ORIGINAL ARTICLE

Assessment of atrial electromechanical delay and P wave dispersion in patients with chronic obstructive pulmonary disease

Kronik obstrüktif akciğer hastalarında atriyal elektromekanik gecikmenin ve P dalga dispersiyonun değerlendirilmesi

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ABSTRACT

Objective: Chronic obstructive pulmonary disease (COPD) is associated with atrial fibrillation (AF) and reduced forced expiratory volume (FEV1) is an independent predictor for new onset AF. The aims of this study were (1) to analyze the atrial electromechanical delay (AEMD) and P wave dispersion which are two predictors of AF development in patients with COPD and without any cardiovascular disease, and (2) to assess the relationship of those with pulmonary functions as quantified by FEV1 measurements.

Methods: The study included 41 patients with COPD (33 male; mean age: 51 years) and 32 healthy controls. P wave dispersion was calculated as the difference between the maximum and minimum P wave duration in a 12-lead surface electrocardiography (ECG) recording. AEMD, defined as the time interval from the P wave onset on the ECG to the initiation of the late diastolic (Am) wave using a tissue Doppler examination, was measured from the lateral mitral annulus (LAEMD), septal annulus (SAEMD), and tricuspid lateral annulus (TAEMD).

Results: P wave dispersion was significantly longer in the COPD group than those in the controls (76±19 ms vs. 45±10 ms; p<0.001). All of the AEMD measurements demonstrated significant prolongation in patients with COPD (LAEMD: 74±9 ms vs. 64±11 ms; SAEMD: 66±10 ms vs. 57±12 ms; and TAEMD: 65±9 ms vs. 46±7 ms; p<0.001 for all). The only correlation with FEV1 was observed in the TAEMD values of the COPD group (rs: -401; p<0.009).

Conclusion: Both P wave dispersion and AEMD parameters were significantly longer in COPD patients without any established structural or functional cardiac abnormalities, indicating an increased tendency for AF development, beginning from the initial stages of the disease.

ÖZET

Amaç: Kronik obstrüktif akciğer hastalığı (KOAH) ile atriyal fibrilasyonu (AF) ilişkidir ve azalmış birinci saniye zorlu ekspiratuvar volümü (ZEV1) yeni başlangıçlı AF için bağımsız bir etkendir. Bu çalışmanın amacı bilinen kardiyovasküler hastalığı olmayan KOAH hastalarında 2 AF öngördürücüsünün; P dalga dispersiyonunun ve atriyal elektromekanik gecikmenin (AEMG) değerlendirilmesidir ve bunların ZEV1 ile nicelenen solunum fonksiyonlarıyla ilişkisinin değerlendirilmesidir.

Yöntemler: Çalışmaya 41 KOAH hastası (33 erkek, ortalama yaş 51) ile 32 sağlıklı birey katıldı. P dalga dispersiyonu elektrokardiyogram üzerinde 12 derivasyon arasında maksimum ve minimum P dalga süreleri arasındaki fark alınarak hesaplandı. P dalgasının başlangıcından doku Doppler görüntülemesi ile saptanan geç diyastolik dalgasına (Am dalgası) kadar olan süre olarak tanımlanan AEMG ölçümü; lateral mitral anulusdan (LMAEMG), septal (SMAEMG) ve lateral triküspit anulusdan (LTAEMG) yapıldı.

Bulgular: P dalga dispersiyonu KOAH grubunda kontrol grubundan anlamlı olarak uzundu (76±19 ve 45±10 ms, p<0.001). Tüm AEMG ölçümleri hasta grubunda anlamlı uzama gösterdi (LMAEMG: 74±9 ve 64±11 ms, SMAEMG: 66±10 ve 57±12 ms ile LTAEMG: 65±9 ve 46±7 ms; hepsi için p<0.001). Ayrıca, FEV1 ile yalnız LTAEMG arasında ilişki gözlendi (rs: -401, p <0.009).

Sonuç: Hem P dalga dispersiyonu hem atriyal elektromekanik gecikme parametreleri hastalığın erken dönemlerinden başlamak üzere yapısal ve fonksiyonel kardiyak hastalığı olmayan KOAH hastalarında AF'ye artmış eğilimin göstergesi olarak anlamlı uzundu.

