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RESEARCH ARTICLE
KLİNİK ÇALIŞMA

Echocardiographic evaluation from a different perspective in asthmatic patients

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ABSTRACT

Echocardiographic evaluation from a different perspective in asthmatic patients

Introduction: *It is known that there is a complex interaction between asthma and cardiovascular physiology. Some investigations on echocardiography and electrocardiography (ECG) in asthmatic patients have revealed many findings such as pulmonary hypertension (PHT) and arrhythmia. In this study, we aimed to perform tissue Doppler imaging (TDIE) and conventional echocardiographic (CEI) assessment with many indexes of arrhythmia on electrocardiography (ECG) in asthmatic patients.*

Materials and Methods: *A total of 89 patients, 63 females (70.8%) and 26 males (29.2%), were included in this study. Patients were divided into three groups, and then each group was separated in two groups as mild-moderate and severe asthma.*

Results: *There was no difference among groups with respect to age, sex and anthropometric data. There was no difference between the groups with respect to indexes of arrhythmia on ECG (p> 0.05). Mitral annular plane systolic excursion (MAPSE), tricuspid annular alane systolic excursion (TAPSE) and both ventricular diastolic velocities on CEI were similar between the groups, except for left ventricular A wave velocity which was higher in severe asthmatic patients (p< 0.05). Investigation of time intervals of both ventricular diastolic filling velocities (e' and a') at the mitral lateral, septal and tricuspid lateral annulus revealed significant difference at Pa'm-3 and Pa's-3 intervals based on TDEI (p< 0.05). Only maximal volume of the LA was higher in severe asthmatic patients (p< 0.05). However, there was no significant difference between LA-VpreA and LA-Vmin (p> 0.05).*

Conclusion: *Based on these results, it can be suggested that LA mechanical functions and intra-atrial LA electromechanical durations were impaired in severe asthmatic patients.*

Key words: *Electromechanical conduction delay; atrial volume; asthma*

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ÖZ

Astımlı hastalarda farklı bir bakış açısıyla ekokardiyografik değerlendirme

Giriş: *Astım ile kardiyovasküler fizyopatoloji arasında karmaşık bir etkileşim olduğu bilinmektedir. Astımlı hastalarda ekokardiyografik (EKO) ve elektrokardiyografik (EKG) değerlendirmelerle yapılan araştırmalarda, pulmoner hipertansiyon (PHT) ve aritmiye neden olduğu tespit edilmiştir. Bu çalışmada, astım tanılı hastalarda, EKG'de aritmi indeksi, Doku Doppler görüntüleme (TDIE) ve konvansiyonel ekokardiyografik (CEI) değerlendirme amaçlanmıştır.*

Materyal ve Metod: *Çalışmaya 63'ü kadın (%70,8), 26'sı erkek (%29,2) toplam 89 hasta dahil edildi. Hastalar üç gruba ayrıldıktan sonra her grup hafif-orta ve ağır astım olmak üzere iki gruba ayrıldı.*

Bulgular: *Gruplar arasında yaş, cinsiyet ve antropometrik veriler açısından fark yoktu. EKG'de aritmi indeksleri açısından da gruplar arasında fark yoktu (p> 0,05). Ağır astım tanılı hastalarda daha yüksek olan sol ventrikül A dalga hızı dışında, mitral anüler düzlem sistolik hareketi (MAPSE), triküspit kapak anüler planın apekse doğru sistolik hareketi (TAPSE) ve her iki ventriküler diyastolik CEI hızları gruplar arasında benzerdi (p< 0,05). Mitral lateral, septal ve triküspit lateral anulusta her iki ventriküler diyastolik dolum hızlarının (e' ve a') zaman aralıkları incelendiğinde TDEI'ye göre Pa'm-3 ve Pa's-3 aralıklarında anlamlı farklılık saptandı (p< 0,05). Ağır astım tanılı hastalarda LA'nın sadece maksimum hacmi daha yüksekti (p< 0,05). Ancak LA-VpreA ve LA-Vmin arasında anlamlı bir fark yoktu (p> 0,05).*

Sonuç: *Bu sonuçlara dayanarak ağır astım tanılı hastalarda SA mekanik fonksiyonlarının ve intraatriyal SA elektromekanik sürelerinin bozulduğu ileri sürülebilir.*

