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Assessment of atrial fibrillation and ventricular arrhythmia risk in patients with asthma by P wave/corrected QT interval dispersion

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Abstract. – OBJECTIVE: Although the relationship between obesity-asthma, obesity-atrial fibrillation (AF) and obesity-sudden cardiac death is clearly known, the risk of AF and ventricular arrhythmia has not been clearly determined in asthmatic patients. The aim of this study was to investigate whether AF, ventricular arrhythmia, and sudden cardiac death risk were increased in asthmatic patients using P wave dispersion (PWD) and corrected QT interval dispersion (CQTD).

PATIENTS AND METHODS: The study was designed as a cross-sectional study. A total of 164 participants (88 patients with asthma and 76 healthy volunteers) were enrolled into the study. PWD and CQTD were measured and recorded in both groups. The statistical difference between the two groups was examined.

RESULTS: PWD was higher in the asthma patients than in control subjects (31.53 ± 3.18 *vs.* 30.33 ± 3.53, $p = 0.023$). However, there was no statistically difference between the groups in terms of CQTD measurement (43.9 ± 1.84 *vs.* 43.63 ± 2.06, $p = 0.385$). In comparison between control group and asthma subgroups (mild, moderate and severe), there was a statistically significant difference among these four groups in terms of PWD ($p = 0.017$). Subgroup analyses showed that this difference was mainly due to patients with severe asthma.

CONCLUSIONS: PWD value was elevated in asthmatic compared to the control group. The CQTD was not statistically significant between the groups. These results indicate that the risk of developing AF in asthmatic patients might be higher than in the normal population. Ventricular arrhythmia and sudden cardiac death risk may not be high in asthmatic patients.

Key Words:
Asthma, P wave dispersion, QT interval dispersion, Atrial fibrillation, Ventricular arrhythmia.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and often requires treatment in adults. The prevalence in adults is approximately 3.0%, and increases with age[1]. The mortality related to cardiovascular disease and other causes, including stroke and heart failure, is increased in patients with AF[2,3]. Obesity is a known risk factor for the development of AF, and the risk is correlated with increased body mass index (BMI)[4]. In obese patients, not only AF, but also ventricular arrhythmias and risk of sudden cardiac arrest are increased[5].

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough, which varies over time and, in most cases, it is accompanied by variable expiratory airflow limitation[6]. There are many risk factors defined for asthma, including obesity. As the severity of obesity increases, the risk of developing asthma increases as well[7].

P-wave dispersion (PWD) is defined as the difference between the widest and narrowest P-wave durations using 12 lead ECG and the role of predicting AF risk is well known[8]. Similarly, QT interval dispersion (QTD) is defined as the difference between the longest and shortest QT intervals measured in a 12 lead ECG. It is known that QTD is associated with increased risk of sudden cardiac death and ventricular arrhythmia[9].

Although the relationship between obesity-asthma, obesity-AF, and obesity-sudden

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cardiac death is known, the risk of AF and ventricular arrhythmia has not been clearly demonstrated in asthmatic patients. Since both diseases share the same risk factors, we investigated whether AF, ventricular arrhythmia, and sudden cardiac death risk were increased in asthmatic patients using PWD and QTD measurements.

Patients and Methods

Patients

The study was designed as a cross-sectional study. A total of 164 participants (88 patients with asthma and age-sex matched 76 healthy volunteers) were admitted to Baskent University Adana Hospital outpatient clinic between January 1, 2016 and February 28, 2017 and enrolled. The following patients were excluded: patients with known coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, advanced heart valve disease, persistent or paroxysmal atrial fibrillation, ventricular arrhythmia (sustained or non sustained ventricular tachycardia), sudden cardiac death story, patients with pacemaker, presence of active infection, diabetes mellitus, familial hyperlipidemia, hypertension, smoking, malignancy, chronic renal disease requiring dialysis, chronic liver disease, autoimmune diseases, use of systemic steroids, pregnancy, chronic lung diseases other than asthma, age under 18 years or over 65 years, non-persistent asthma, patients with acute asthma attack.

Persistent asthma was diagnosed according to clinical findings (history, physical examination), lung function tests, and the criteria in the Global Initiative for Asthma (GINA)[6] guidelines. Patients were divided into three groups based on asthma severity according to the GINA 2016 guidelines as mild, moderate, and severe[6]. Asthma control questionnaire (ACQ) scores of patients were calculated. The demographic, anthropometric, and laboratory values of the patients and control groups were recorded. PWD and corrected QTD (CQTD) were measured and recorded in both groups. The statistical difference between the two groups was examined. The study was carried out in accordance with the criteria of the Helsinki Declaration and approval was obtained from the local Ethics Committee (KA16/335). Written consent form was obtained from all participants.

