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ORIGINAL ARTICLE

The effects of simulated obstructive apnea and hypopnea on arrhythmic potential in healthy subjects

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Abstract Preliminary evidence supports an association between OSA and cardiac dysrhythmias. Negative intrathoracic pressure, as occurring during OSA, may provoke cardiac dysrhythmias. Thus, we aimed to study the acute effects of simulated apnea and hypopnea on arrhythmic potential and measures of cardiac repolarization [QT_C and T_{peak} to T_{end} intervals ($T_pT_{e_c}$)] in humans. In 41 healthy volunteers, ECG was continuously recorded prior, during and after simulated obstructive hypopnea (inspiration through a threshold load), simulated apnea (Mueller maneuver), end-expiratory central apnea and normal breathing in randomized order. The number of subjects with premature beats was significantly higher during inspiration through a threshold load ($n = 7$), and the Mueller maneuver ($n = 7$) compared to normal breathing ($n = 0$) ($p = 0.008$ for all comparisons), but not during end-expiratory central apnea ($n = 3$, $p = 0.125$). Inspiration through a threshold load was associated with a non-significant mean (SD) increase of the QT_C interval [+5.4 (22.4) ms, 95 %CI −1.7 to +12.4 ms, $p = 0.168$] and a significant increase of the $T_pT_{e_c}$ interval [+3.7 (8.9) ms, 95 %CI +0.9 to +6.6 ms, $p = 0.010$]. The Mueller maneuver induced a significant increase of the QT_C interval [+8.3 (23.4) ms, 95 %CI 0.9 to +15.6 ms, $p = 0.035$] and the $T_pT_{e_c}$ interval (+4.2 (8.2) ms, 95 %CI +1.6 to +6.8 ms, $p = 0.002$). There were no significant changes of the QT_C and $T_pT_{e_c}$ intervals during central end-expiratory apnea. These data indicate that simulated obstructive apnea and hypopnea are associated with an increase of premature beats and prolongation of QT_C and $T_pT_{e_c}$ intervals. Therefore, negative intrathoracic pressure changes may be a contributory mechanism for the association between OSA and cardiac dysrhythmias.

Keywords Heart rhythm · Cardiac dysrhythmia · Premature beats · Intrathoracic pressure · Obstructive sleep apnea

Abbreviations

AF	Atrial fibrillation
Ap	End-expiratory central apnea
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
iTH	Inspiration through inspiratory threshold
MM	Mueller maneuver
OSA	Obstructive sleep apnea
QT	QT interval
QT_C	Heart rate-corrected QT interval by Bazett's formula
SD	Standard deviation
SPB	Supraventricular premature beats
T_pT_e	T_{peak} to T_{end} interval

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$T_pT_{e_c}$ Heart rate-corrected T_{peak} to T_{end} interval by Bazett's formula

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder affecting up to 30 % of middle-aged adults in Western countries (Stradling and Crosby 1991; Young et al. 1993). OSA is characterized by repetitive interruption of ventilation during sleep caused by collapse of the upper airway resulting in apnea/hypopnea. Apnea/hypopnea leads to oxygen desaturations, increased inspiratory efforts, arousals from sleep and as a consequence to increased daytime sleepiness.

Symptomatic OSA has been shown to be a causal factor in the pathogenesis of hypertension and proposed as an independent risk factor for stroke and myocardial ischemia (Haentjens et al. 2007; Kohler et al. 2008; Marin et al. 2005; Pepperell et al. 2002). There are three major biological mechanisms underpinning the association between OSA and vascular disease: (1) intermittent hypoxia leading to increased oxidative stress, systemic inflammation and increased sympathetic activity, (2) arousal-induced reflex sympathetic activation with resultant acute repetitive blood pressure rises and (3) intrathoracic pressure changes leading to mechanical wall stresses on the heart and aorta (Kohler and Stradling 2010; Stöwhas et al. 2011).

