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Assessment of atrial conduction time by tissue Doppler echocardiography and P-wave dispersion in smokers

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Abstract
Introduction The aim of this study was to evaluate the relationship between cigarette smoking and atrial rhythm disorders with the use of noninvasive methods.
Methods The study population consisted of 50 healthy volunteer smokers and 40 healthy volunteer non-smokers who had normal echocardiographic parameters and similar sex and age profiles. P-wave dispersion (PWD) was calculated from the 12-lead surface ECG. Left ventricle (LV) end-systolic and end-diastolic diameters, LV ejection fraction, and interatrial and intraatrial electromechanical delay were measured by tissue Doppler imaging and conventional echocardiography.
Results Isovolumetric relaxation time and deceleration time were significantly higher (91.5±11 vs. 82.35±8.6, $p<0.0001$; 215.7±37.1 vs. 175.3±17.7, $p<0.0001$, respectively), and HDL cholesterol was significantly lower in smokers (39.34±7.5 vs.44.3±8.07, $p=0.003$). There were no significant differences between the groups with respect to Sm and Em values, Am value, and E/A and E/Em ratios. However, the Em/Am ratio was significantly lower in smokers (1.28±0.21 vs. 1.44±0.33, $p<0.006$). Inter- and intraatrial electromechanical delay were significantly higher in smokers when compared with non-smokers (51.11±1.54 vs. 27.30±3.36, $p<0.0001$, and 30.63±3.2 vs. 12.24±3.26, $p<0.0001$, respectively). The amount of smoking was strongly correlated with interatrial electromechanical delay ($r=0.567$, $p<0.0001$), and a significant correlation was detected between PWD and interatrial electromechanical delay ($r=0.653$, $p=0.001$).
Conclusion We have demonstrated the relationship between inter- and intraatrial electromechanical delay and PWD. These parameters may be useful predictive markers for the development of AF in the asymptomatic period before cardiac rhythm disturbances occur. This finding may indicate that smokers have an increased risk of developing atrial rhythm disturbances.

Keywords Atrial electromechanical delay · Cigarette smoking · P-wave dispersion

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1 Introduction

Smoking harms the heart through several mechanisms. In general, smoking causes or aggravates endothelial dysfunction and atherosclerosis and causes cardiac rhythm disorders through the combined effects of nicotine, carbon monoxide,

and polycyclic aromatic hydrocarbons [1–7]. Smoking may thus change the myocardial substrate as well as action potentials. Both processes provoke and facilitate atrial fibrillation (AF). Several case reports are presented on the onset of AF after the ingestion of nicotine [8, 9], but the results of population-based studies on the association between smoking and AF are conflicting [10–15].

Electrophysiologic and electromechanical abnormalities resulting from intra- and interatrial conduction disorders are associated with a higher risk of AF [16]. The prolongation of intra- and interatrial electromechanical delay and the inhomogeneous propagation of sinus impulses are well-known electrophysiological characteristics of the atrium prone to fibrillate [16–18]. With recent developments in tissue Doppler imaging (TDI), it is possible to evaluate electrical events of different regions with high temporal resolution. Atrial electromechanical delay can be measured from the onset of the P-wave on the electrocardiogram (ECG) to the onset of atrial contraction determined by TDI [18]. Atrial electromechanical delay has been demonstrated to be longer in patients with paroxysmal AF than in controls [19].

The aim of this study is to evaluate the relationship between smoking and atrial rhythm disorders by use of noninvasive methods.

2 Materials

The study population consisted of 50 volunteer healthy smokers and 40 volunteer healthy non-smokers who had normal echocardiographic parameters and similar sex and age profiles. Smokers were defined as subjects who had been smoking a minimum of ten or more cigarettes per day for at least 3 years and had never quit smoking. For the smokers, the amount of smoking was calculated by multiplying the number of cigarettes (defined by pack) smoked per day with the duration of smoking (defined by years) and expressed as pack-years, and the controls were defined as subjects who had never smoked.

