The Effect of Bronchial Asthma on Interatrial Electromechanical Delay Coupling Obtained Using Tissue Doppler Imaging

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Abstract

Background: Asthma is a predisposing factor for the development of atrial fibrillation. Asthma disturbs the electrophysiology in the right and left atrium. The aim of this study was to evaluate atrial electromechanical delay by coupling obtained from tissue Doppler imaging (TDI) in children.

Methods: A cross-sectional study was conducted on 50 patients with Bronchial Asthma, compared with 50 healthy children. The intra-right atrial conduction time (IRCT), intra-left atrial conduction time (ILCT), and interatrial conduction time (IACT) were calculated. The function of systolic and diastolic right ventricular (RV) was assessed by TDI, conventional echocardiography, and pulse Doppler wave. The pulmonary function test was carried out for all the subjects by spirometry. We used an independent Student’s t test and Pearson’s correlation test for analyzing the data.

Results: The findings revealed normal shape in both atrial intervals between the two groups. The diastolic RV function was not significantly different between the subjects as measured by the pulse wave Doppler in the tricuspid flow. Patients in the experimental group had significantly higher intra and interatrial electromechanical delays (P=0.007) than the control group. This difference was statistically significant with regard to IRCT (P=0.0001) and IACT (P=0.005). IRCT/IACT and myocardial performance index (r=0.35, P=0.004; and r=0.52, P=0.008) correlated with isovolumetric relaxation time (r=0.46, P=0.003; and r=0.58, P=0.008).

Conclusion: We found that IRCT and IACT prolonged in pediatric asthmatic children. Also, it was found that there was a correlation between IRCT and IACT, on one hand, and RV myocardial performance index, on the other hand, but they were not related to TDI diastolic parameters.

Keywords: Asthma ● Echocardiography ● Right ventricular dysfunction ● Pediatrics

Introduction

One of the common chronic diseases in children is bronchial asthma. The incidence of asthma in children has been on the rise in the world. Similarly, the incidence of atrial fibrillation (AF) has increased in asthmatic adults. Electrocardiographic abnormalities are not rare in patients with asthma. Asthma is a predisposing factor...
for the development of AF and sinus tachycardia and bradycardia, right axis deviation, and right bundle branch block.\(^1\) Two major therapies for patients with asthma are \(\beta_2\)-adrenergic receptor agonists and corticosteroids.\(^2\) It has been shown that the incidence of arrhythmias is higher in asthmatic patients treated with \(\beta_2\)-adrenergic receptor agonists.\(^2\) The \(\beta_2\)-adrenergic receptor agonists such as inhaled salbutamol can alter cardiac electrophysiologiy conduction.\(^3\) Salbutamol not only enhances atrioventricular nodal conduction and decreases atrioventricular nodal, atrial, and ventricular refractoriness but also induces positive chronotropic effects. These alterations can contribute to the generation of spontaneous arrhythmias. However, other etiologies may also contribute to the cardiac arrhythmia. Atrial enlargement and atrial stretch may disrupt the inhomogeneous and continuous electrophysiological properties of the atrium.\(^4,\) \(^5\) The electrophysiological abnormalities of the atrium may increase the risk of AF.\(^1\) These abnormalities in bronchial asthma increase atrial electromechanical delay (AED) and P-wave dispersion (PWD). PWD is a parameter of inhomogeneous propagation between right and left atrial tissues. Increased AED and PWD leads to a higher risk of AF.\(^6,\) \(^7\) Chronic bronchial asthma may cause pulmonary arterial hypertension, which causes RV hypertrophy and dilatation. Systolic and diastolic dysfunction happened in right ventricular hypertrophy. The level of right ventricular diastolic dysfunction depends on the degree of right ventricular hypertrophy and total pulmonary resistance.\(^5,\) \(^8\) Pulse Doppler wave (PWD) and TDI is the best non-invasive method to assess ventricular diastolic dysfunction.\(^10,\) \(^11\) PWD and TDI are useful techniques that provide a quantitative measure of regional myocardial function. PWD and TDI parameters can detect subclinical right ventricular dysfunction in the early stages of the disease, even when routine echocardiography parameters are normal. The results of a study on children revealed that the atrial electromechanical time was higher in patients with asthma and that it deteriorated the electrophysiological properties of the right atrium.\(^3\) Çiftel et al. found that the intra-right atrial conduction time increased in patients with asthma. There was a correlation between the increase in the intra-right atrial conduction time and Right ventricular dysfunction.\(^4\) In the same study, they reported that pulmonary hypertension did not take place. In our paper, we aimed to examine the reliability of this finding in younger children. Accordingly, the aim of our study was to evaluate AED coupling obtained by TDI in children with asthmatic disease treated with inhaled corticosteroids.