Calculation of QTD with Electrocardiogram Characteristics and PWD

Standard ECG (25 mm/s and 10 mm/mV) and 50 mm/s and 10 mm/mV specific ECGs of all patients were drawn and recorded. ECGs were performed in the supine position and the electrodes were withdrawn at standard sites[10]. In the ECG taken at high speed, the duration of the P wave in all the leads was measured at 3 consecutive heart beats, and the average of the measured values was used to calculate the P wave duration in each derivation. The PWD was calculated by subtracting the value of the lead at which the peak of the P wave was measured from the value of the lead at which the lowest was measured. Similarly, in high-velocity ECGs, the QT interval was measured in all the leads and the CQT was calculated with the Bazett formula ($CQT = QT(s)/\sqrt{RR(s)}$). In each derivation, CQT was calculated at 3 consecutive heartbeats and averages of these 3 measurements were obtained. The difference between the highest measured CQT and the lowest measured lead was calculated and the CQT dispersion (CQTD) was also calculated. Both PWD and CQTD measurements were made at different times by 2 different cardiologists; the averages of the values found by these 2 operators were taken.

Statistical Analysis

Variables are presented as mean ± SD or median (range, interquartile range [IQR]) for continuous data and as proportion for categorical data. Categorical parameters were analyzed by x^2 test. Continuous variables with normal distribution were analyzed with one-way ANOVA or independent simple *t*-test as appropriate. Continuous variables with non-normal distribution were analyzed using Mann-Whitney U test or Kruskal-Wallis test. Kolmogorov-Smirnov test was used to identify whether continuous variables were normally distributed. The degrees of association between continuous variables were evaluated by using Pearson correlation. Two-sided p-values < 0.05 were considered significant. Statistical analysis was performed using commercially available computer program (SPSS version 21.0 for Windows, Armonk, NY, USA).

Results

A total of 164 individuals, including 88 persistent asthmatic patients and 76 healthy volunteers (control group), were included in this study.

Groups were similar to each other in terms of demographic and anthropometric measurements. Among these 88 persistent asthmatic patients, 33 (37.5%) had mild grade asthma, 30 (34.1%) had moderate grade asthma, and 25 (28.4%) had severe grade asthma. There were no statistically significant differences between control and asthma subgroups in terms of clinic, demographic, anthropometric, and baseline laboratory values ($p > 0.05$). The clinic, demographic, anthropometric, and laboratory values of four groups are shown in Table I. The median duration, starting from first asthma diagnosis of patients, was 12 (6-24; IQR = 18) months.

Patients with asthma had statistically higher PWD than the control group, (31.53±3.18 msec *vs.* 30.33 ± 3.53 msec, $p = 0.023$). The CQTD was found to be 43.63 ± 2.06 msec in the control group, 43.90 ± 1.84 msec in the asthma group. There was no statistically significant difference between groups in terms of CQTD measurements ($p = 0.385$). The comparisons of PWD and CQTD measurements are summarized in Figure 1 and Figure 2.

In comparison of control group and asthma subgroups (mild, moderate, and severe), there was a statistically significant difference among these four groups in terms of PWD ($p = 0.017$). There was no significant difference between the control group and the mild and moderate asthma groups ($p > 0.05$); however, the difference between the control and severe asthma groups was significant ($p < 0.001$). Conversely, there was no statistically significant difference among these four groups in terms of CQTD ($p = 0.09$). The comparison of control and asthma subgroups' PWD and CQTD measurements are summarized in Table II and Figure 3. PWD was negatively correlated with FEV_1 ($r = -0.326$, $p = 0.002$), but it was positively correlated with ACQ score ($r = 0.278$, $p = 0.009$). On the other hand, there was not a significant correlation between CQTD and FEV_1, CQTD and ACQ score ($r = 0.201$, $p = 0.061$ and $r = 0.203$, $p = 0.058$), respectively. Correlation analysis of PWD, CQTD, FEV_1, and ACQ score are shown in Figure 4.

Discussion

Our study is the first report to evaluate both PWD and CQTD in adult asthmatic patients. We found that PWD value is elevated in patients with asthma compared to the control group, whereas CQTD score was similar between the groups. These results indicate that the risk of developing AF in asthmatic patients might be higher than in the normal population. However, ventricular arrhythmia and sudden cardiac death risk may not be increased in asthmatic patients. Few researches studies have been published about arrhythmias in asthmatic patients. Chan et al[11] underlined increased risk of new AFs development in asthmatic patients. In addition, this work also showed

Table I. Baseline characteristics of the study population.