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Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and is predicted to be the third leading cause of mortality worldwide by 2030.[1] Atrial fibrillation (AF) is independently associated with COPD, but the underlying pathophysiological mechanisms are complex and not well understood.[2] The frequent coexistence of COPD and cardiovascular disease (CVD) makes it difficult to understand the specific mechanisms by which COPD leads to AF and complicates the prediction of AF development risk. Predicting the development of AF and the appropriate management may help to prevent fatal cardioembolic complications and clinical exacerbations in patients with COPD. Therefore, a reliable indicator for risk assessment of AF development in COPD patients is needed. Reduced forced expiratory volume in 1 second (FEV1) was shown to be an independent predictor of new onset AF in the Copenhagen City Heart Study.[3] The risk of new AF upon re-examination after 5 years was 1.8-times higher for those with a FEV1 measurement of between 60% and 80% of the predicted percentage compared with a FEV1 value of ≥80% after adjustment for sex, age, smoking, blood pressure, diabetes and body mass index.[3] Based on the data derived from that study, the European Society of Cardiology management of AF guidelines highlighted the association between COPD and AF according to the stated FEV1 cut-off values.[4]

In heart physiology, electromechanical delay is defined simply as the time interval between electrical depolarization and heart muscle contraction.[5] Atrial electromechanical delay (AEMD) determined by echocardiographic examination using tissue Doppler imaging (TDI) and P wave dispersion on a 12-lead surface electrocardiogram (ECG) have also been suggested as predictors for AF in different clinical settings.[6,7]

The primary aim of this study was to analyze 2 predictors of AF development in patients with COPD without documented cardiovascular disease, namely, AEMD measured by TDI and P wave dispersion observed on a surface ECG. The secondary aim was to assess the relationship to pulmonary function as quantified by FEV1 measurements.

METHODS

Study population

Between 2015 and 2016, a total of 41 patients with COPD who were followed up in the department of chest diseases and 32 age- and gender-matched healthy volunteers were included in the study. All of the subjects underwent echocardiographic, ECG, and pulmonary function examinations. The exclusion criteria were a left ventricular ejection fraction (EF) of <50%, symptomatic heart failure, moderate or severe valvular heart disease, documented coronary artery disease (myocardial infarction, coronary angiogram showing at least 50% stenosis in a major coronary artery, positive non-invasive ischemia test, Q waves on a surface ECG, or wall motion disturbance on the transthoracic echocardiography), angina-related symptoms, congenital heart disease, documented AF, pacemaker implantation, pre-excitation syndrome observed on the surface ECG, hypertension (requiring medication or an arterial blood pressure of >140/90 mmHg), diabetes mellitus (requiring diabetic medication and/or a fasting blood glucose level of ≥126 mg/dL), systemic inflammatory and autoimmune disorders, renal failure, or anemia (hemoglobin of <10 g/dL). This cross-sectional study was approved by the local ethics committee on 9/4/2015 (no: 107645), and written, informed consent was provided by the patients.

Abbreviations:

AEMD	*Atrial electromechanical delay*
AF	*Atrial fibrillation*
COPD	*Chronic obstructive pulmonary disease*
ECG	*Electrocardiography*
EF	*Ejection fraction*
FEV1	*Forced expiratory volume in 1 second*
FVC	*Forced vital capacity*
HsCRP	*High-sensitivity C-reactive protein*
LAEMD	*Lateral mitral annulus atrial electromechanical delay*
LVEDD	*Left ventricle end-diastolic dimension*
LVESD	*Left ventricle end-systolic dimensions*
PASP	*Pulmonary artery systolic pressure*
Pmax	*Maximum P wave duration*
Pmin	*Minimum P wave duration*
SAEMD	*Septal mitral annulus atrial electromechanical delay*
TAEMD	*Tricuspid lateral annulus atrial electromechanical delay*
TAPSE	*Tricuspid annular plane systolic excursion*
TDI	*Tissue Doppler imaging*

Pulmonary function test

All of the patients underwent spirometry testing (Flowhandy ZAN100 USB, Nspire Health GmbH, Oberthulba, Germany), the results of FEV1 and forced vital capacity (FVC) evaluation were recorded, and the ratio of FEV1/FVC was calculated. COPD was defined according to the Global Initiative for Obstructive Lung Disease criteria as the presence of symptoms and/or a history of exposure to risk factors for the disease with a post-bronchodilator FEV1/FVC of <0.70 estimated using spirometry results.