Anahtar kelimeler: *Elektromekanik iletim gecikmesi; atriyal hacim; astım*

INTRODUCTION

There is a complex interaction between asthma and cardiovascular physiology. The final effect of asthma due to recurring hypoxemia and hypercapnia periods on the patient is chronic inflammation in pulmonary and right ventricular (RV) systems, which cause pulmonary vasoconstriction (PV) and subsequently pulmonary hypertension (PHT). Echocardiographic imaging can basically show hypertrophy/dilatation of the RV during this disease period. Tissue doppler imaging echocardiography (TDIE) can detect subclinical abnormalities while conventional echocardiographic imaging (CEI) findings are still within normal ranges (1). In later times, PV and PHT may alter and decrease left ventricular functions, and left ventricular diastolic and systolic dysfunction (LV-DD and LV-SD, respectively) may occur (1-3). Evaluation of volume and mechanical function of left atrium (LA) and atrial electromechanical conduction delay (EMCD) as a novel parameter revealed that parameters would be identified as indicator of arrhythmias and other cardiac diseases like systolic, diastolic heart failure (HF) and paroxysmal atrial fibrillation (PAF). A trial EMCD is calculated as an interval from the onset of P wave on the surface electrocardiography (ECG) to the beginning of the late diastolic wave (a') at various annular location in both atrium on TDIE (4-8). Mitral and tricuspid annular plane systolic excursion (MAPSE and TAPSE) is another impaired parameter in asthmatic patients and represent longitudinal systolic function of LV and RV ejection fraction (2). Myocardial transmural dispersion of repolarization (TDR) was proposed to show by measuring the time between the peak and end of the T wave (Tpeak-Tend: Tp-Te) on the surface of ECG (9). QT interval is another measurement method for depolarization-repolarization dispersion of the myocardial tissue. QTc interval (heart rate-corrected form of QT interval) and Tp-Te, Tp-Te/QT ratio have been proposed as risk factors for ventricular arrhythmia (VA) or sudden cardiac death (SCD) in various clinical scenarios like HF, Brugada syndrome and general population. In groups of patients with an increased risk of arrhythmias, Tp-Te value has been found to be generally more than 100 ms (10). Based on this knowledge, in this study, we aimed to investigate various quantitative measurements of ECG, CEI and TDIE areal velocities, the intervals and the systolic and diastolic functions of myocardium to search any possible relationship between the severity of asthma and cardiovascular functions (11).

MATERIALS and METHODS

Study Population

This cross-sectional study consisted of 89 patients (63 females [%70.8] and 26 males [%29.2]) who accepted to take part in the study in our outpatient clinic from September 2019 to March 2020. The study protocol was approved by the Ethical Committee at Kırşehir Ahi Evran University (No: 2019-02-17, date: 29-01-2019) and the informed consent was obtained from each patient.

Inclusion criteria: Patients aged between 18 and 40 years were accepted in the study. The diagnosis of persistent asthma was described according to clinical findings, pulmonary function tests, and the criteria in the Global Initiative for Asthma (GINA) guidelines for all patients (12). We categorized patients into three groups based on asthma severity in accordance with the GINA 2016 guidelines as mild, moderate, and severe asthma (12).

Exclusion criteria: Exclusion criteria were determined based on other comorbid diseases such as upper or lower respiratory infection, allergic rhinitis, gastroesophageal reflux, chronic cardiovascular, pulmonary or systemic diseases and acute asthma attack during the last four weeks.

Evaluation protocol: First of all, demographic data including age and sex were recorded. After that, complete physical examinations and anthropological data including measurements of weight, height, calculation of body mass index (BMI) were recorded.

Pulmonary function test: Pulmonary function tests were performed according to the American Thoracic Society Guidelines by a single physician using a spirometer (SensorMedics Vmax spectra 229; Bilthoven, The Netherlands) to determine forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) in estimated percentage for both and FEV_1/FVC ratio (12). The Asthma Control Test (ACT®) and Childhood Asthma Control Test (C-ACT®) were used to assess asthma examination. Based on the American Thoracic Society Guidelines, scores on the ACT and C-ACT are ranged from 0 to 27 and 5 to 25, respectively. Scores of ≥22 for C-ACT and ≥23 for the ACT indicate adequate asthma control. Scores below 20 are commonly considered as indicative of inadequate asthma control (13).

