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ORIGINAL ARTICLE

Assessment of atrial electromechanical delay and influential factors in patients with obstructive sleep apnea

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Abstract
Purpose The interaction between moderate-to-severe obstructive sleep apnea (OSA) and cardiac arrhythmias, especially atrial fibrillation (AF), is well known. We aimed to determine whether atrial electromechanical parameters assessed by tissue Doppler imaging (TDI) would be affected in moderate-to-severe OSA, and detect the influential factors of atrial electromechanical parameters in these patients.
Methods and results Interatrial and intra-atrial electromechanical delay was measured by TDI in patients with moderate-to-severe OSA (n=64) and control subjects (n=39). P-wave dispersion (PWD) was calculated on the 12-lead ECG. Interatrial and intra-atrial electromechanical delay was significantly higher in the OSA group when compared with the controls (52.26±12.9 vs 29.61±11.26, P<0.0001 and 18.90±8.13 vs 8.71±5.46, P<0.0001; respectively). PWD was higher in the OSA group (46.09±13.40 ms vs 34.10±10.75 ms, P<0.0001). Interatrial electromechanical delay had a positive correlation with PWD (r=0.490, P<0.0001), left atrial (LA) diameter (r=0.383, P=0.002), LA volume index (r=0.354, P=0.004), and apnea–hypopnea index (r=0.365, P=0.003). In addition, interatrial electromechanical delay was negatively correlated with the magnitude of the lowest oxygen saturation percentage (r=−0.498, P<0.0001).
Conclusion This study showed that interatrial and intra-atrial electromechanical delay and PWD were prolonged in patients with moderate-to-severe OSA. LA dilatation, hypoxemia, and the severity of the disease may contribute a prolongation in interatrial electromechanical delay via atrial structural and electrical alterations, which may predict the risk of future AF development in patients with moderate-to-severe OSA.

Keywords Atrial electromechanical delay · Obstructive sleep apnea

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of decreased or total cessation of respiratory airflow during sleep and occurs in approximately 9–15% of the population [1, 2]. OSA is an important health problem and associated with cardiovascular diseases, such as heart failure, left ventricular (LV) and right ventricular (RV) dysfunction, myocardial infarction, and arrhythmias [3, 4]. Atrial fibrillation (AF) is the most common arrhythmia in clinical practice [5]. Recent prospective studies have confirmed a high prevalence of OSA in patients with AF and an independent association between the two conditions as well [6]. However, the predisposing mechanisms of OSA to AF are poorly understood.

The prolongation of intra-atrial and interatrial conduction times and the inhomogeneous propagation of sinus impulses are well-known electrophysiological characteristics of the atrium prone to fibrillate [7–10]. Recently, it

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has been possible to perform precise analysis of atrial motion among different regions at high temporal resolution with tissue Doppler imaging (TDI) [9]. Atrial electromechanical delay as measured by TDI has been demonstrated to detect atrial impairment in paroxysmal AF [10].

The purpose of our study was to determine whether atrial electromechanical parameters assessed by TDI would be affected in moderate-to-severe OSA and the influential factors of atrial electromechanical parameters in these patients.

Methods and procedures

Study population

The patient group consisted of 64 untreated patients (21 female, mean age 48.98±12.01 years) who were referred to the Sleep Disorders Center of Inonu University Hospital and were diagnosed as moderate-to-severe OSA [apnea–hypopnea index (AHI) ≥15 events/h] on polysomnographic testing. The control group consisted of 39 healthy subjects (15 female, mean age 46.28±11.85 years) who were found not to have OSA (AHI ≤5 events/h) on polysomnographic testing.

Patients and controls with a history or clinical evidence of LV wall motion abnormality, LV ejection fraction (EF) less than 50%, primary cardiomyopathy, valvular heart disease, arrhythmia, bundle branch block, atrioventricular conduction abnormality on electrocardiogram, pericarditis, thyroid dysfunction, anemia, electrolyte imbalance, renal failure, pulmonary disease, and use of medications known to affect the electrocardiographic parameters were excluded from the study. All of the subjects had sinus rhythm. The study was carried out according to the principles of the Declaration of Helsinki and approved by Inonu University, School of Medicine, investigational review board. Using standard laboratory methods, blood samples were drawn after an overnight 12-h fasting to determine levels of blood glucose, electrolytes, and total cholesterol.