There is preliminary evidence from observational studies that OSA may be related to cardiac dysrhythmias such as premature ventricular contractions, second-degree atrioventricular block, sinus arrest as well as atrial fibrillation (AF) (Gami et al. 2004; Guilleminault et al. 1983; Hoffstein and Mateika 1994; Namtvedt et al. 2011). The finding that patients with OSA have an increased risk of sudden cardiac death at night suggests a causal association between OSA and sudden cardiac death (Gami et al. 2005). However, as there is no data from randomized interventional trials proving this association and many patients with OSA also have significant cardiovascular comorbidities, a controversy remains as to whether OSA is a self-contained etiologic factor for cardiac dysrhythmias (Somers et al. 2008).

The mechanisms through which OSA may promote cardiac dysrhythmias are insufficiently understood. Several mechanisms by which OSA may affect heart rhythm have been proposed, including intermittent hypoxia, sympathetic and parasympathetic activation as well as intrathoracic pressure changes, leading to an increase in ventricular ectopic activity (Rogers et al. 1973; Shepard et al. 1985). Recent data from an animal model suggest that excessive negative intrathoracic pressure, as found during apnea/hypopnea in patients with OSA, may shorten the atrial refractory period and thus enhance the inducibility of AF by single premature beats (Linz et al. 2011).

Currently, there are no data on the physiological effects of experimentally simulated apnea and hypopnea and concomitant negative intrathoracic pressure changes on heart rhythm and indices of heart repolarization in humans. We have addressed this uncertainty by investigating the acute effects of simulated apnea and hypopnea on cardiac arrhythmic potential and ECG-derived measures of transmural dispersion of repolarization in healthy humans.

Methods

Subjects

The study was conducted at the University Hospital of Zurich, Zurich, Switzerland. Subjects were eligible for the study if they were between 18 and 75 years old and healthy. Exclusion criteria were a previous diagnosis of OSA, arterial hypertension, or any cardiac or aortic disease. The study was approved by the University of Zurich research ethics committee (EK 1672). Written informed consent was obtained from all participants.

Measurements

Anthropometrics

Weight, height, neck circumference as well as waist and hip circumference were measured and body mass index (BMI) was calculated.

Breathing maneuvers

A total of three breathing maneuvers were performed for 20 s each and compared to a period of normal breathing. Prior to the measurements, participants were instructed on the performance of inspiration through an inspiratory threshold load device, a Mueller maneuver to maintain a target intrathoracic pressure of −40 mmHg and a voluntary end-expiratory central apnea.

A nose clip was placed before the maneuvers. To generate an inspiratory threshold load, a threshold device with an incorporated negative pressure valve was used (Threshold®IMT from Respironics, New Jersey, Inc., Parsippany, NJ, USA). This device contains an inspiratory resistance which cannot be overcome unless a threshold pressure of −30 mmHg is generated at the mouth. For the Mueller maneuver, an occluded mouthpiece with a small air leak to prevent complete closure of the glottis was used.

At the end of resting expiration, inspiration was carried out against the occluded mouthpiece.

Electrocardiogram (ECG) and blood pressure were continuously recorded during (1) steady state normal breathing for 20 s; (2) one continuous inspiration through an inspiratory threshold load for 20 s; (3) Mueller maneuver lasting 20 s; (4) end-expiratory apnea (without respiratory effort) lasting 20 s. Maneuvers were performed in randomized order with 1 min of rest between each maneuver, which was long enough to allow blood pressure and heart rate to return to baseline levels.

Electrocardiography

Participants were asked to abstain from alcohol, tobacco or caffeine on the day the measurements were taken. 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 performed.

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. Prior to the measurements, participants rested for 5 min in the supine position, at the end of which 20 s of baseline ECG data were obtained. ECG was then recorded continuously throughout all breathing maneuvers, and the beginning and end of each maneuver were manually marked.