Electrocardiographic evaluation

A 12-lead surface ECG (25 mm/s, 0.1mV/mm) recording was obtained from each patient in the supine position. The P wave duration was measured using medical image measurement software (Cardio Calipers; Iconico, Inc., New York, NY, USA). The onset and offset of the P wave were determined as the intersection point of the upward or downward deflection of the P wave and the isoelectrical line. P wave dispersion was calculated as the difference between the maximum P wave duration (Pmax) and the minimum P wave duration (Pmin) in a 12-lead ECG.[8] (Fig. 1).

Echocardiographic evaluation

A transthoracic echocardiographic examination was performed by a cardiologist who was blind to the clinical features of the patients using a Philips iE 33 echocardiography device (Koninklijke Philips N.V., Amsterdam, Netherlands) with a 2–4 MHz phased array transducer. The images were obtained in the left lateral decubitus position from standard acoustic views (parasternal, apical, and subcostal) and evaluated according to the recommendations of the American Society of Echocardiography guidelines.[9] The diameter of the left atrium, left ventricle end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), and interventricular septum and posterior wall thickness were measured in the parasternal long-axis view. The left ventricle EF was assessed as using the Simpson method. The early diastolic E-wave, late diastolic A-wave, and E/A ratio were estimated from the apical 4-chamber view using pulsed wave Doppler. Right ventricle dimensions, right atrium diameter, and tricuspid annular plane systolic excursion (TAPSE) were measured in the apical 4-chamber view. Pulmonary artery systolic pressure (PASP) was measured from the peak tricuspid regurgitation velocity using the Bernoulli equation and the diameter of the inferior vena cava.

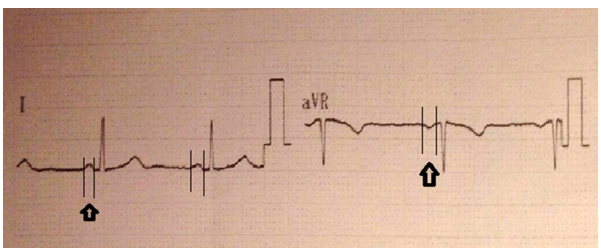

Figure 1. Measurement of the P wave dispersion on a surface electrocardiogram. Arrows show the P wave duration measurements of 2 derivations as an example. The value was calculated for all leads to determine the maximum and minimum P wave duration.

Atrial electromechanical delay evaluation

TDI echocardiography was performed with a transducer frequency of 3.5 to 4.0 MHz, adjusting the spectral pulsed Doppler signal filters to obtain a Nyquist limit of 15 to 20 cm/second with the minimal optimal gain settings. The monitor sweep speed was set at 50 to 100 mm/second to optimize the spectral display of myocardial velocities. A simultaneous ECG was recorded during the echocardiography. AEMD, defined as the time interval from the P wave onset on the ECG to the initiation of the late diastolic wave (Am wave) using TDI, was obtained from the lateral mitral annulus (LAEMD), septal mitral annulus (SAEMD), and tricuspid lateral annulus (TAEMD) (Fig. 2).

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA). Baseline demographic variables were expressed as the mean value±SD, median, and percentage. The Kolmogorov-Smirnov test was used to assess the distribution of the variables. Differences between the groups were tested using a chi-square test or the Mann-Whitney U-test. Relationships between variables were analyzed using Spearman's correlation test. A p value of<0.05 was accepted as indicating statistical significance.