Polysomnography

Full-night polysomnography was performed using conventional instrumentation and analysis according to the recommendations on syndrome definition and measurement techniques published by the American Academy of Sleep Medicine [11]. Sleep stages were detailed by standard electroencephalographic, electrooculographic, and electromyographic criteria. Apneas and hypopneas were recorded by oronasal flow cannulae attached to a pneumotachograph. Arterial oxygen saturation was measured by pulse oximetry using a finger probe. Thoracic and abdominal movements were recorded by using inductive plethysmography to document respiratory effort. Periodical limb movements were recorded from surface EMG electrode on tibialis anterior muscle of the lower extremity. Obstructive apneas were defined as absence of airflow for longer than 10 s, obstructive hypopneas as a 50% decrease in airflow or a clear but lesser decrease in airflow if coupled with either a desaturation of >3% or an arousal in the context of ongoing respiratory effort. All records were scored manually for sleep stage, arousals, apneas, and hypopneas. The groups were defined as controls (AHI ≤5 events/h) and moderate-to-severe (AHI ≥15 events/h) OSA.

Echocardiography

In all subjects, echocardiographic examinations (ATL HDI–5000; Bothell, WA, USA) were performed by a cardiologist who was blinded to the clinical details and results of the other investigations of each patient and control. During echocardiography examination, a one-lead ECG was recorded continuously. M-mode measurements were performed according to the criteria of the American Society of Echocardiography. Three consecutive cycles were averaged for every parameter. Left atrial (LA) dimension, LV end-systolic and end-diastolic diameters were measured. LVEF was estimated by Simpson's rule. LA volume was calculated at end systole of the LV in the apical four-chamber view using the methods of disks (Simpson's rule). LA volume was indexed to body surface area and expressed in milliliter per square meter.

For Doppler tissue, echocardiography was performed by the same echocardiograph machine, adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15–20 cm/s was reached and using the minimal optimal gain. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. In an apical four-chamber view, the pulsed Doppler sample volume was placed at the level of LV lateral mitral, septal mitral, and RV tricuspid annuli. The time interval from the onset of the P wave on surface ECG to the beginning of the late diastolic wave (Am wave) on TDI, which is named PA, was obtained from the lateral mitral (lateral PA), septal mitral (septal PA), and RV tricuspid annuli (tricuspid PA); respectively (Fig. 1). The difference between lateral PA and tricuspid PA (lateral PA−tricuspid PA) was defined as interatrial electromechanical delay, and the difference between septal PA and tricuspid PA (septal PA−tricuspid PA) was defined as intra-atrial electromechanical delay [9].

P-wave dispersion measurements on 12-lead ECG

Twelve-lead surface ECGs were obtained for each subject in the supine position at a paper speed of 50 mm/s. The P-

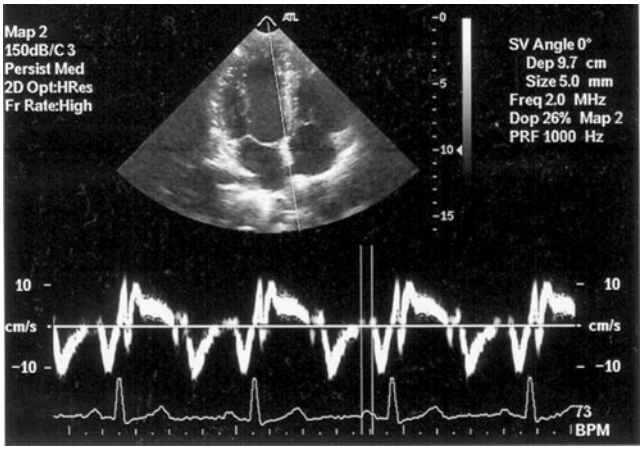

Fig. 1 Measurement of the time interval from onset of the P wave on surface ECG to the beginning of the Am wave with tissue Doppler echocardiography