All ECGs were analyzed by the same investigator who was not aware of the order in which the maneuvers had been performed. The number of ventricular and supraventricular premature beats as well as any other dysrhythmia was noted during the baseline resting breathing period, during the maneuvers and immediately thereafter according to standard definitions (Crawford et al. 1999). Supraventricular premature beats were defined by the following characteristics: P wave with aberrant morphology and/or changed vector and shortened RR or PP interval compared to the previous heart cycle, usually followed by a compensatory pause. Ventricular premature beats were defined as follows: a QRS complex with a duration of >120 ms, a deformed morphology that does not resemble usual electric conduction (typically resembling right or left bundle branch block) and which is followed by a compensatory pause (Crawford et al. 1999, Rodríguez-Sotelo et al. 2009; http://www.americanheart.org).

Measurements of the ECG intervals were performed using dedicated ECG analysis software (DatInf® Measure 2.1d, DatInf GmbH, Tübingen, Germany). For the analysis, lead V5 was used and when unsuitable, lead II. Indices of transmural dispersion of repolarization were determined as follows: 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 (Lepeschkin and Surawicz 1952), and the T_{peak} to T_{end} interval (T_pT_e) as the time from the peak of the T wave to the end of the T wave. 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 (Perkiömäki et al. 1995). The QT interval and T_pT_e intervals were corrected for heart rate using Bazett's formula (Bazett 1920; Mincholé et al. 2011). ECG-interval times were determined from the 10 s preceding each maneuver, 20 s during the maneuver and 10 s immediately after the maneuver, and the mean value of the last two heart cycles of each period was used for further analysis.

Blood pressure

Non-invasive continuous beat-to beat measurements of arterial blood pressure was performed in supine position using a Finapres device (Finometer Midi, Finapres Medical Systems B.V., Amsterdam, The Netherlands). Changes in blood pressure during the respiratory maneuvers were assessed using the mean values of the 10 s immediately prior (baseline), 20 s during the maneuver as well as the 10 s immediately after termination of the maneuver (post).

Statistical analysis

All values are presented as mean (SD) unless otherwise stated. All statistical analyses were performed with Statistica V6.0 (StatSoft, Tulsa, OK, USA). Frequencies of premature beats occurring during normal breathing and breathing maneuvers were compared by McNemar tests. The differences in ECG-interval times between baseline, during the maneuver and post-maneuver were assessed by ANOVA for repeated measurements with Fisher post hoc analyses. Statistical significance was assumed at a probability of $p < 0.05$.

Results

Subjects

A total of 41 healthy subjects (17 females) with a mean age of 30.1 years (range 21–58) were included in the study and completed the protocol. The baseline characteristics of the participants are presented in Table 1. The comparison of subjects with supraventricular premature beats (SPB) and without SPB during inspiration through a threshold load device and during the Mueller maneuver is presented in Table 2.

Table 1 Participant characteristics

	Subjects ($n = 41$)
Age (years)	30.1 ± 8.7
Sex (female/male)	17/24
Height (cm)	175.4 ± 8.1
Weight (kg)	70.7 ± 12.9
Body mass index (kg/m^2)	22.8 ± 3.2
% Smokers	12.2
Systolic blood pressure (mmHg)	117.8 ± 12.5
Diastolic blood pressure (mmHg)	62.9 ± 6.5
Mean blood pressure (mmHg)	82.9 ± 7.8
Heart rate (beats/min)	66.0 ± 10.4
P wave (ms)	104.9 ± 17.8
PQ time (ms)	159.0 ± 20.8
QRS complex (ms)	90.2 ± 9.4
QT interval (ms)	387.7 ± 24.5
QT_C interval (ms)[a]	403.8 ± 20.3
T_{peak} to T_{end} (ms)	83.7 ± 7.7
T_{peak} to T_{end} (ms)[a]	87.3 ± 8.3