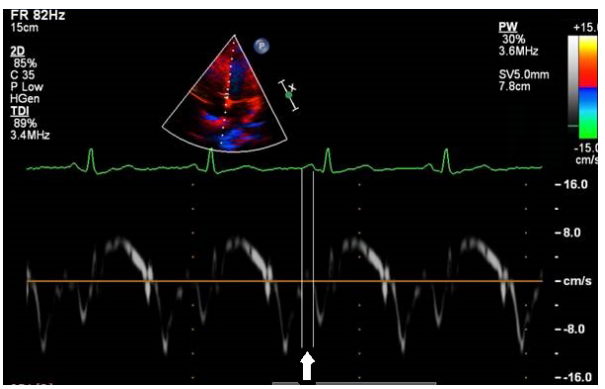

Figure 2. Atrial electromechanical delay measurement on the electrocardiogram from the P wave onset to the start of the late diastolic wave (Am wave) using tissue Doppler imaging, which was obtained from the lateral mitral annulus, septal mitral annulus, and tricuspid lateral annulus.

RESULTS

Forty-one patients with the diagnosis of COPD (8 females, 33 males; mean age: 51±8 years) and 32 healthy individuals were included in the study. Baseline demographic characteristics of the study groups are shown in Table 1. There was no significant difference between the 2 groups with respect to gender (COPD: 33 [80.5%] vs. controls: 24 [75%]; p=0.574). The smoking ratio was significantly higher, and the FEV1 and FEV1/FVC values were significantly lower in the COPD group compared with the control group. Among the echocardiographic parameters, only the E/A ratio and the PASP were significantly different between the 2 groups.

The P wave dispersion, Pmax, Pmin, and AEMD measurements are presented in Table 2. The Pmax was significantly higher and the Pmin was significantly lower in the COPD group (Pmax: 132±20 ms vs. 117±11 ms, Pmin: 56±9 ms vs. 71±11 ms, respectively; p<0.001 for both). As a result, the P wave dispersion was significantly longer in the COPD group (P dispersion: 76±19 ms vs. 45±10 ms; p<0.001). However, there was no significant correlation between P wave dispersion and spirometric measures. The LAEMD (COPD: 74±9 ms; control: 64±11 ms), SAEMD (COPD: 66±10 ms; control: 57±12 ms), and TAEMD

Table 2. P wave dispersion and atrial electromechanical delay in the COPD and control groups

	COPD	Control	*p* value
	Mean±SD	Mean±SD	
LAEMD (ms)	74±9	64±11	<0.001
SAEMD (ms)	66±10	57±12	<0.001
TAEMD (ms)	65±9	46±7	<0.001
Pmin (ms)	56±9	71±11	<0.001
Pmax (ms)	132±20	117±11	<0.001
Pdisp (ms)	76±19	45±10	<0.001

COPD: Chronic obstructive pulmonary disease; LAEMD: Lateral mitral annulus atrial electromechanical delay; Pmax: Maximum P wave duration; Pmin: Minimum P wave duration; Pdisp: P wave dispersion; SAEMD: Septal mitral annulus atrial electromechanical delay; TAEMD: Tricuspid lateral annulus atrial electromechanical delay; SD: Standard deviation.

Table 1. Baseline characteristics of the study groups

	COPD (n=41)	Controls (n=32)	*p* value
Age (years)	51 (45–60)	50 (45–57.5)	0.800
Body mass index (kg/m^2)	27.6 (25.6–28)	27.5 (24.7–30.5)	0.483
Smoking (pack–years)	35 (18–57.5)	0.75 (0–15)	<0.001
FEV1 (%)	59 (47–76)	99.5 (90–110)	<0.001
FEV1/FVC	56 (47–66)	82 (76–86)	<0.001
Systolic blood pressure (mmHg)	117 (105–125)	120 (100–130)	0.541
Diastolic blood pressure (mmHg)	75±7	82±7	0.541
Ejection fraction (%)	60 (59–62)	60.5 (60–62)	0.705
Interventricular septum (mm)	10 (9–11)	10 (9–10)	0.321
Posterior wall (mm)	10 (9–11)	10 (9–10)	0.255
Left ventricle end-diastolic dimension (mm)	46 (44–48)	45.5 (42–48)	0.569
Left ventricle end-systolic dimension (mm)	29 (26–31)	28 (26–30)	0.252
Right ventricle (mm)	33 (29–37)	32 (30–35)	0.406
Right atrium (mm)	33 (31–36)	32 (31–35)	0.603
Left atrium (mm)	35 (33–38)	35 (32–36)	0.223
Pulmonary artery systolic pressure (mmHg)	28 (25–32)	24 (22–27)	<0.001
Tricuspid annular plane systolic excursion (mm)	23 (22–25)	24 (21–26)	0.784
Early diastolic/late diastolic transmitral flow velocity	0.9 (0.7–1.1)	1.1 (1–1.3)	<0.001
E/Ea	7.1 (6–8)	7.3 (6.6–8)	0.373