wave durations were measured manually by two investigators unaware of patient assignment by using calipers and a magnifying lens (10-fold magnification) to define the electrocardiogram deflections. The onset of the P wave was defined as the junction between the isoelectric line and the beginning of P-wave deflection. The offset was defined as the junction between the end of the P-wave deflection and the isoelectric line. The longest atrial conduction time measured on any of the 12 leads was defined as P maximum (Pmax), and the shortest time was defined as P minimum (Pmin). The difference between Pmax and Pmin was calculated and defined as P-wave dispersion (PWD, PWD=Pmax−Pmin). The patients who had indiscernible P waves in more than four leads on a baseline 12-lead ECG were not enrolled in the study.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0 software (SPSS Inc., Chicago, IL). All continuous variables were expressed as mean ± SD, and categorical variables were defined as percentages. Categorical data were compared using the chi-square test. Continuous variables were compared between the groups using the Student's *t* test or Mann–Whitney *U* test, depending on whether they distributed normally or did not, as tested by the Shapiro–Wilk test. Pearson's correlation analysis was used to estimate the relationship between the test parameters. A P value <0.05 was considered to be statistically significant.

Results

Baseline clinical and laboratory characteristics of the study population are shown in Table 1. The two groups were similar regarding age, sex, blood pressure, smoking status, total cholesterol, and glucose levels. Body mass index and AHI were higher in the OSA group (34.24±6.66 vs 28.91±3.06, P<0.001; 45.59±24.61 vs 1.71±1.39, P<0.0001;

Table 1 Clinical characteristics of the study population

	OSA (n=64)	Controls (n=39)	P value
Age (years)	48.98±12.01	46.28±11.85	NS
Female, *n* (%)	21 (33)	15(38)	NS
BMI (kg/m^2)	34.24±6.66	28.91±3.06	<0.0001
Diabetes mellitus, *n* (%)	14 (22)	4(10)	NS
Hypertension, *n* (%)	18(28)	8(20)	NS
Smokers, *n* (%)	21 (33)	11 (28)	NS
SBP (mmHg)	126.92±23.03	126.64±14.15	NS
DBP (mmHg)	86.71±13.49	86.56±14.03	NS
Total cholesterol (mg/dl)	201.23±38.39	196.66±31.09	NS
Fasting blood glucose (mg/dl)	115.47±34.75	107.82±48.24	NS
AHI (events/h)	45.59±24.61	1.71±1.39	<0.0001
Lowest oxygen saturation (%)	70.09±12.89	88.47±4.09	<0.0001
LV ejection fraction (%)	63.90±4.01	65.10±4.86	NS
LVEDD (mm)	45.14±2.63	44.59±2.59	NS
LVESD (mm)	29.22±2.57	28.05±3.01	NS
Septal thickness (mm)	10.42±1.31	9.95±1.21	NS
PW thickness (mm)	10.16±1.34	9.90±1.42	NS
Left atrial diameter (mm)	38.80±3.27	35.44±3.53	<0.0001
Left atrial volume index (ml/m²)	25.69±3.94	23.41±4.52	<0.008

LV left ventricular, *LVEDD* LV end-diastolic dimension, *LVESD* LV end-systolic dimension, *PW* posterior wall, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AHI* apnea–hypopnea index, *NS* non-significant

Table 2 Comparison of the electrocardiographic and atrial electromechanical parameters

	OSA (n=64)	Controls (n=39)	P value
Heart rate (beats/min)	79.17±13.18	77.78±10.75	NS
Pmax (ms)	115.08±13.31	102.69±9.51	<0.0001
Pmin (ms)	68.98±11.45	68.59±10.38	NS
PWD (ms)	46.09±13.40	34.10±10.75	<0.0001
Lateral PA (ms)	94.84 ±13.48	71.67±12.89	<0.0001
Septal PA (ms)	61.48±10.41	50.77±8.99	<0.0001
Tricuspid PA (ms)	42.58±6.78	42.05±6.14	NS
Lateral PA−tricuspid PA[a] (ms)	52.26±12.9	29.61±11.26	<0.0001
Septal PA−tricuspid PA[b] (ms)	18.90±8.13	8.71±5.46	<0.0001

[a] Interatrial electromechanical delay

[b] Intra-atrial electromechanical delay

NS non-significant

respectively). Lowest oxygen saturation percentage was found to be lower in the OSA group (70.09±12.89 vs 88.47±4.09, P<0.0001). In addition, interventricular septum thickness, LV posterior wall thickness, LV end-diastolic dimension, LV end-systolic dimension, and LVEF were similar between the OSA and the control groups. LA diameter (38.80±3.27 vs 35.44±3.53 mm, P<0.0001) and LA volume index (25.69±3.94 vs 23.41±4.52 ml/m² P=0.008) were significantly higher in the OSA group.