ECG: All ECGs were recorded using a General Electric MAC 5000 (GE Healthcare, Milwaukee, WI, USA). All 12-lead ECGs were recorded at 25 mm/s with standard lead position. All records were magnified up to 200% for clarity, and the QT intervals were measured. To eliminate both interobserver variability and bias, all measurements were performed in each of the 12 leads by a single observer who was blinded to all clinical findings. The QT intervals were taken to be from the onset of the QRS complex to the end of the T wave. Bazett's formula (n/RR) was applied to the QT intervals to obtain QTc values (QT heart rate correction). The Tp-Te interval was defined as the interval from the peak of T wave to the end of T wave. The Tp-Te/QT ratio was calculated as the ratio of Tp-Te in that lead to the corresponding to the QT interval (10).

Echocardiography: We used Vivid 5 pro echocardiographic unit (GE Healthcare, GE, USA) including 3.5 MHz probe for echocardiographic assessment. All test subjects were evaluated by a standard two-dimensional and Doppler evaluation according to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) by a single experienced cardiologist who was blinded to the test subjects and all clinical findings (12). The following parameters were obtained by CEI: LV end-diastolic dimension (LV-Dd), LV systolic dimension (LV-Sd), LV ejection fraction (LVEF, %) according to the method of Simpson's method; MAPSE and TAPSE by the M mode at mitral lateral and tricuspid lateral annulus, LV and RV diastolic functions from the filling velocities (early peak (E) and late diastolic (A) wave velocities, E/A ratios with deceleration times (DT) using pulsed wave doppler with the sample volume positioned at the tips of the mitral and tricuspid valve leaflets. Epicardial fat thickness (EFT) was considered as the echo-free distance between the outer surface of the myocardium and the visceral stratum of the pericardium (12). We measured EFT values from the parasternal long-axis imaging at vertical to the right ventricular free wall the end of the diastole. The TDIE study was performed in the lateral mitral annulus, interatrial septum, and lateral tricuspid annulus. The recordings of all diastolic functions of LV were obtained by evaluation of early peak (e') and late (a') diastolic wave velocities. In addition, e'/a' ratio, DT of e' wave from mitral lateral annulus, as well as systolic velocity of tricuspid lateral annulus (t-S´) and pulmonary annular systolic (Pu-S') velocity at pulmonary valve annulus from RV outflow tract short-axis view were also obtained by the TDIE. Additionally, LA volumes were assessed using the Simpson's method in the apical four-chamber view.

1. The maximal LA volume (LA-Vmax) or end-systolic volume was measured just before the opening of the mitral valve.

2. The pre-atrial contraction LA volume (LA-VpreA) was measured at the onset of the P wave.

3. The minimal LA volume (LA-Vmin) or end-diastolic volume was measured at the closure of the mitral valve.

All LA volumes were indexed to body surface area (BSA) for all patients (5,14). To find differences of EMCD, investigation of time intervals was performed from both the atrium and ventricle and were listed below.

1: The time intervals of diastolic filling velocities were obtained from the tips of mitral and tricuspid leaflets by CEI. A) Intervals at the tips of mitral leaflets (Figure 1): 1) EPm-1: The time interval from the onset of the early diastolic flow velocity (E) wave on echocardiography to the beginning of the P wave on the ECG.

2) PAm-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity (A) wave.

3) PAm-3: The time interval from the onset of the late diastolic flow velocity (A) wave to the end of the late diastolic flow velocity (A) wave. B) Intervals at the tips of tricuspid leaflets: 1) EPt-1: The time interval from the onset of the early diastolic flow velocity wave (E) on echocardiography to the beginning of the P wave on the ECG. 2) PAt-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity (A) wave. 3) PAt-3: The time interval from the onset of the late diastolic flow velocity (A) wave to the end of the late diastolic flow velocity (A) wave. 2: The time intervals of TDIE diastolic velocities where were obtained from the mitral lateral, interatrial septal and tricuspid lateral wall annulus. A) Intervals for the mitral lateral wall annulus: 1) e'Pm- 1: The time interval from the onset of the early diastolic flow velocity wave (e') on TDIE to the beginning of the P wave on the ECG. 2) Pa'm-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity wave (a') wave. 3) Pa'm-3: The time interval from the onset of the late diastolic flow velocity wave (a') wave to the end of the late diastolic flow velocity (a') wave. B) Intervals for the interatrial septal wall annulus: 1) e'Ps- 1: the time interval from the onset of the early diastolic flow velocity wave (e') on echocardiography to the beginning of the P wave on the ECG. 2) Pa's-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity wave (a') wave. 3) Pa's-3: The time interval from the onset of the late diastolic flow velocity wave (a') wave to the end of the late diastolic flow velocity (a') wave. C) Intervals for the tricuspid lateral wall annulus: 1) e'Pt- 1: The time interval from the onset of the early diastolic flow velocity wave (e') on echocardiography to the beginning of the P wave on the ECG. 2) Pa't-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity wave (a') wave. 3) Pa't-3: The time interval from the onset of the late diastolic flow velocity wave (a') wave to the end of