**Materials and Methods**

**Study Population**

This cross-sectional study was carried out on asthmatic children from April 2015 to April 2016 at Amir-kabir Hospital affiliated to Arak University of Medical Sciences, Arak, Iran. The study protocol was approved by the Research Ethics Committee of Arak University (IR.ARAKMU.REC.1395.19). Prior to the study, written informed consents were obtained from the children’s parents. A sample size of \(n=40\) was estimated for each group according to the study of Murat Çiftel et al. with \(\alpha\) and \(\beta\) error of 0.05 and 0.2, respectively.\(^4\)

We examined 40 asthmatic patients in the age range of 5–15 years and 40 healthy subjects who were homogenous to the experimental group in terms of age and sex. The patients in the intervention group were referred by the Pediatrics Allergy Clinic, and subjects in the control group were selected among the non-asthmatic children of patients’ family.

Physical examination was performed for all subjects. In both groups, age, BMI, and systolic and diastolic blood pressure were measured. The asthmatic patients who had received a low dose (125 micro/ day) of inhaled corticosteroids for at least one year were included in the study. The patients who had received high doses of inhaled corticosteroids or used oral corticosteroids and a short- or long-acting \(\beta_2\)-adrenergic receptor agonist in the last 12 months, leading to the beginning of this study, were excluded from the study. The patients who had received high doses of inhaled corticosteroids were excluded as it reduced pulmonary arterial pressure and pulmonary vascular resistance, thereby disrupting the right ventricular function.

**Spirometry Testing**

A comprehensive physical examination and spirometry were performed according to the consensus standards set by the European Respiratory Society.\(^12\) The pulmonary function test was administered to all subjects using spirometry (peak expiratory flow [PEF] forced expiratory volume 1 [FEV1], forced vital capacity [FVC], and the ratio of FEV1 to FVC).

**Standard Echocardiography**

Standard echocardiography was performed for all subjects. The average measurement of 3 to 5 consecutive beats was calculated. Echocardiography was performed by a 3-7MHz...
transducer (Vivid 6s GE, Vingmed Ultrasound, USA). Left ventricular ejection fraction (LVEF) was determined using M-mode echocardiography in the parasternal long-axis view.

In the apical four-chamber view, the maximum and minimum dimensions of the right and left atrium were meticulously measured. The left atrium (LA) length was measured from the mid-point of the segment joining hinge points of mitral leaflets up to the inner layer of the posterior wall of LA. The LA minor dimension was measured from the lateral wall to the interatrial septum. The right atrium (RA) length was measured from the mid-point of the segment joining hinge points of the tricuspid leaflets up to the inner layer of the posterior wall RA. The RA minor dimension was measured from the anterolateral wall to the interatrial septum.

**Echocardiographic Measurements**

TDI is a useful method for detecting subclinical systolic and diastolic dysfunction, which is less depended on preload, afterload, heart rate, and age. PWD and TDI are useful for indicating early systolic and diastolic myocardial dysfunction. PWD and TDI were performed based on the recommendations of the American Society of Echocardiography.

The electrocardiography was continuously recorded for the evaluation of the atrial electromechanical delay during echocardiography, and parameters such as intra-right atrial conduction time (IRCT), intra-left atrial conduction time (ILCT), and interatrial conduction time (IACT) were calculated.

In the apical four-chamber view, the PWD parameters were applied to mitral and tricuspid valves; peak early diastolic (E) flow, peak late diastolic (A) flow, E/A ratio, and E wave deceleration time (E-DT) were measured. All indices were averaged for three consecutive beats. The sampling volume was placed parallel to the myocardial flow as closely as possible.

In the apical four-chamber view, TDI was performed from free wall RV. A Nyquist limit of 15-20 cm/s was placed for the minimal optimal gain, and the sweep speed was set at 50-100 mm/s to optimize myocardial velocities. The TDI parameters were measured from the lateral tricuspid annulus. The peak early velocities (E'), late diastolic velocities (A'), E'/A' ratio, isovolumetric relaxation time (IVRT), S’-wave velocities, and myocardial performance index (MPI) were recorded. All indices were averaged for three consecutive beats.

**Atrial Electromechanical Delay Measurements**

The mechanical activation time of all three parts of lateral mitral, septal mitral, and RV tricuspid annular depend on their distance to the sinus node. The RV tricuspid annulus and the lateral mitral annulus are the shortest and longest segment activated by the impulse arising from the sinus node, respectively. The mechanical delay can then be determined based on the difference between the two parts, which reflects the conduction time of these two parts.

AED was estimated as time intervals from the onset of P wave on ECG to the beginning of A’-wave, and PA from the lateral mitral annulus, septal mitral annulus, and RV tricuspid annulus. These time intervals were called lateral PA, septal PA, and RV PA, respectively.