Values are presented as mean ± SD where applicable

[a] Heart rate corrected

Effects of intrathoracic pressure changes on heart rhythm

The number of subjects with premature beats was significantly higher during inspiration through a threshold load ($n = 7$, supraventricular 6, ventricular 1) and during the Mueller maneuver ($n = 7$, supraventricular 7, ventricular 0) compared to normal breathing ($n = 0$) ($p = 0.008$ for all comparisons), but not during end-expiratory central apnea ($n = 3$, supraventricular 2, ventricular 1, $p = 0.125$). The number of subjects with premature beats during the breathing maneuvers is shown in Fig. 1, panel a, and the total number of observed premature beats is shown in Fig. 1, panel b. Apart from premature beats, no other cardiac dysrhythmias and no signs of disturbed cardiac conduction (such as AV block) were observed. In one subject (female, baseline heart rate of 50 beats/min, baseline QT_C of 416 ms and baseline $T_pT_{e_c}$ of 73 ms), ventricular premature beats, one during inspiration through a threshold load and one during end-expiratory central apnea, were observed.

Effects of intrathoracic pressure changes on ECG intervals

Inspiration through a threshold load

ECG-interval times prior, during and post-inspiration through a threshold load are shown in Table 3. During the maneuver, there was a non-significant increase of the QT_C interval [+5.4 (22.4) ms, 95 % CI −1.7 to +12.4 ms, $p = 0.168$) that reached statistical significance after release of the maneuver [+14.0 (23.9) ms, 95 % CI +6.4 to +21.5 ms, $p < 0.001$] compared to prior to the maneuver. The $T_pT_{e_c}$ interval showed a significant increase during the maneuver [+3.7 (8.9) ms, 95 % CI +0.9 to 6.6 ms, $p = 0.010$] and a trend toward a longer $T_pT_{e_c}$ interval after release of the maneuver [+2.1 (10.1) ms, 95 % CI −1.1 to +5.3 ms, $p = 0.144$] compared to prior to the maneuver.

Mueller maneuver

ECG-interval times prior, during and post-Mueller maneuver are shown in Table 4. There was a significant increase of the QT_C interval [+8.3 (23.4) ms, 95 % CI +0.9 to +15.6 ms, $p = 0.035$) and $T_pT_{e_c}$ interval [+4.2 (8.2) ms, 95 % CI +1.6 to +6.8 ms, $p = 0.002$) compared

Table 2 Comparison of subjects with supraventricular premature beats (SPB) and without SPB during inspiration through a threshold load device and Mueller maneuver

	Subjects ($n = 10$) with SPB	Subjects ($n = 31$) without SPB	p value
Age (years)	26.9 ± 4.8	31.1 ± 9.4	0.187
Sex (female/male)	4/6	13/18	0.914
Systolic blood pressure (mmHg)	117.4 ± 9.9	117.9 ± 13.4	0.917
Diastolic blood pressure (mmHg)	62.8 ± 7.7	63.0 ± 6.2	0.961
Mean blood pressure (mmHg)	81.5 ± 8.6	83.2 ± 7.6	0.544
Heart rate (beats/min)	64.4 ± 11.1	66.5 ± 10.3	0.557
P wave (ms)	99.8 ± 25.6	106.5 ± 14.6	0.305
PQ time (ms)	151.0 ± 24.9	161.5 ± 19.1	0.177
QRS complex (ms)	92.2 ± 9.6	89.5 ± 9.4	0.443
QT interval (ms)	386.0 ± 28.00	388.2 ± 23.7	0.809
QT_C interval (ms)[a]	396.9 ± 19.5	406.0 ± 20.3	0.218
T_{peak} to T_{end} (ms)	85.0 ± 10.8	83.2 ± 6.5	0.531
T_{peak} to T_{end} (ms)[a]	87.4 ± 9.1	87.2 ± 8.2	0.969