	Control (n = 76)	Mild (n = 33)	Moderate (n = 30)	Severe (n = 25)	p
Age years	45.05 ± 11.57	45 ± 13.76	41 ± 14.63	46.96 ± 13.03	0.347
BMI (kg/m^2)	29.3 ± 3.87	28.64 ± 3.18	28.85 ± 4.24	30.52 ± 3.85	0.267
Female gender n (%)	43 (56.57)	16 (48.48)	17 (56.66)	14 (56)	0.877
EF (%)	58.96 ± 2.98	59.06 ± 2.77	58.93 ± 3.42	58.08 ± 2.61	0.581
Creatinine (mg/dL)	0.77 ± 0.11	0.82 ± 0.15	0.74 ± 0.15	0.78 ± 0.1	0.1
Hemoglobin (gr/dL)	13.75 ± 1.33	13.84 ± 1.48	13.8 ± 1.3	13.87 ± 1.35	0.978
WBC (/mm^3)	8114 ± 1431	8058 ± 1498	8607 ± 1778	8968 ± 1827	0.063
Platelets (100/mm^3)	320 (310-341)	310 (278-350)	320 (314-330)	345 (295-348)	0.069
İnhaled corticosteroid n (%)	NA	33 (100)	30 (100)	25 (100)	1
β_2-Mimetics n (%)	NA	20 (60.66)	22 (73.33)	25 (100)	0.002
Theophylline n (%)	NA	3 (9.1)	10 (33.33)	18 (72)	< 0.001
Antihistaminic n (%)	NA	7 (21.21)	6 (20)	6 (24)	0.935
LTRBA4 n (%)	NA	10 (30.33)	12 (40)	19 (76)	0.002
FEV_1 % of predicted	NA	86.45 ± 15.6	81.97 ± 14.56	76.20 ± 17.51	0.056
ACQ Score	NA	0.67 ± 0.45	0.95 ± 0.47	1.7 ± 0.5	< 0.001

ACQ: Asthma control questionnaire; BMI: Body mass index; EF: Ejection fraction; FEV_1: Forced expiratory volume in 1 second; LTRA4: leukotriene receptor antagonist; NA: Non available; WBC: White blood cell.

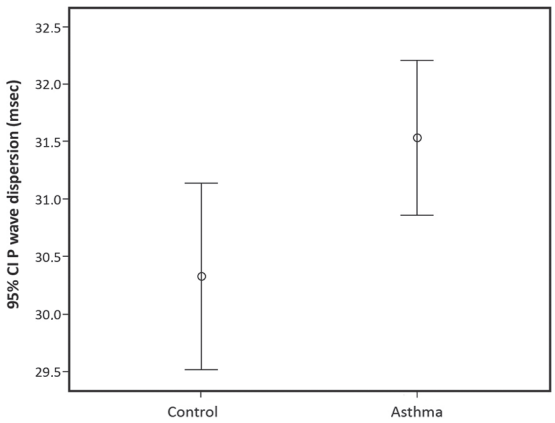

Figure 1. Comparison of P wave dispersion of the patients with asthma and control subjects.

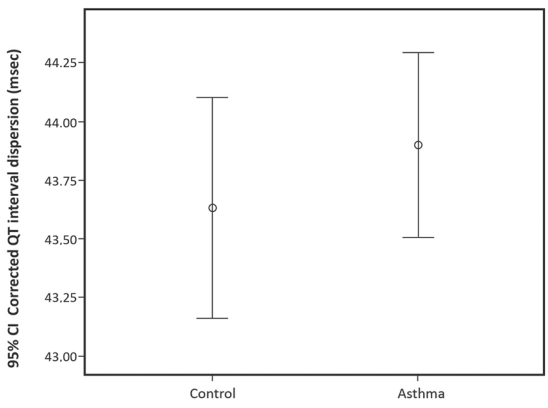

Figure 2. Comparison of corrected QT interval dispersion between patients with asthma and control group.

a high risk of developing asthma in AF patients. The reason why more frequent AF has been observed in the patients with asthma may be due to the fact that obesity is a risk factor for both diseases, and it is more common in obese patients. It is known that the frequency and severity of AF are higher in obese patients[12,13]. Reduced weight has been reported to improve the success of AF ablation and reduce AF recurrences[14]. Elevated left ventricular diastolic pressure, increased sympathetic activation, and inflammation, are some of the reasons why AF is more common in obese patients[15]. According to our results, the BMI value of the severe asthmatic patient group was higher than the other groups even though it was not statistically significant. In addition, increased PWD values, especially in the severe group compared to the other groups, may explain the relation between asthma and AF.