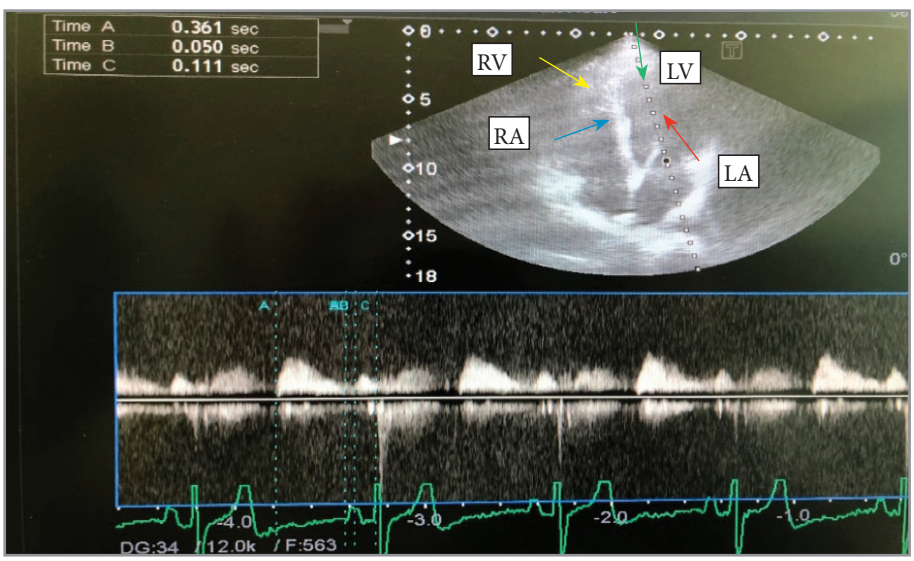

Figure 1. The time intervals of diastolic filling velocities where were obtained from the tips of mitral leaflets by CEI.
Green Arrow: Left ventricle (LV), red arrow: Left atrium (LA), blue arrow: Right atrium (RA), yellow arrow: Right ventricle (RV).

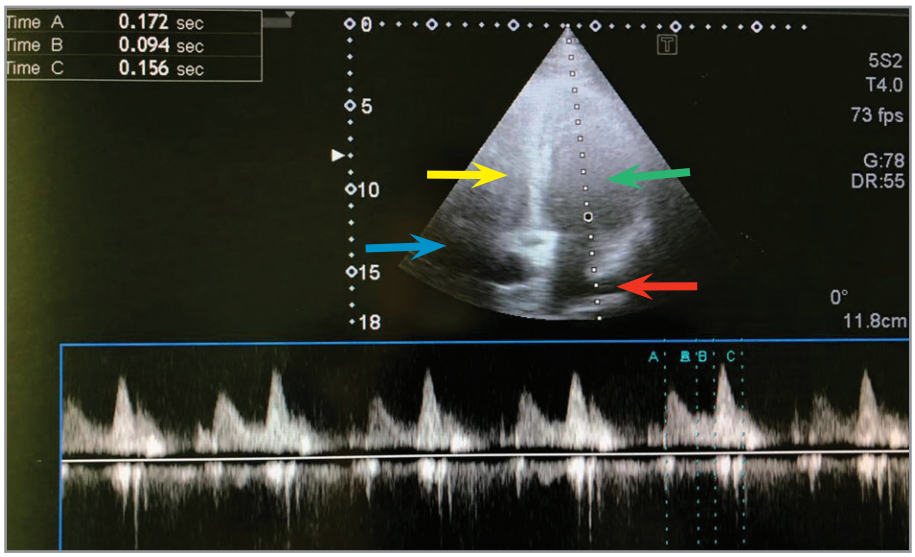

Figure 2. The time intervals of diastolic filling velocities where were obtained from the tips of mitral leaflets by CEI.