P-wave measures are shown in Table 2. Statistically significant differences were found in Pmax and PWD values between the OSA and the control groups (115.08±13.31 vs 102.69±9.51 ms, P<0.0001; 46.09±13.40 vs 34.10±10.75 ms, P<0.0001).

The atrial electromechanical parameters are reported in Table 2. PA lateral and PA septum durations were significantly higher in the OSA group compared with the controls (94.84±13.48 vs 71.67±12.89 ms, P<0.001; 61.48±10.41 vs 50.77±8.99 ms, P<0.0001; respectively). However, PA tricuspid duration was similar between both groups (42.58±6.78 vs 42.05±6.14 ms, P>0.05). Moreover, interatrial and intra-atrial electromechanical delay was significantly higher in the OSA group when compared with the controls (52.26±12.9 vs 29.61±11.26, P<0.0001 and 18.90±8.13 vs 8.71±5.46, P<0.0001; respectively).

A significant correlation was detected between PWD and interatrial electromechanical delay (r=0.490, P<0.0001). Interatrial electromechanical delay had a positive correlation with LA diameter (r=0.383, P=0.002), LA volume index (r=0.354, P=0.004), and AHI (r=0.365, P=0.003). In addition, interatrial electromechanical delay was negatively correlated with the magnitude of the lowest oxygen saturation percentage (r=−0.498, P<0.0001) (Fig. 2).

Discussion

OSA is associated with twofold to threefold increased risk for the occurrence of atrial fibrillation [12]. The large-scale Sleep Heart Health Study has also recently demonstrated that AF has occurred in 5% of those with severe OSA and only in 1% of those without OSA [13]. Kanagala et al. have found that patients with untreated OSA have had a higher risk of recurrence of AF after successful cardioversion in

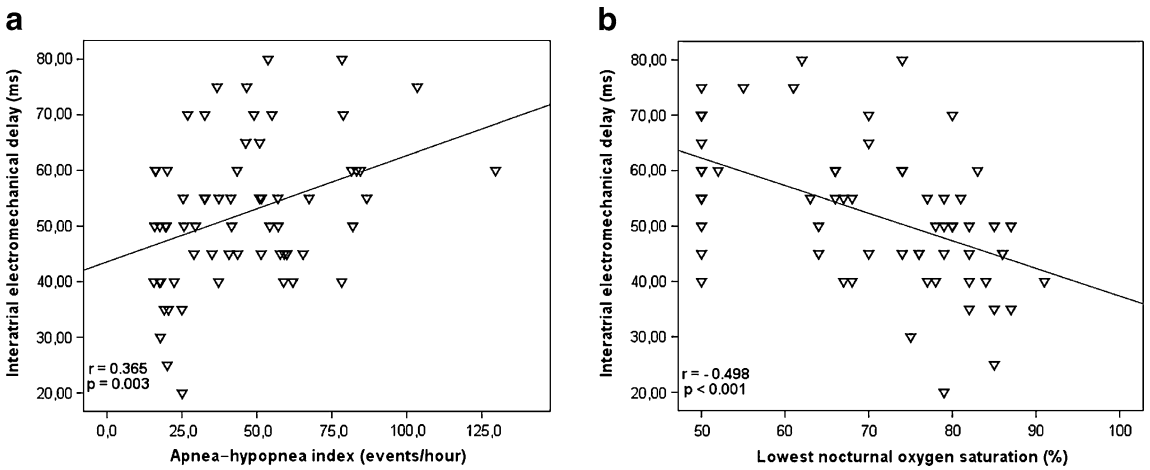

Fig. 2 Positive correlation between interatrial electromechanical delay and apnea–hypopnea index (**a**) and between interatrial electromechanical delay and lowest nocturnal oxygen saturation (**b**)

contrast with the patients without known sleep apnea [14]. Several pathophysiological mechanisms such as episodes of repetitive and prolonged hypoxaemia, sympathovagal imbalance, LV diastolic dysfunction, systemic inflammation, and exaggerated intrathoracic pressure oscillations with increased cardiac wall stress can contribute the occurence of AF in patients with OSA [14–17].