Another mechanism involved in the pathogenesis of both asthma and AF is increased systemic inflammation. Tarnowski et al[16] showed decreased CD11b expression in monocytes and granulocytes in patients with successful AF ablation, but not in patients with failed ablation. As a result of this study, it was emphasized that AF might be a part of the inflammatory process. Important mediators of inflammation such as CRP and IL-6, have been found to be high in patients with AF, and their influence on the success of the AF ablation have been shown[17,18]. Increased systemic inflammation plays an important role not only in the pathogenesis of AF, but also asthma[19]. Serum IL-6, CRP, plasminogen activator inhibitor 1, eotaxin, vascular endothelial growth factor (VEGF), and TNF-α levels, were found to be high in obese asthmatics[20,21]. These markers, which are increased in asthma, may be the cause of chronic airway inflammation and systemic inflammation. Furthermore, it has been shown that arterial inflammation increases in patients with asthma and it was emphasized that bronchial asthma is associated with increased arterial inflammation status in addition to airway inflammation[22].

In our paper, the drugs used by patients may be the reason for the high PWD in the severe asthma group. Although in all asthmatic subgroups were on the treatment of inhaled corticosteroids or beta-mimetics, patients with severe grade asthma were using these drugs in high doses and more

Table II. Comparison of P wave and corrected QT interval dispersion between control group and asthma subgroups.

	Control (n = 76)	Mild (n = 33)	Moderate (n = 30)	Severe (n = 25)	p
PWD (msec)	30.33 ± 3.53	30.97 ± 3.77*	31.10 ± 3.05*	32.80 ± 2.02**	0.017
CQTD (msec)	43.63 ± 2.06	43.33 ± 1.83	43.97 ± 1.75	44.56 ± 1.80	0.09

*The *p*-value is non-significant when compared to control group ($p > 0.05$). ** The *p*-value is significant when compared to control group ($p < 0.001$). BMI: Body mass index; CQTD: Corrected QT interval dispersion; PWD: P wave dispersion.

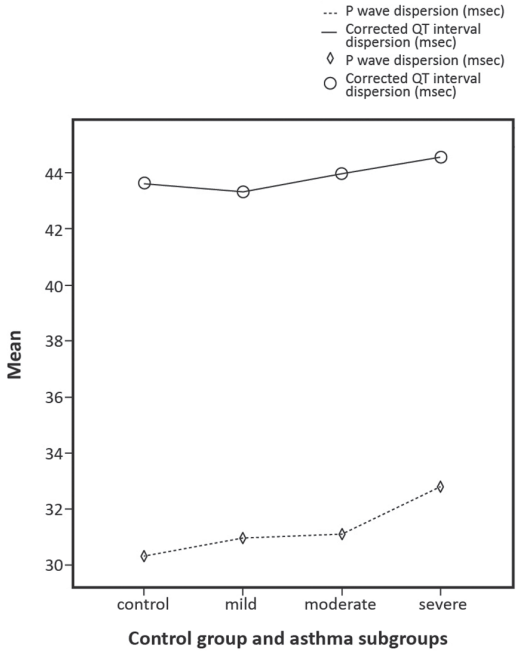

Figure 3. Comparison of P wave dispersion and corrected QT interval dispersion between control group and asthma subgroups.

intensively. Studies have shown that AF frequency is higher in patients with asthma using corticosteroids, beta-mimetic[11]. Huerta et al[23] showed that oral steroids and theophylline are associated with the risk of atrial fibrillation and ventricular arrhythmias development related to beta-adrenoceptors.

There are some other researches that are not consistent with the results of our work. In a cross sectional study by Warnier et al[24], the AF rate was not high in asthmatic patients; however, in this study arrhythmia was evaluated by using only momentarily ECGs. It should be kept in mind that silent arrhythmias that the patient does not feel or an arrhythmia that is not present when the ECG is withdrawn, may be missed or, may not be, documented.