Data shown as median (25th and 75th percentile). COPD: Chronic obstructive pulmonary disease; E/Ea: Early diastolic transmitral flow velocity/early diastolic mitral annular velocity; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity.

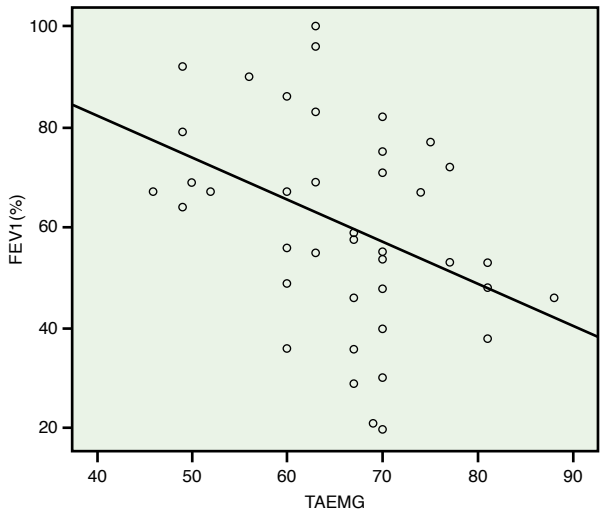

Figure 3. A plot diagram illustrating the significant negative correlation between the tricuspid lateral annulus atrial electromechanical delay (TAEMD) and forced expiratory volume in 1 second (FEV1) in the chronic obstructive pulmonary disease group (rs: -401; p<0.009).

(COPD: 65±9 ms; control: 46±7 ms) were significantly higher in the COPD group (p<0.001). In addition, the TAEMD was significantly negatively correlated with FEV1 in the COPD group (rs=-401; p<0.009) (Fig. 3).

DISCUSSION

The findings of this study indicated that in COPD patients without known cardiovascular disease, the AEMD determined from TDI echocardiography and the P wave dispersion on a 12-lead ECG measurement were significantly higher when compared with the healthy controls, indicating a greater tendency to develop AF despite the absence of significant structural differences on echocardiography. In addition, AEMD obtained from the TAEMD was negatively correlated with FEV1, suggesting that reduced lung function may contribute to this tendency.

As a result of the frequent coexistence of CVD and COPD, more patients with mild and moderate COPD die from CVD than from COPD, and individuals with COPD are more at risk of developing of AF.[10] Recently, a prospective cohort study demonstrated that COPD subjects had a 28% greater AF risk, which further increased with frequent exacerbations and an enlarged left atrium.[11]

P wave dispersion has been proven as a sensitive and specific ECG predictor of AF in different clinical settings.[6,12] In a study comparing 40 COPD patients and 33 healthy individuals, all of the P wave intervals (Pmax, Pmin, and P wave dispersion) were higher in the COPD patients compared with the controls.[13] In addition, the P wave dispersion was significantly greater in COPD patients with AF compared with patients without AF.[13] Consistent with previous studies, our research also revealed a significantly longer P wave dispersion in patients with COPD but without known cardiac disease in comparison with normal subjects.