The intra-right atrial conduction time (IRCT-echo) was measured as the difference between septal PA and RV PA (septal PA–RV PA). The intra-left atrial conduction time (ILCT-echo) was also measured as the difference between lateral PA and septal PA (lateral PA–septal PA). The interatrial conduction time (IACT-echo) was estimated as the difference between lateral PA and RV PA (lateral PA–RV PA). All values were averaged for three consecutive beats.

**P-Wave Dispersion Measurement**

Standard 12-lead ECG was performed using a recorder set at of 25-mm/s and 1-mV/cm (cardiMax, FX-7202). The PWd was measured as the difference between the maximum and minimum P-wave durations. Then, the mean of the three measurements was obtained. The maximum and minimum P-wave (P- max, P-min) durations were measured from the 12-lead ECG, in at least 8 out of 12 ECG leads.

**Statistical Analysis**

The mean±SD was calculated for all data. Data were analyzed by SPSS 23 software (SPSS, Inc., Chicago, IL, USA). Quantitative variables were compared using the independent Student's t test. Pearson's correlation test was also used to assess the correlation between quantitative data. Kolmogorov Smirnov test was utilized to check the normal distribution of data. A P-value of <0.05 was considered as statistically significant.

**Results**

In our study, 40 asthmatic patients (18 men and 22 women) were compared with 40 healthy subjects (17 men and 23 women). The demographic and physical characteristics of subjects in both groups are summarized in table 1. The two groups were not significantly different in this regard.
As noted in table 2, Spirometry findings, such as PEF, FEV1, FVC, and FEV1/FVC, were significantly different between the two groups. According to table 3, asthma and control groups were not significantly different in terms of ejection fraction (EF) and other parameters. The assessment of diastolic RV and LV by PWD in the mitral and tricuspid flow did not show any significant difference among subjects. Subclinical systolic and diastolic dysfunction was measured by using TDI in the right ventricular. The E/E' ratio was identical in both groups.

ECG variables revealed a significant difference between the two categories. There was inhomogeneous propagation of sinus impulses between the two groups (table 4). As shown in table 4, AED is depicted in patients with asthma. The RV PA was higher in patients in the intervention group. The IRCT-echo and IACT-echo were also higher in patients with asthma compared to the control group.

We did not find any correlation between IRCT-echo, IACT-echo, and TDI or PWD in the asthmatic patients. The results of Pearson's correlation coefficient in asthmatic patients revealed a positive correlation between IRCT-echo, IACT-echo, and MPI (r=0.35, P=0.004; and r=0.52, P=0.008, respectively) and also between IRCT-echo, IACT-echo, and IVRT (r=0.46, P=0.003; and r=0.58, P=0.008, respectively).

### Discussion

In our patients, the geometry of right and left ventricular was similar in both groups. The RV wall thickness and RV, RA, and LA diameters were in the normal range. The RV dysfunction diagnosis was established using tissue Doppler echocardiography. The lateral tricuspid annulus E', A', MPI, and IVRT had increased in patients with asthma. The impaired atrial conduction time and RV dysfunction parameters were correlated with each other. According to the findings, IACT in asthmatic children was significantly longer than that of healthy subjects. Also interatrial electromechanical function in children with asthma was significantly impaired. IRCT, ILCT, PWd, P max, and P min were similar in both groups.

The correlation between asthma and atrial arrhythmias has been reported in adolescent patients. Previous studies have shown that pulmonary dysfunction affects patients with asthma and it is an independent risk factor for AF. AF has been shown to be higher in patients with chronic obstructive pulmonary disease (COPD). The relationship between asthma and AF has also been documented in adults. The AF increases the mortality rate of patients with COPD, but its mechanism is not clear.

The right atrial conduction time was higher in patients with COPD secondary to pulmonary dysfunction and pulmonary hypertension. Atrial depolarization time was also higher in patients with asthma. The inhomogeneous propagation of sinus node depolarization was higher in right atrial enlargement (RAE), which may explain atrial arrhythmias such as AF and atrial flutter. Shedeed revealed RV diastolic dysfunction in asthmatic patients. In the present study, using

### Table 1: Comparison of demographic information and results from physical examination

|                      | Case group (mean±SD) | Control group (mean±SD) | P     |
|----------------------|----------------------|-------------------------|-------|
| Male/female (%)      | 18 / 22 (45%/55%)    | 17 / 23 (42.50%/41.5%)  | 0.822 |
| age (years)          | 8.61±0.91            | 8.40±2.49               | 0.585 |
| BMI (Kg/M2)          | 16.90±2.8            | 16.30±2.42              | 0.061 |
| Respiratory rate (BPM)| 19.90±8.70           | 17.10±6.40              | 0.105 |
| Heart rate (bpm)     | 83.50±8.30           | 80.90±4.90              | 0.093 |
| SBP (mmHg)           | 102.12±5.31          | 100.87±6.93             | 0.368 |
| DBP (mmHg)           | 67.45±5.24           | 65.87±4.38              | 0.147 |

|                      |                      | BMI: Body mass index; Bpm: Beat per minute; BPM: Breath per minute; SBP: Systolic blood pressure; DBP: Diastolic blood pressure |