The time intervals of diastolic filling velocities where were obtained from the tips of mitral leaflets by CEI. A) Intervals at the tips of mitral leaflets : 1) EPm- 1: The time interval from the onset of the early diastolic flow velocity (E) wave on echocardiography to the beginning of the P wave on the ECG. 2) PAm-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity (A) wave. 3) PAm-3: The time interval from the onset of the late diastolic flow velocity (A) wave to the end of the late diastolic flow velocity (A) wave. Green Arrow: Left ventricle (LV), red arrow: left atrium (LA), blue arrow: right atrium (RA), yellow arrow: right ventricle (RV).

the late diastolic flow velocity (a') wave. 3: The time intervals of ventricular outflow systolic velocity recordings were obtained from the just proximal to the aortic and pulmonary valve by CEI. A) Intervals for the aortic valve: 1) Ao- 1: The time interval from the onset of the QRS wave on the ECG to the beginning of the aortic systolic ejection wave or pre-LV ejection period or pre-aortic valve opening time (Pre-ejection period). 2) Ao-2: The time interval from the onset of the LV ejection period to the end of LV ejection period (Total LV ejection time). 3) Ao-3: The time interval from end of the LV ejection period (closing the aortic valve) to the beginning of the mitral early (E) diastolic flow velocity wave (opening the mitral valve, isovolumetric relaxation time [IVRT]). B) Intervals for the pulmonary valve leaflets: 1) Pu-1: The time interval from onset of the QRS wave on the ECG to the beginning of the pulmonary systolic flow wave. 2) Pu-2: The time interval from the onset of the pulmonary systolic velocity wave to the end of pulmonary systolic wave (right ventricular systolic period). 3) Pu-3: Time interval from end of the pulmonary systolic wave (closing the pulmonary valve) to the beginning of the tricuspid early (E) diastolic flow velocity wave [opening the tricuspid valve, (IVRT)]. All measurements were done twice by one operator who was blinded to the subjects during different times, and the average of the measurements was obtained.

Statistical Analysis

Statistical analyses were performed with MedCalc Statistical Software version 12.7.7 [MedCal Software bvbv, Ostend, Belgium; 2013). Continuous variables showing normal distribution were reported as mean (standard deviation (SD)] and non-normal variables were expressed as median. All categorical variables were defined as frequency and percentage. Continuous variables were checked for normality using the Kolmogorov-Smirnov test. Accordingly, normal variables were compared using the unpaired Student's t test, while non-normal variables were compared using the Mann-Whitney U test. For categorical variables, the Chi-square test was used. The p-values of less than 0.05 were regarded as statistically significant.

RESULTS

Baseline Comparison

A total of 89 patients [26 males (29.2%) and 63 females (70.8%)] with an average age of 33 ± 8.22 were included in the study. Distribution of the groups according to points of asthma severity chart is shown in Table 1. The baseline characteristics of the groups are shown in Table 2. The ECG results are summarized in Table 3 and echocardiographic results are listed in Tables 4 and 5. While Group 1 consisted of 4 patients (4.5%), Group 2 and Group 3 included 42 (47.2%) and 43 (48.3%) patients, respectively. Due to very few patients in Group 1, Group 1 and 2 were combined for more reliable statistical analysis. There was no significant difference among the groups with respect to age, sex and anthropometric data (p> 0.05) and no difference was detected between the groups with regard to indices of TDR in ECG results (p> 0.05) (Table 3). Results of CEI and TDIE parameters are shown in Table 4. Although LV-Sd was similar between groups, LV- Dd was higher in severe asthma group (p= 0.031). It was found that EFT values were also similar between the groups (3.42 ± 1.72 vs. 4.05 ± 2.27, p= 0.197). All time intervals obtained from both ventricular outflow systolic velocity recordings at the just proximal to the aortic and pulmonary valve were found to be similar (p> 0.05). Mitral annular plane systolic excursion and TAPSE values were also not statistically different between groups (p> 0.05). Parameters showing ventricular diastolic functions E, A, E/A ratios and DT were not remarkable between groups, except for left ventricular A wave velocity which was higher in severe asthmatic group (p= 0.042). However, no significant difference was detected between the groups with respect to the rates of LV-DD and RV-DD. Again, as new parameters, the time intervals of diastolic filling velocities were found

