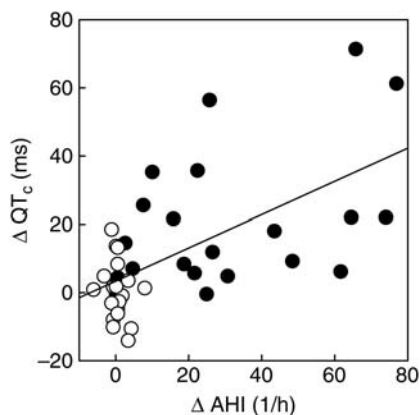
**Figure 3** Data are presented as mean and standard error. Black bars represent the subtherapeutic continuous positive airway pressure group and white bars represent the therapeutic continuous positive airway pressure group. There was a significant increase in the length of the T<sub>peak</sub> to T<sub>end<sub>c</sub></sub> at 2 weeks in the subtherapeutic continuous positive airway pressure group compared with the therapeutic continuous positive airway pressure group. \**P* < 0.001 for comparisons of changes from baseline between groups.

identified the inherited as well as acquired QT prolongation as a risk factor for the occurrence of malignant cardiac dysrhythmias and SCD.<sup>28,29</sup>

The T<sub>peak</sub>-to-T<sub>end</sub> (TpTe) interval is a measure of cardiac transmural dispersion of repolarization, which is explained by a gradient of action potential duration from endo- (longest) to epicardial cells (shortest).<sup>30,31</sup> A prolongation of the TpTe interval leads to increased vulnerability for the occurrence of early afterdepolarizations and has been associated with ventricular tachycardia and an increased risk for SCD.<sup>32-34</sup> Specifically, recent

findings from Panikkath et al.<sup>33</sup> suggest that patients with an uncorrected TpTe interval >100 ms in the resting ECG are at increased risk of SCD.

In the current study, QT<sub>c</sub> and TpTe<sub>c</sub> intervals at baseline were already considerably longer in the CPAP-treated study population than in a group of healthy young adults in one of our previous studies<sup>35</sup> (416.1 vs. 403.8 and 114.7 vs. 87.3 ms, respectively) possibly due to a high rate of comorbidities seen in our OSA population. However, we found that CPAP withdrawal for 2 weeks was

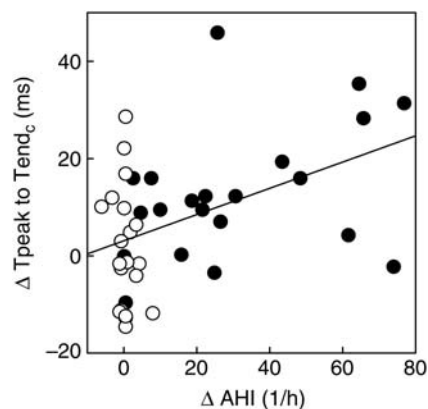


**Figure 4** Correlation between the change in the  $QT_c$  interval (change from baseline to 2 weeks) and change in the apnoea/hypopnoea index ( $r = 0.60$ , 95% CI 0.36–0.77,  $P < 0.001$ ,  $n = 41$ ). Black circles represent patients in the subtherapeutic continuous positive airway pressure group and white circles represent patients in the therapeutic continuous positive airway pressure group.

associated with further, statistically significant prolongation of the  $QT_c$  and  $TpTe_c$  intervals. The withdrawal of CPAP was also associated with an increase in the uncorrected mean  $TpTe$  interval from 104 to 114 ms; as a result, 71% of patients in the subtherapeutic CPAP group were shifted to  $TpTe$  values  $>100$  ms and 55% were shifted to  $QT_c$  values  $>430$  ms. Since these cut-offs were previously associated with an elevated risk for SCD,<sup>33</sup> our data imply that many OSA patients without CPAP treatment may fall into this category. Moreover, our data demonstrate an increase in the effect of CPAP withdrawal on cardiac repolarization parameters across 2 weeks (Figures 2 and 3), indicating that further withdrawal may result in an even more pronounced increase in these values.

The increase in the length of the  $QT_c$  and  $TpTe_c$  intervals was positively correlated with the change in the severity of sleep-disordered breathing (Figures 4 and 5) suggesting that the risk for SCD increases with the severity of OSA. There is also preliminary data from uncontrolled studies in patients with OSA showing that QT intervals are longer during the night-time compared with the daytime,<sup>21</sup> and longer at the onset of an apnoea episode compared with the period after an apnoea.<sup>36</sup> In an observational study, OSA has been shown to be associated with the increased QT interval variability during sleep, possibly reflecting alterations in the sympathetic outflow to the ventricular myocardium.<sup>37</sup>

In addition to the prolonged  $QT_c$  and  $TpTe_c$  intervals, an increased  $TpTe/QT$  ratio, a measure of disproportional prolongation of global dispersion relative to the QT interval, may have an important role in arrhythmogenesis.<sup>16</sup> This ratio has the advantage of more reliably eliminating the confounding effects of the heart rate variability in the ECG and the inter-individual variation in the length of the QT interval.<sup>14</sup> We were able to demonstrate an increase in the  $TpTe/QT$  ratio after CPAP withdrawal, further substantiating a potential risk for arrhythmias in this situation.