Another result of the study was that FEV_1 and PWD were negatively but ACQ score and PWD was positively correlated. In previous investigations it was shown that lower FEV_1 is associated with increased atrial fibrillation rates[25-27]. Impaired lung function increases the risk of AF

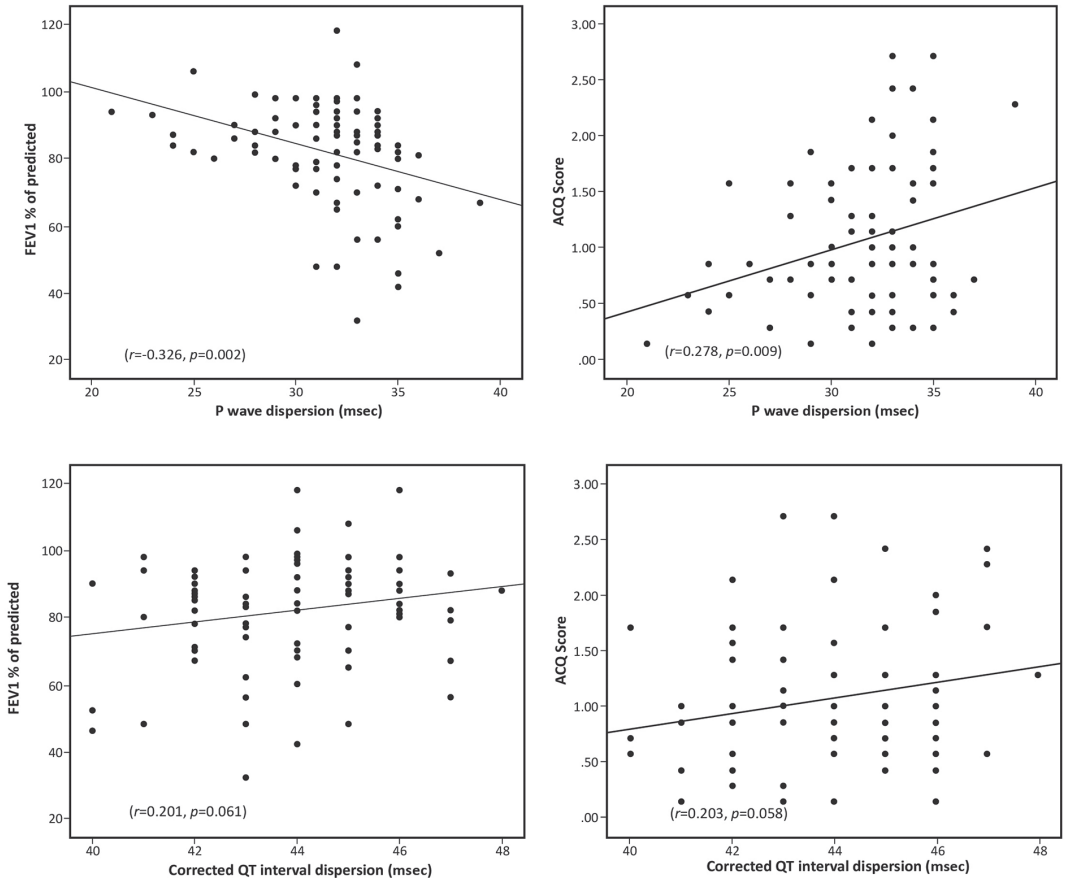

Figure 4. Correlation analysis between PWD, CQTD and FEV_1 % of predicted, ACQ score.

through increased chronic systemic inflammation and endothelial dysfunction[26].

A large-scale work investigating ventricular tachycardia in patients with asthma is not available in the literature. We did not assess whether ventricular tachycardia was present in our asthmatic patients; however, it has been shown that the CQTD shows the risk of ventricular tachycardia development[9]. It is known that ventricular tachycardia and sudden cardiac death risk is higher in patients with obesity[5]. However, it is not clear how and which limit of obesity leads to an increased risk of ventricular tachycardia. The low number of patients who were relatively obese and that constituted a severe asthma group may have affected the outcomes of the study. To validate our findings, future researches should be focused on a larger patient cohort. Our work has some limitations. Firstly, was conducted in a single center and the number of patients was limited, which does not reflect the overall population. Secondly, patients were admitted to the clinic without emergency and their asthma was stable. We do not know how the PWD and CQTD would change if the same patients were admitted with acute asthma attack. Thirdly, the study was designed as a cross-sectional where a cross-sectional ECG was evaluated with PWD and CQTD. Fourthly, the patients enrolled were on the treatment of asthma. The doses of medications were different from each other and further investigation is needed to determine how the drug doses affect these ECG changes.

Conclusions

We found that PWD value is elevated in patients with asthma compared to the control group whereas CQTD score was similar between the groups. These results indicate that the risk of developing AF in asthmatic patients might be higher than in the normal population. However ventricular arrhythmia and sudden cardiac death risk may not be increased in asthmatic patients.

Financial Disclosure
The authors have indicated they have no financial relationships relevant to this article to disclose.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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