Table 1. Distribution of groups according to points of asthma severity assessment chart

	Individual distribution of groups
	Total
Groups	Count
Group 1(Mild asthma)	(count & percent in total)
Group 2 (Intermediate asthma)	(count & percent in total)
Group 3 (Severe asthma)	(count & percent in total)

Table 2. Distribution of baseline demographic and anthropometric features of groups					
		Baseline demographic and anthropometric data of groups			
Variables					
Groups	Count	Group 1 and 2 n= 46 (51.6%)	Group 3 n= 43 (48.4%)	Total n= 89 (100%)	p¥, Ω
Age (years)	Mean ± std	31.6 ± 9.45	34.43 ± 6.54	33 ± 8.22 (min= 18; max= 62)	0.113
Height (cm)	Mean ± std	163.69 ± 9.62	167.38 ± 9.85	165.47 ± 9.85 (min= 147; max= 192)	0.081
Weight (kg)	Mean ± std	70.1 ± 14.49	75.46 ± 15.81	72.69 ± 15.29 (min= 45; max= 115)	0.102
BMI (kg/m^2)	Mean ± std	26.22 ± 5.31	26.92 ± 5.4	26.56 ± 5.33 (min= 18.5; max= 46.4)	0.540
Sex					
Female (n, %)	(count & percent in total)	36 (40.4%)	27 (30.3%)	n= 63 (70.8%)	0.170
Male (n, %)	(count & percent in total)	10 (11.2%)	16 (17.9%)	n= 26 (29.2%)	

cm: Centimeter, kg: Kilogram, std: Standart deviation, min: Minimum, max: Maximum, ¥: Independent-samples t test, Ω: Chi-square test.

Table 3. Distribution of ECG findings among the groups

Variables	Count	Group 1 and 2 n= 46 (51.6%)	Group 3 n= 43 (48.4%)	Total n= 89 (100%)	p¥
QTc (ms)	Mean ± std	398 ± 52.13	398.32 ± 47.7	398.15 ± 49.75 (min= 268; max= 466)	0.977
Tp-Te (ms)	Mean ± std	74.98 ± 15.72	76.71 ± 15.44	75.81 ± 15.51 (min= 45; max= 120)	0.610
Tp-Te/QTc ratio	Mean ± std	0.19 ± 0.05	0.2 ± 0.05	0.19 ± 0.05 (min= 0.1; max= 0.31)	0.689

std: Standard deviation, ms: Millisecond, min: Minimum, max: Maximum, QTc: The interval which was taken from the onset of the QRS complex to the end of the T wave (heart rate-corrected form), Tp-Te: The interval from the peak of T wave to the end of T wave, ¥: Independent- Samples t test.

to be similar among groups (p> 0.05). Assessment of LA mitral lateral annulus TDIE velocities (mitral- e', a' and dt') did not show any differences between groups (p> 0.05). Analysis of time intervals for both ventricular diastolic filling velocities (e' and a') from the mitral lateral, septal and tricuspid lateral annulus showed significant difference between the groups at Pa'm-3 and Pa's-3 intervals on TDEI (p= 0.027; p= 0.033; respectively). The intervals of Pa'm-3 and Pa's-3 reflected the total time of LA late diastolic (a') wave at mitral lateral and septal annulus. Along with this finding, an analysis of the LA functions or volumes revealed that only maximal volume (LA-Vmax) was higher in severe asthmatic group (12.49 ± 3.64 vs. 14.59 ± 5.37; p= 0.035). However, LA-VpreA and LA-Vmin were not found to be different between groups (p> 0.05). To find cut-off levels of these variables (Mitral- A velocity, LA-Vmax, Pa'm-3, Pa's-3) with the best sensitivity and specificity, Receiver Operating Characteristic (ROC) analysis was conducted (Table 6). Based on this analysis, cut-off levels were calculated as = 80.500 cm/s for mitral-A velocity; as =0.065 s for Pa'm-3, as =0,085 s for Pa's-3 and as = 9.750 mm3 for LA-Vmax. However, none of these levels reached the significance level (p> 0.05 for all).