Values are presented as mean ± SD where applicable

[a] Heart rate corrected

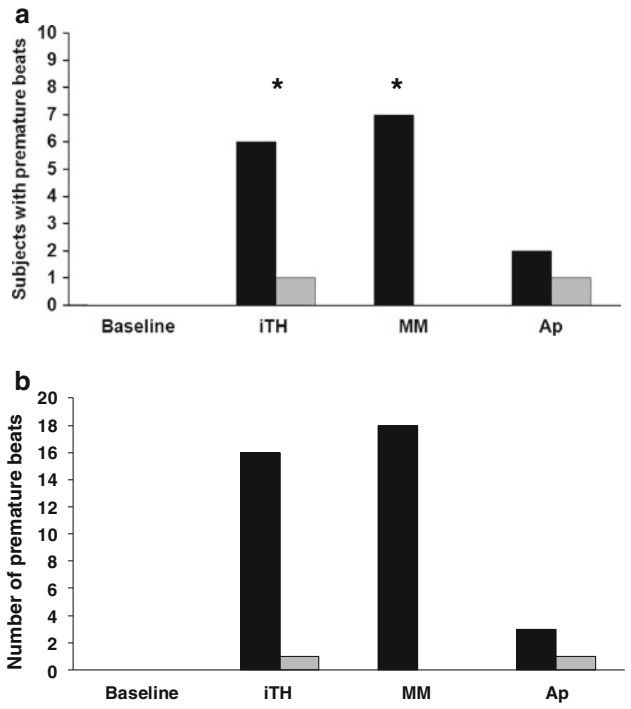

Fig. 1 **a** The *black bars* represent the number of subjects with supraventricular premature beats, and the *gray bars* represent the number of subjects with ventricular premature beats during breathing maneuvers (*iTH* inspiration through inspiratory threshold, *MM* Mueller maneuver, *Ap* end-expiratory central apnea). Compared to normal breathing, significantly more subjects had supraventricular premature beats during breathing maneuvers associated with negative intrathoracic pressure (iTH, MM). **b** The *black bars* represent the total number of supraventricular premature beats, and the *gray bars* represent the total number of subjects with ventricular premature beats observed during the different breathing maneuvers (*iTH* inspiration through inspiratory threshold, *MM* Mueller maneuver, *Ap* end-expiratory central apnea)

to prior to the maneuver. This increase of the QT_C interval persisted after release of the maneuver [+8.8 (26.7) ms, 95 % CI +0.4 to +17.2 ms, $p = 0.024$), while the $T_pT_{e_c}$ interval returned to baseline value [+0.8 (9.6) ms, 95 % CI −2.19 to +3.88 ms, $p = 0.971$].

End-expiratory apnea

ECG-interval times prior, during and post end-expiratory central apnea are shown in Table 5. There were no statistically significant changes in ECG-interval times during or after termination of the maneuver.

Discussion

To the best of our knowledge, this is the first study investigating the effects of simulated apnea and hypopnea on heart rhythm and ECG measures of cardiac repolarization in healthy humans. We found that simulated obstructive apnea and hypopnea were both associated with a significant increase in supraventricular premature beats as well as with prolongation of the QT and T_pT_e intervals. These findings may provide a possible mechanistic link between OSA, dysrhythmias and sudden cardiac death.

Obstructive apneas and hypopneas are associated with repeated inspiratory efforts against the collapsed upper airways associated with large changes in intrathoracic pressure, which may be as high as 60 mmHg. During apnea and hypopnea, the negative intrathoracic pressure exerts a direct tension on intrathoracic structures such as the heart and aorta. Cardiac wall stress is additionally augmented by considerable changes in atrial and ventricular volume occurring during apnea/hypopnea (Koshino et al. 2010; Orban et al. 2008; Virolainen et al. 1995).

To assess the effect of intrathoracic pressure changes on arrhythmic potential and ECG measures of cardiac repolarization, we simulated apnea and hypopnea by performing a Mueller maneuver and an inspiration through an inspiratory threshold device, respectively. Both maneuvers have previously been shown to lead to a fall in intrathoracic pressure as well as to sympathetic activation and hemodynamic changes similar to those occurring in OSA (Bradley et al. 2001; Somers et al. 1995). The number of subjects with premature beats (primarily supraventricular) was significantly higher during simulated apnea and hypopnea compared to normal breathing, and this was not observed during voluntary central apnea. These findings are consistent with data from in vitro experiments on myocardial tissue showing that acute atrial stretch (similar to the atrial stretch occurring during apnea/hypopnea) induces both early and delayed after-depolarizations, which may trigger premature myocardial contractions (Kamkin et al. 2000; Nazir and Lab 1996). Recently, Linz et al. (2011) reported a shortening of right atrial refractory period and increased susceptibility to premature beats and atrial fibrillation induced by negative intrathoracic pressure during obstructive respiratory events in an animal model. Thus, intrathoracic pressure changes may be an important mechanism explaining the high prevalence of supra- and ventricular premature beats and more malignant dysrhythmias found in patients with OSA (Alonso-Fernández et al. 2005; Mehra et al. 2006).