Exclusion criteria of the study were abnormal heart valves, any chronic inflammatory diseases, an overactive thyroid gland or any other metabolic imbalance, overweight (BMI >31.1), use of drugs acting on heart rhythm, long-term consumption of alcohol, and the risk parameters of the Atherosclerosis Risk in Communities (ARIC) study's AF scoring system [20] for developing AF such as age >50 years, body height ≥173, hypertension and hypertension medication use, precordial murmur, left atrium (LA) enlargement, left ventricular hypertrophy, diabetes mellitus, coronary artery disease, and congestive heart failure.

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, uric acid, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. High-sensitivity C-reactive protein (hsCRP) was calculated by the nephelometric method (Behring Nephelometer Analyzer; Dade Behring, Marburg, Germany) and expressed as milligrams per liter.

2.1 Echocardiography

All echocardiographic examinations (HDI-5000; ATL Bothell, Washington) were performed by a cardiologist who was blinded to the clinical details and results of the other investigations of each healthy smoker and healthy control. During echocardiography examination, a 12-lead ECG was recorded continuously. M-mode measurements were performed according to the criteria of the American Society of Echocardiography. Individuals were instructed to hold their breath, and images were coupled with electrocardiographic recordings. Three consecutive cycles were averaged for every parameter. LA dimension and left ventricle (LV) end-systolic and end-diastolic diameters were measured. LV ejection fraction was estimated by Simpson's rule. LA volume was calculated at end systole of the LV in the apical four- and two-chamber views using the methods of disks (Simpson's rule). LA volume was indexed to height and expressed in milliliters per meter.

Transmitral pulsed-wave Doppler velocities were recorded from the apical four-chamber view with the Doppler sample placed between the tips of the mitral leaflets. Early (*E*) and late (*A*) wave velocities, *E*/*A* ratio, *E* deceleration time (DT), and isovolumetric relaxation time (IVRT) were measured from the mitral inflow profile. For TDI, the same echocardiography machine was used to acquire TDI data at high frame rates. The Nyquist limit was set at 15–20 cm/s, and minimal optimal gain was used.

The myocardial systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities were obtained at the septal and lateral mitral annulus by placing a tissue Doppler sample volume. The E/Em and Em/Am ratios were subsequently calculated. The pulsed sample volume was placed at the level of the LV lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus in order to obtain electromechanical parameters.

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 annulus (lateral PA), septal mitral annulus (septal PA), and right ventricular tricuspid annulus (tricuspid PA), respectively (Fig. 1). The difference between lateral PA and tricuspid PA (lateral PA−tricuspid PA) was defined as interatrial electromechanical delay, the difference between

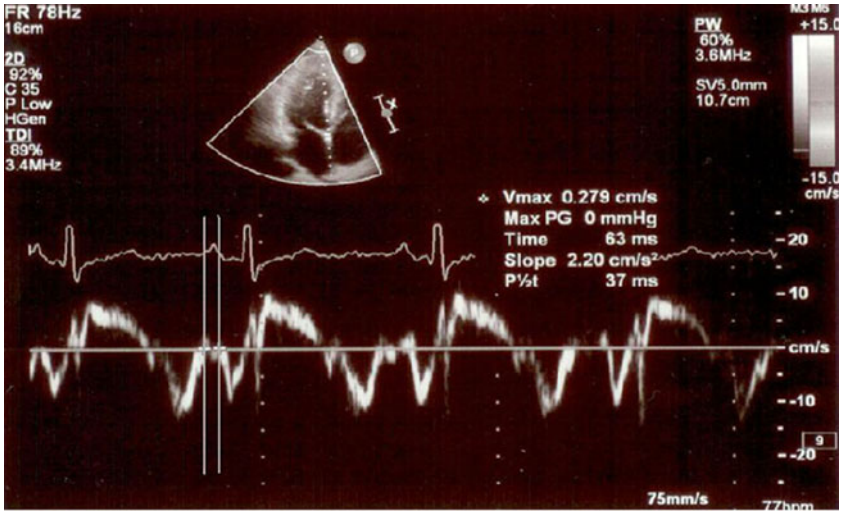

Fig. 1 Measurement of the time interval from onset of the P-wave on surface ECG to beginning of the Am wave (PA) with tissue Doppler echocardiography

septal PA and tricuspid PA (septal PA−tricuspid PA) was defined as intraatrial electromechanical delay, and the difference between lateral PA and septal PA (lateral PA−septal PA) was defined as intraleft atrial mechanical delay [18]. Reproducibility of electromechanical parameters was assessed by coefficients of variation (standard deviation of differences between the repeated measurements divided by the mean value and expressed as percent) between measurements. Intraobserver variability was calculated from 25 randomly selected subjects among the obese group. Intraobserver variability was 5% for PA lateral, 4.5% for PA septal, and 5.8% for PA tricuspid, respectively.