### Table 2: Comparison of Spirometry results

|                      | Case group (mean±SD) | Control group (mean±SD) | P     |
|----------------------|----------------------|-------------------------|-------|
| PEF                  | 83.05±6.81           | 89.80±7.21              | 0.0001 |
| FEV1                 | 80.82±10.33          | 87.53±8.74              | 0.002 |
| FVC                  | 89.11±9.53           | 93.20±7.82              | 0.039 |
| FEV1/FVC             | 80.40±8.94           | 90.74±7.93              | 0.0001 |

PEF: Peak expiratory flow; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity

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TDI echocardiography, we found subclinical systolic dysfunction in the RV. These changes may cause atrial arrhythmia or any other atrial conduction disorder. PWd is an index of inhomogeneous propagation of sinus impulses. The right atrial enlargement (RAE) intensifies PWd and atrial conduction disorder.

The RAE and RA stretching may disturb intra-atrial or interatrial conduction.

Yücel et al. showed that PWd or maximum P-wave duration did not increase in patients with asthma. According to our results, there were no significant differences between the maximum and minimum P-wave duration, but PWd was lower in the case group than in the control group. This finding suggests that PWd is a more sensitive marker than P-wave duration alone.

In conclusion, TDI echocardiography provides valuable information about the atrial conduction system and may be a useful tool in the assessment of atrial arrhythmias. Further studies are needed to investigate the role of PWd in the diagnosis and management of atrial arrhythmias.
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significantly different between the two groups.

Daubert et al. found that intra-atrial and interatrial conduction times, such as electrophysiological parameters, were longer in patients with atrial arrhythmias, especially paroxysmal AF.7 The deterioration of electrophysiology may increase the risk of AF. We found that RV PA, IRCT, and IACT were significantly different between subjects in the two groups. However, in our case, subjects did not have any atrial arrhythmia.

Nagarakanti et al. revealed that diastolic dysfunction was an independent risk factor for AF.20 We found that Tricuspid S’ (cm/s), E’ (cm/s), A’ (cm/s), and E’/A’ by TDI were significantly different between the two groups. Furthermore, diastolic dysfunction was observed in our study, but AF or other atrial arrhythmias were not found in our asthmatic patients.

Akyüz Özkan et al. showed that cardiac systolic function was impaired in asthmatic patients, but diastolic dysfunction was not impaired. They found a positive correlation between FEV1 and isovolumetric relaxation time (IVRT) and mitral ET; also, PEF was negatively correlated with myocardial fiber stresses (MFS, g/cm²), such as the RV and LV work index.21

Schotten showed that atrial stretch and enlargement caused electro anatomical disorders and, consequently, inhomogeneous propagation of sinus impulses. These histologic changes, which lead to dilated atrium, promotes re-entrant conductions inside the atrium.22

B2-adrenoceptors, theophylline, and high-dose inhaled steroids are used for the treatment of asthma though they may increase the risk of AF.23

Van der Hooft et al. showed that low-dose oral steroids or inhaled steroids did not increase the risk of AF,24 but our patients received low doses (125 micro/day) of inhaled corticosteroids (fluticasone propionate, budesonide).

Ciftel et al. found that IRCT-echo and IACT-echo disorders were significantly higher in patients with asthma while RV PA was also found to be high in them. They found a correlation between IACT-echo and RV dysfunction.6 We found that PWD was higher in patients with asthma, but maximum P-wave duration and minimum P-wave duration were identical in subjects of the two groups. We also evaluated the geometry of right atrial and left atrial in both groups, which were not considered by Ciftel et al.4 The atrium can also be involved in patients with asthma. We observed that atrial conduction time was impaired in patients with asthma.

In both studies, PWD in RV was significantly different between the two groups. However, using TDI, we found that systolic subclinical function was significantly different between asthmatic patients and healthy subjects, and the patients had subclinical diastolic dysfunction, but these factors were not considered by Ciftel et al.4

Due to the patients’ lack of cooperation, we were not able to perform 24-hour Holter monitoring as to precisely diagnose rhythm disorders.

Conclusion

Despite the normal geometry RA and LA, we found that IACT-echo, IRCT-echo, and Lateral PA were higher in asthmatic children. We also found a positive correlation between IACT-echo, IRCT-echo, IVRT, and MPI. Accordingly, it is suggested that the assessment of the right atrium electrophysiology could be useful in determining the risk of atrial dysrhythmias in patients with asthma. Thus, it is recommended that this study be conducted with a larger sample size, Holter monitoring, and longer follow-up.

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Conflict of Interest: None declared.

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