The QT interval on the surface ECG is the electrocardiographic representation of ventricular depolarization and repolarization. Numerous studies have shown the importance of QT prolongation as a risk factor for the occurrence of malignant cardiac dysrhythmia, such as torsade de pointes, and of sudden cardiac death (Elming et al. 2002; Viskin 1999). In addition, T_{peak} to T_{end} (T_pT_e), the interval measured from the peak of the T wave to the end of the T wave, has been shown to be a measure of transmural

Table 3 ECG times and blood pressure during inspiration through a threshold load

	Pre-maneuver	During-maneuver	Post-maneuver
MBP (mmHg)	90.28 ± 10.45	82.20 ± 9.77*	85.53 ± 10.90*,†
HR (min^{-1})	69.93 ± 11.71	72.43 ± 12.99	76.74 ± 12.49*,†
P (ms)	102.21 ± 14.19	98.71 ± 14.94*	104.11 ± 13.72†
PQ (ms)	162.06 ± 20.60	155.37 ± 25.55*	161.88 ± 23.06†
QRS (ms)	91.09 ± 12.09	90.63 ± 12.92	90.70 ± 12.17
QT (ms)	387.81 ± 26.41	386.96 ± 29.24	382.85 ± 26.40*,†
QT_C (ms)	415.40 ± 23.05	420.77 ± 24.49	429.38 ± 26.16*,†
T_pT_e (ms)	86.27 ± 10.68	88.53 ± 11.51	84.19 ± 11.15†
$T_pT_{e_c}$ (ms)	92.82 ± 13.07	96.55 ± 13.95*	94.90 ± 15.72

Values are mean ± SD

* $p < 0.05$ versus pre-maneuver

† $p < 0.05$ maneuver versus post-maneuver

Table 4 ECG times and blood pressure during Mueller maneuver

	Pre-maneuver	During-maneuver	Post-maneuver
MBP (mmHg)	91.07 ± 9.77	87.87 ± 12.31*	97.02 ± 12.17*,†
HR (min^{-1})	70.39 ± 11.30	72.43 ± 11.53	74.27 ± 10.45*
P (ms)	101.98 ± 14.87	102.13 ± 14.25	104.78 ± 15.94
PQ (ms)	161.99 ± 19.81	160.70 ± 21.20	162.16 ± 20.71
QRS (ms)	91.72 ± 15.01	91.17 ± 13.94	91.82 ± 11.65
QT (ms)	386.37 ± 28.67	389.36 ± 27.83*	383.97 ± 25.56†
QT_C (ms)	415.91 ± 24.27	424.16 ± 21.05*	424.73 ± 22.56*
T_pT_e (ms)	86.14 ± 11.23	88.88 ± 9.52*	84.45 ± 10.90†
$T_pT_{e_c}$ (ms)	92.88 ± 12.66	97.09 ± 11.76*	93.73 ± 13.94†

Values are mean ± SD

* $p < 0.05$ versus pre-maneuver

† $p < 0.05$ maneuver versus post-maneuver

Table 5 ECG times and blood pressure during end-expiratory central apnea

	Pre-maneuver	During-maneuver	Post-maneuver
MBP (mmHg)	89.92 ± 9.63	90.41 ± 10.05	96.51 ± 10.84*,†
HR (min^{-1})	69.95 ± 11.71	67.91 ± 10.17	68.93 ± 11.47
P (ms)	104.85 ± 14.19	103.07 ± 14.71	100.36 ± 19.43*
PQ (ms)	162.70 ± 20.68	159.98 ± 22.47	160.14 ± 22.08
QRS (ms)	91.95 ± 12.92	91.50 ± 13.74	91.82 ± 14.21
QT (ms)	387.97 ± 29.10	389.50 ± 27.54	388.30 ± 28.17
QT_C (ms)	415.25 ± 20.22	411.64 ± 23.39	412.50 ± 27.25
T_pT_e (ms)	84.34 ± 8.98	84.80 ± 9.38	85.32 ± 8.92
T_pT_{ec} (ms)	90.48 ± 10.04	89.93 ± 12.07	91.02 ± 11.95