2.2 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 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=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.

2.3 Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 16.0 software (SPSS, Chicago, IL). All continuous variables were expressed as mean±SD, and categorical variables were defined as percentages. Categorical data were compared using the χ^2 test. Continuous variables were compared between the groups using Student's *t* test or the 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.

3 Results

Basic clinical and laboratory characteristics of 50 smokers (mean age, 38.5±10 years) and 40 normal subjects (mean age, 42.08±10 years) are listed in Table 1. There was no significant difference between the smokers and the controls in terms of age, gender, BMI, body height, systolic and diastolic blood pressures (BP), heart rates, hsCRP, total cholesterol, LDL cholesterol, uric acid, and glucose, whereas HDL cholesterol was significantly lower in the smokers (39.34±7.5 vs. 44.3±8.07, p=0.003).

There was no significant difference between the smokers and the control subjects in terms of ARIC's AF risk score except smoking history (smokers having 3 points and the control subjects having 0 point). There was no difference between the smokers and the control subjects in terms of height (163.46±6.8 and 162.68±16, respectively). ARIC's AF risk scores of the smokers involved in our study were 4 or less; 12 of them had a risk score of 4, and 38 of them had 3.

The results of the echocardiographic measurements are shown in Table 2. LV end-diastolic and end-systolic diameters, LV ejection fraction, interventricular septum thickness, LA diameter, LA volume, LA volume index, LV posterior wall thickness, and *A* and *E* velocities were also similar between the groups. IVRT and DT were significantly higher (91.5±11 vs. 82.35±8.6, p<0.0001; 215.7±37.1 vs. 175.3±17.7, p<0.0001; respectively). There was no significant difference between the groups with respect to Sm and Em values, Am value, E/A ratio, and E/Em ratio. However, the

Table 1 Clinical characteristics of the study population and laboratory data

	Smokers *(n=50)*	Controls (*n*=40)	*p* value
Age (years)	38.5±10	42.08±10	NS
Female (%)	16 (%)	16 (%)	NS
BMI (kg/m^2)	25.66±3.11	24.54±2.06	NS
SBP (mmHg)	118±8.8	110.5±6.8	NS
DBP (mmHg)	78±6.4	74.3±5.5	NS
Total cholesterol (mg/dl)	192.48±29.8	186.52±27.2	NS
LDL cholesterol (mg/dl)	129.94±26	116.88±21.5	NS
HDL cholesterol (mg/dl)	39.34±7.5	44.3±8.07	0.003
Triglycerides (mg/dl)	163.92±63.3	146.95±30.8	NS
Fasting blood glucose (mg/dl)	94.06±7.8	94.95±7.0	NS
Uric acid (mg/dl)	3.3±1.5	3.2±3.2	NS
hsCRP (mg/l)	1.34±1.5	1.09±0.98	NS
Body height (cm)	163.46±6.82	162.68±16.3	NS

NS not significant, *CRP* C-reactive protein, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Em/Am ratio was significantly lower in the smokers (1.2±0.21 vs. 1.44±0.33, $p<0.006$).

P-wave indices and TDI parameters are shown in Table 3. Statistically significant differences were found in *P*max and PWD values between the smokers and the control subjects (111.02±10.3 vs. 99.55±12, $p<0.0001$, and 49.5±10.1 vs. 35.95±5.6, $p<0.0001$, respectively). PA lateral and PA septum durations were significantly higher in the smokers when compared with the controls (89.12±1.08 vs. 64.78±6.44, $p<0.0001$, and 62.43±7.24 vs. 43.65±4.86, $p<0.0001$, respectively). However, PA tricuspid duration was similar between both groups. Moreover, inter- and intraatrial electromechanical delay were significantly higher in the smokers when compared with the controls (51.11±1.54 vs. 27.30±3.36, $p<0.0001$, and 30.63±3.2 vs. 12.24±3.26, $p<0.0001$, respectively). Correlation analysis showed a positive correlation between interatrial electromechanical delay and PWD ($r=0.653$, $p=0.001$; Fig. 2) and the amount of smoking ($r=0.567$, $p<0.0001$; Fig. 2).