**Figure 5** Correlation between the change in the  $TpTe_c$  interval (change from baseline to 2 weeks) and change in the apnoea/hypopnoea index ( $r = 0.45$ , 95% CI 0.17–0.67,  $P = 0.003$ ,  $n = 41$ ). Black circles represent patients in the subtherapeutic continuous positive airway pressure group and white circles represent patients in the therapeutic continuous positive airway pressure group.

These findings are in line with the preliminary evidence from observational studies, suggesting that the severity of OSA is also associated with the worsening of QT dynamicity parameters (QT/RR slope), an indicator of abnormal rate adaption of ventricular repolarization.<sup>19,37</sup> This may be due to a relative lack of parasympathetic tone in patients with OSA and, thus, be a predictor of myocardial vulnerability and tendency to cardiac dysrhythmias.<sup>19,38</sup>

A prolongation of QRS duration, i.e. a prolongation of ventricular depolarization, has been suggested to be associated with an increased propensity for SCD.<sup>39</sup> In our study, we found a small increase in QRS duration in the CPAP withdrawal group, which was, however, not statistically significant (1.1 ms,  $P = 0.96$ ). The risk of SCD associated with QRS prolongation is mainly interpreted as a result of overt coronary artery disease (ischaemia or scar).<sup>40,41</sup> However, in our study population, only three patients (two in the CPAP group and one in the CPAP withdrawal group) had (stable) coronary artery disease. Thus the chances of finding a significant prolongation of the QRS complex during the CPAP withdrawal were likely to be much smaller than it would have been in patients with overt coronary heart disease. This is in contrast to the more subtle markers of repolarization such as  $TpTe_c$ . It hence remains unclear at present whether OSA directly affects ventricular depolarization in the longer term, and further studies are required to conclusively answer this question.

There may be several mechanisms explaining the disturbance of repolarization and the high incidence of atrial and ventricular dysrhythmias and SCD in OSA patients. Obstructive apnoea and hypopnoea are associated with repeated inspiratory efforts against the collapsed upper airways associated with large swings in the intrathoracic pressure, which may be as high as 60–80 mmHg. During each obstructive apnoea and hypopnoea, the

negative intrathoracic pressure exerts a direct distending force on the heart and aorta.<sup>42</sup> Cardiac wall stress is additionally augmented by considerable acute changes in the atrial and ventricular volume during obstructive apnoea and hypopnoea.<sup>43–45</sup> *In vitro* experiments on myocardial tissue have shown that acute atrial stretch (similar to the atrial stretch occurring during apnoea/hypopnoea) induces both early and delayed after-depolarizations which may trigger premature myocardial contractions.<sup>44,45</sup> In an animal model, Linz *et al.*<sup>46</sup> reported shortening of the right atrial refractory period and the increased susceptibility to premature beats and AF induced by negative thoracic pressure during obstructive respiratory events. This mechanism, repeated during each apnoeic phase, may lead in the long-term to the electrical and mechanical remodelling of both the atria and left ventricle,<sup>47,48</sup> thereby possibly explaining the high prevalence of AF in patients with OSA.<sup>49,50</sup>

A further possible mechanism for the alteration of cardiac repolarization may be autonomic nervous system imbalance which has been shown to be present in OSA patients.<sup>6</sup> Baumert *et al.*<sup>51</sup> showed that experimentally induced increased cardiac sympathetic activity is positively correlated with QT variability in hypertensive patients. We previously reported an increased sympathetic activity as assessed by the urinary noradrenaline (mean increase 43.7%) and heart rate (mean increase 9.7%) after 2 weeks of CPAP withdrawal in the current study population.<sup>20</sup> In addition, there was a correlation between the change in the QT<sub>c</sub> and change in the heart rate ( $r = 0.45$ ,  $P = 0.003$ , data not shown) as well as between the change in the QT<sub>c</sub> and change in the urinary noradrenaline levels ( $r = 0.37$ ,  $P = 0.020$ , data not shown). These findings suggest that increased sympathetic nervous system activity may be one of the underlying mechanisms between OSA and the increased dispersion of cardiac repolarization, but further studies are warranted.

In summary, the increased susceptibility to dysrhythmias may therefore be explained by structural remodelling (resulting in the formation of an arrhythmogenic substrate),<sup>48</sup> electrical remodelling (manifesting as disturbed repolarization), increased sympathetic activation, and triggers (including acute episodes of apnoea and hypopnoea), which may eventually lead to the onset of ventricular dysrhythmias (Coumel's triangle).<sup>47</sup>

The current study has some inherent limitations. We performed standard resting 12-lead ECG and not continuous 24-h ECG, thus it is not possible to determine from the current study, the effects of CPAP withdrawal on ECG for longer periods, or during sleep. Therefore, further data from randomized controlled studies are needed to evaluate the effect of CPAP on measures of repolarization during sleep and longer daytime periods. Future interventional studies will also need to address the question as to which mechanisms underpin the association between OSA and both the prolongation and the increased dispersion of cardiac repolarization. The question as to whether OSA is associated with chronic and irreversible alterations of the ECG will need to be addressed in future trials with conventional design, however, due to ethical issues related to a long-term control group, it will be very difficult to perform a randomized controlled trial to answer this question. In addition, the findings of a study that selects patients with

high CPAP compliance cannot be generalized without caution to the untreated OSA population usually seen in a sleep clinic.

In conclusion, we have found that CPAP withdrawal for 2 weeks was associated with prolongation as well as increased dispersion of cardiac repolarization. These findings may provide a possible mechanistic link between OSA, cardiac arrhythmias, and SCD.

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