Despite inconsistent results among epidemiological studies, smoking is accepted as associated with an increased risk of AF.[4,14] Akturk et al.[15] compared the P wave dispersion and AEMD values of 50 healthy volunteer smokers and 40 healthy non-smokers who had normal echocardiographic parameters. The authors demonstrated that the P wave dispersion was significantly longer and the LAEMD and SAEMD were significantly higher in the smokers.[15] In our study, despite a higher smoking ratio in the COPD group, there was no correlation between the amount of smoking, defined as pack-years, and the AEMD or P wave dispersion. The direct effects of cigarette smoking potentially involved in the etiology of AF include oxidative stress,[16] inflammation,[16] and atrial fibrosis.[17] Smoking may also predispose individuals to AF indirectly through the cardiovascular system and reduced lung function.[18] Further studies are needed to determine the precise biological role of smoking on the development of AF.

Atrial activation time, which was defined the interval of time from the initiation of the ECG P wave (lead II) until the peak of the local lateral left atrial TDI signal, has been proposed as a reliable method to estimate the total atrial electrical activation time, which is a powerful predictor of AF.[7] Subsequently, AEMD measured by TDI was evaluated in a wide range of clinical settings: mitral stenosis,[19] paroxysmal AF,[20] heart failure,[21,22] type 1 diabetes mellitus,[23] type 2 diabetes mellitus,[24,25] and heart transplantation.[26] Recently, 2 studies have assessed the AEMD in patients with COPD. Caglar et al.[27] compared 41 patients with COPD and 41 healthy subjects in terms of P wave dispersion and AEMD measured using TDI. In their study, the P wave dispersion interval was significantly longer and the AEMD measured from the TAEMD with TDI was significantly prolonged in the COPD group.[27] In another study, Acar et al.[5] compared the AEMD and biological markers, such

as the plasma level of high-sensitive C-reactive protein (hsCRP), and oxidative stress parameters in 43 patients with COPD and 50 healthy individuals and found that the corrected AEMD measured from the LAEMD, SAEMD, and TAEMD were significantly higher in patients with COPD. The plasma level of hsCRP and malondialdehyde, an indicator of oxidative stress, were also higher in the patient group.

A number of pathophysiological mechanisms (apart from pulmonary hypertension and ventricular diastolic dysfunction) have been proposed to explain the predisposition to AF in patients with COPD: hypoxia,[28] hypercapnia,[29] oxidative stress,[30] inflammation,[31] and inhaled beta-agonists.[32] Other mechanisms, such as exosomes and microRNA, can mediate a cross-talk between lungs and atrium.[33] Another large population-based cohort study documented that impaired lung function was an independent risk factor for AF after adjustment for age, weight, height, systolic blood pressure, and chronic inflammation as measured by the erythrocyte sedimentation rate.[34] According to the literature, reduced FEV1 was associated with an increased risk of AF in both smoking and non-smoking patients, and this suggests that reduced lung function can play a role in the development of AF independently of smoking. Although it has been suggested that impaired lung function induced AF through hypoxia, the risk of AF increased gradually over the range of FEV1 and was not limited to patients with very low values.[34] Acar et al.[5] revealed that the corrected TAEMD was negatively correlated with the FEV1/FVC ratio. Caglar et al.[27] also reported a negative correlation between AEMD measured from the TAEMD and FEV1 values. Similarly, our study documented a negative correlation between TAEMD and FEV1 in the COPD group. In our findings, the mean value of the FEV1 in patients with COPD was relatively lower than that of the other studies described above.

Limitations

This was a single-center study with a limited patient population. Due to the cross-sectional design, follow-up data of the patients were not pursued and associations between surrogate indicators of AF and the clinical development of AF could not be documented. Prospective studies with large populations and long-term follow-up are required to further evaluate AEMD and its relationship with AF and FEV1 in these patients.

Conclusion

The AEMD measurement obtained from the LAEMD, SAEMD, and the TAEMD was significantly higher and P wave dispersion was significantly longer in COPD patients without an established structural or functional cardiac abnormality. FEV1 was independently related to AEMD obtained from TAEMD. Our findings suggest that AEMD could be a potential predictor of AF development in patients with COPD. In addition, reduced lung function may be related to the prolongation of AEMD in these patients.

Ethics Committee Approval: The study was approved by the local ethics committee on 9/4/2015 (no: 107645).

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