4 Discussion

Tobacco smoke contains a mixture of more than 4,000 gaseous chemicals [6]. Of these, nicotine and carbon monoxide especially are well known to be very toxic to the heart.

Table 2 Echocardiographic parameters of the study population

	Smokers (*n*=50)	Controls (*n*=40)	*p* value
LV ejection fraction (%)	67.21±2.24	68.06±2.84	NS
Left atrial diameter (mm)	32.78±2.53	32.62±2.21	NS
Left atrial volume (ml)	35.44±4.79	34.02±4.04	NS
Left atrial volume index (ml/m)	25.12±44.5	24.33±4.01	NS
LVEDD (mm)	45.94±3.38	44.9±2.49	NS
LVESD (mm)	29.1±2.94	28.58±3.61	NS
Septal thickness (mm)	10.02±0.86	9.8±0.88	NS
PW thickness (mm)	9.9±0.88	9.65±0.86	NS
Mitral E velocity (cm/s)	89.57±11.9	89.91±12.6	NS
Mitral A velocity (cm/s)	64.84±6.9	62.06±10	NS
DT (ms)	221.65±31.24	186.45±32.14	<0.0001
E/A	1.38±0.24	1.41±1.9	NS
IVRT (ms)	98.21±10.19	79.40±8.41	<0.0001
Sm (cm/s)	11.21±1.85	10.32±1.53	NS
Em (cm/s)	12.11±1.56	13.36±2.7	NS
Am (cm/s)	9.58±1.29	9.19±1.76	NS
Em/Am	1.28±0.21	1.44±0.33	<0.0006
E/Em	7.5±1.33	7.46±1.31	NS

LV left ventricular, *LVEDD* LV end-diastolic dimension, *LVESD* LV end-systolic dimension, *PW* posterior wall, *E* mitral early diastolic velocity, *A* mitral late diastolic velocity, *DT* mitral E-wave deceleration time, *IVRT* isovolumetric relaxation time, *Sm* LV systolic myocardial velocity, *Em* LV myocardial early diastolic velocity, *Am* LV myocardial late diastolic velocity, *NS* not significant

Table 3 Comparison of the electrocardiographic and atrial electromechanical parameters

	Smokers (n=50)	Controls (n=40)	p value
Heart rate (beats/min)	79.3±13.5	76.7±13.6	0.4
Pmax (ms)	111.02±10.38	99.55±12.01	<0.0001
Pmin (ms)	61.88±6.16	62.88±8.27	NS
PWD (ms)	49.5±10.1	35.95±5.86	<0.0001
Lateral PA (ms)	73.16±14.64	57.82±7.9	<0.0001
Septal PA (ms)	54.16±11.26	43.4±6.93	<0.0001
Tricuspid PA (ms)	34.94±5.08	36.2±4.35	NS
Lateral PA–tricuspid PA[a] (ms)	51.11±1.54	27.30±3.36	<0.0001
Septal PA–tricuspid PA[b] (ms)	30.63±3.2	12.24±3.26	<0.0001
Lateral–septal PA[c]	15.2±6	13.3±5.2	0.14

PA time interval from the onset of the P-wave on surface electrocardiogram to the beginning of the late diastolic wave, *Pmax* P maximum, *Pmin* P minimum, *PWD* P-wave dispersion, *NS* not significant

[a] Interatrial electromechanical delay

[b] Intraatrial electromechanical delay

[c] Intraleft atrial mechanical delay

Carbon monoxide may both influence the automaticity of the heart and reduce the exercise tolerance of the heart by reducing oxygen-carrying capacity and oxygen release of hemoglobin [21], and the main cardiovascular effect of nicotine is sympathetic neural stimulation causing an increase in heart rate and blood pressure [5, 22]. Although the effects of smoking on the cardiovascular system is well known, it is not clear whether the arrhythmogenic potential of smoking is related to its cardiovascular and pulmonary effects or its direct effect on the cardiovascular system.