Recent studies have assessed atrial electromechanical delay with TDI echocardiography, which is a noninvasive method alternative to invasive electrophysiological studies, in patients with mitral stenosis, and type 1 diabetes mellitus [9, 18]. Also, Roshanalli et al. have found that atrial electromechanical interval is a predictor of AF emerging after coronary artery bypass grafting and shown that the preoperative administration of amiodarone to patients having longer atrial electromechanical interval has decreased the postoperative AF incidence [19]. These studies have shown that prolonged electromechanical interval seems to reflect atrial remodeling for an arrhythmogenic substrate [10, 19]. In our study, we demonstrated that the intra-atrial and interatrial electromechanical delay, which was a technique estimating the risk of future AF development, was significantly longer in patients with moderate-to-severe OSA than in the controls.

It is accepted that increased P-wave duration and PWD on the standard surface ECG indicates an atrial conduction disorder. Moreover, Can et al. have found PWD and P-wave duration high in patients with OSA, and this has been associated with severity of the diease [20]. Our results were consistent with their findings demonstrating that values of PWD and P_{max} were higher in patients with OSA than in the controls. We also found a significant correlation between PWD and interatrial electromechanical delay.

Larger LA dimension predisposes to a greater risk of AF development [21] and accounts for an independent predictive value for determining the risk of AF. Increased nonuniform anisotropy and conduction delay are the main characteristics of the structural and electropysiological changes in dilated atria, and these changes are associated with a higher risk of paroxysmal atrial tachyarrhythmias [10]. LA dilatation has already been reported in patients with OSA in previous studies [22, 23]. Gami et al. have pointed out that concomitant obesity, via larger body mass and increased total blood volume, is responsible for LA enlargement [24]. In a study of middle-aged adults, it has been found that LA volume indices, while still within the normal range, have been greater in subjects with OSA [22]. In our study, we also detected a greater LA diameter and LA volume index in patients with OSA. We found that interatrial electromechanical delay had a significant correlation with LA volume index and LA dimension. Our findings support that increased LA enlargement accompanying OSA may contribute the prolongation of interatrial electromechanical delay. This fact may help to explain the increased risk of AF in such patients.

Another finding of our study is the significant correlation between interatrial electromechanical delay and the lowest nocturnal oxygen saturation and AHI. Hypoxemia and hypercapnia have direct adverse effects on cardiac electrical stability [25]. It has long been known that hypoxia, as a consequence of OSA, can result in arrhythmias [26]. During obstructive apneas, the patients generate negative intrathoracic pressure against an occluded upper airway that leads to swings in intrathoracic pressure, thereby causing atrial chamber enlargement and increasing atrial vulnerability [27, 28]. Moreover, hypoxia, as a result of the obstructive apneic episodes, stimulates the sympathetic nervous system potently through reflex mechanisms. The severe elevations of sympathetic activity may activate atrial catecholamine-sensitive ion channels [17]. These electrical and hemodynamic changes may alter atrial conduction properties because of their effects on atrial myocardial remodeling and may be responsible for the atrial electromechanical delay in OSA. Indeed, previous investigations have implicated measures of oxygen desaturation as likely mediators of the interaction between OSA and AF. Gami et al. have found the magnitude of nocturnal oxygen desaturation, which is an important pathophysiological consequence of OSA, is an independent risk factor for incident AF in individuals less than 65 years of age [12]. In addition, Kanagala et al. have found a higher rate of AF recurrence in patients with lower nocturnal oxygen saturation [14].

In conclusion, we found interatrial and intra-atrial electromechanical delay and PWD prolonged in patients with moderate-to-severe OSA. Prolonged interatrial electromechanical delay significantly correlated with PWD, LA volume index, and AHI, and negatively correlated with the magnitude of the lowest oxygen saturation percentage. We concluded that LA dilatation, hypoxemia, and the severity of the disease may contribute a prolongation in interatrial electromechanical delay via atrial structural and electrical alterations, which may predict the risk of future AF development in patients with moderate-to-severe OSA.

The most important limitation of the study is the cross-sectional design of the study, in which the patients were not prospectively followed up for future arrhythmic events. Therefore, we do not know whether prolongation of PWD and atrial electromechanical delay predict atrial arrhythmias in patients with OSA. Further long-term prospective studies are needed to determine the clinical utility and prognostic importance of interatrial electromechanical delay in OSA.

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