Values are mean ± SD

* $p < 0.05$ versus pre-maneuver

† $p < 0.05$ maneuver versus post-maneuver

dispersion during repolarization of the left ventricular myocardium (Antzelevitch 2006; Xia et al. 2005). A prolongation of the T_pT_e interval, indicating enhanced transmural dispersion, is thought to represent increased vulnerability to the occurrence of early after-depolarizations and consequent tachycardia (Yamaguchi et al. 2003; Yan and Antzelevitch 1998). In addition, Panikkath et al. (2011) recently showed that a prolonged T_pT_e interval in the resting ECG is independently associated with an increased risk of sudden cardiac death (SCD). In the current study, we found a significant prolongation of the heart rate-corrected QT interval (QT_C) during simulated obstructive apnea and a trend toward a longer QT_C during simulated obstructive hypopnea. In concordance with the observed QT_C changes, simulated obstructive apnea and hypopnea were both found to be associated with a prolongation of the $T_pT_{e_c}$ interval. These findings support previous preliminary observations that the QT interval is prolonged during apnea/hypopnea in patients with OSA, and continuous positive airway pressure therapy may prevent this (Gillis et al. 1991; Rossi et al. 2012).

In addition to the tension forces induced by intrathoracic pressure changes, cardiac repolarization may also be altered by increased sympathetic activation which has previously been shown to be present in patients with OSA (Somers et al. 1995) and during experimentally simulated obstructive apnea (Somers et al. 1993). Thus, increased sympathetic activation may explain the altered

repolarization during simulated apnea and hypopnea observed in the current study.

The current study has some limitations. During the different maneuvers, we did not directly measure the intrathoracic pressure fluctuations. This is because estimating pressure with an esophageal catheter may induce reflex cardiorespiratory effects possibly affecting the cardiac conducting system and thus induce premature beats (Loomis et al. 1997; Pickering et al. 2002). However, the subjects were carefully instructed in the correct performance of the maneuvers and, as there were substantial and significant changes in blood pressure and heart rate during the different maneuvers, we are confident that the maneuvers induced the expected intrathoracic pressure changes. In addition, we measured intrathoracic pressure during the Mueller maneuver in five subjects using the same technique and an esophageal catheter in a validation experiment. Intrathoracic pressure decreased by a median of 40 mmHg (IQR 3 mmHg), indicating that the proposed intrathoracic pressure changes during the Mueller maneuver were achieved in the current study. Furthermore, the threshold load valve we used generated a sound when the preset inspiratory threshold had been reached, so that the intended negative mouth and intrathoracic pressure, respectively, could be ensured.

One could speculate that patients with OSA react differently to experimentally induced intrathoracic pressure changes, regarding their heart rhythm, due to adaptive mechanisms or in fact may have more pronounced effects due to a high frequency of cardiac disease. Studies looking at the effects of experimentally induced intrathoracic pressure changes on heart rhythm in patients with OSA will be needed to clarify this point.

In conclusion, we found that simulated obstructive apnea and hypopnea are both associated with an increase of premature beats and a prolongation of the QT_C and $T_pT_{e_c}$ intervals. These findings may provide a possible mechanistic link between OSA, dysrhythmias and sudden cardiac death. Further data from randomized controlled interventional studies looking at the effect of CPAP on heart rhythm are needed to define the role of OSA in the pathogenesis of cardiac dysrhythmias.

Conflict of interest No conflict of interest, financial or otherwise, is declared by the authors.

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