The effects of smoking on the heart have been assessed in several studies. Mehta et al. and Miyauchi et al. have shown in their studies that nicotine may cause cardiac arrhythmia and atrial flutter in animals [7, 23]. A previous study has found that smoking has a triggering effect in the initiation of AF and atrial arrhythmias by changing the structure of the atrium and causing atrial fibrosis [24]. Another study has found that the prolonged administration of nicotine is also associated with the loss of intracellular K^+ and the emerging of cardiac necrosis [25].

A strong association between smoking and atrial arrhythmias has been revealed in other studies; Tuan et al. have designed a study evaluating the effects of smoking on LA and right atrium (RA) by electrophysiological study. It has been shown that smoking has a voltage reduction effect on RA and LA, and also, the total activation time of RA has been longer in the smoker patients, but that is not the case in LA [26]. Trial II has revealed that smoking is associated with an increased risk of continuous rapid supraventricular arrhythmias [27]. In this regard, the most comprehensive studies, Rotterdam and ARIC studies, have pointed out that smoking is a predisposing factor in the development of AF [20, 28].

Recent studies have assessed atrial electromechanical delay with TDI echocardiography, which is a noninvasive method alternative to invasive electrophysiological studies [18, 19]. Omi and colleagues have recently evaluated the ability of the atrial electromechanical interval to detect atrial impairment in paroxysmal AF. They found that the atrial electromechanical interval was prolonged in paroxysmal AF

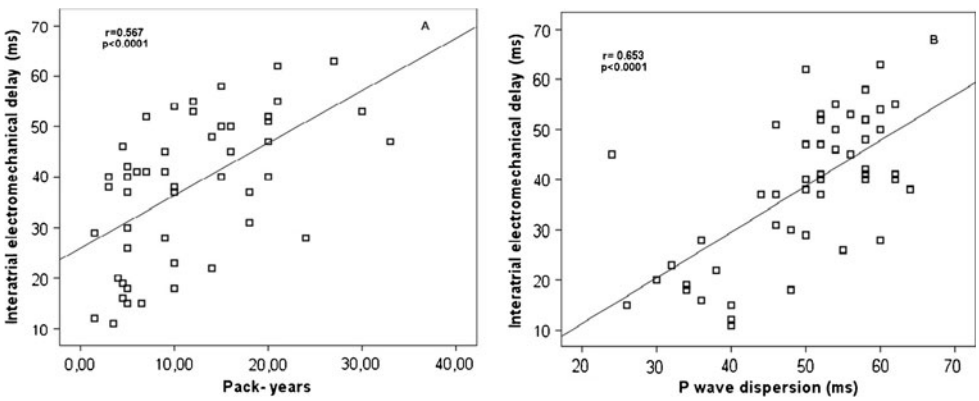

Fig. 2 (**a**) Positive correlation between interatrial electromechanical delay and pack-years, (**b**) between interatrial electromechanical delay and P-wave dispersion

[29]. Roshanali et al. found that the atrial electromechanical interval was a predictor of AF emerging after coronary artery bypass graft and showed that the preoperative administration of amiodarone to patients having a longer atrial electromechanical interval decreased the postoperative AF incidence [30]. These studies showed that a prolonged electromechanical interval seemed to reflect atrial remodeling for an arrhythmogenic substrate [29, 30]. In this study, we demonstrated that intra- and interatrial electromechanical delay, which was a noninvasive technique providing estimated risk of AF, was significantly longer in smokers than in the controls.

It is accepted that increased P-wave duration on standard surface ECG indicates an atrial conduction disorder. PWD appears to correlate with P-wave duration and may be a useful predictive marker for the development of AF [17]. In our study, smokers had higher values of Pmax and PWD when compared with the control group.

Today the most commonly used scoring system for 10-year risk of AF development is based on the Framingham Heart Study and ARIC Study [20, 31–33]. According to this scoring system, a 10-year total risk of developing AF in smokers is 1% or less. Although the percentages of the risk for developing AF were very low in the subjects included in our study, intra- and interatrial electromechanical delay. Therefore, we can speculate that the smoker group is at increased risk for the development of atrial rhythm disturbances, and only smoking might be an independent predictor for the development of atrial arrhythmias

Our study was cross sectional, and the findings in this study need to be supported by long-term follow-up studies with a large patient population, which are taking into account duration and the amount of smoking.

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