DISCUSSION

ECG Results for Asthma Patients

The pathogenesis of cardiac arrhythmias in asthma patients has not been fully explained (18). In our study, it was determined that there was no significant difference between mild/moderate and severe asthma group in terms of the TDR or VA indexes, unlike previously published studies (p> 0.05 for all). Mean Tp-Te intervals were found to be similar between the groups (74.98 ± 15.72 ms vs. 76.71 ± 15.44 ms; p= 0.610).

Echocardiographic Parameters of Patients

RV-DD is an important determinant of prognosis in long-stage asthmatic patients due to the risk of progression to PHT. There is an interaction between RV dysfunction and LV functions which is related to increased LV afterload and decreased LV preload, and thus LV dysfunction (19). Conventional Echocardiographic Imaging and TDIE parameters are given in Table 4. Left ventricular diastolic dysfunction and RV-DD were indifferent between groups, except for LV late diastolic A wave velocity which was higher in the severe asthmatic group in those parameters (p= 0.042). This means that LV-DD and RV-DD were not gotten worse by severity of asthma in our study. The first part of atrial functions was found to be affected by severe asthma. The atrial passive emptying index was higher in patients with severe asthma. In addition to these, the assessment of LV-DD from mitral lateral annulus by TDIE (mitral-e', a' and dt') did not show any difference between groups (p> 0.05). Although we did not find any difference between groups with regard to LV-DD and RV-DD, there are many studies showing significant difference between parameters of LV-DD and RV-DD in asthmatic patients in comparison to healthy individuals (3,11,20-21). It was found that tricuspid E velocity, E/A ratio and IVRT in moderate and severe cases differed significantly from mild cases and control subjects and e', a', e'/a' ratio also e' velocity and IVRT of the lateral tricuspid annulus and IVRT of the medial and lateral mitral annuli were also different between mild cases and moderate to severe cases in these studies. TAPSE and MAPSE are other examinations of CEI. In a cohort study, a TAPSE of less than 18 mm

Table 4. Distribution of findings of CEI and TDI echocardiography among groups

Variables	Count	Group- 1 and 2 n= 46 (51.6%)	Group- 3 n= 43 (48.4%)	Total n= 89 (100%)	p¥, β
LV- Dd (mm)	Mean ± std	42.28 ± 5.34	44.86 ± 5.76	43.53 ± 5.66 (min= 29; max= 58)	0.031*
LV- Sd (mm)	Mean ± std	27.13 ± 6.99	28.23 ± 5.61	27.66 ± 6.35 (min= 16; max= 48)	0.416
EFT (mm)	Mean ± std	3.42 ± 1.72	4.05 ± 2.27	3.73 ± 2.03 (min= 0.6; max= 12.7)	0.197
Pu- S′ (cm/s)	Mean ± std	16.3 ± 6.49	16.94 ± 5.76	16.62 ± 6.11 (min= 6.7; max: 36.7)	0.633
Pu- 1 (s)	Mean ± std	0.08 ± 0.04	0.08 ± 0.02	0.08 ± 0,03 (min= 0.04; max= 0.26)	0.344
Pu-2 (s)	Mean ± std	0.27 ± 0.05	0.26 ± 0.07	0.27 ± 0.06 (min= 0.07; max= 0.44)	0.334
Pu-3 (s)	Mean ± std	0.08 ± 0.04	0.09 ± 0.1	0.09 ± 0.08 (min= 0.01; max= 0.07)	0.454
Ao-1 (s)	Mean ± std	0.1 ± 0.11	0.08 ± 0.02	0.09 ± 0.08 (min= 0.05; max= 0.23)	0.792
Ao-2 (s)	Mean ± std	0.25 ± 0.06	0.25 ± 0.06	0.25 ± 0.06 (min= 0.02; max= 0.36)	0.751
Ao-3 (s)	Mean ± std	0.08 ± 0.03	0.08 ± 0.02	0.08 ± 0.02 (min= 0.04; max= 0.19)	0.999
MAPSE (mm)	Mean ± std	16.24 ± 3.27	15.86 ± 2.95	16.06 ± 3.11 (min= 8.7; max= 24.8)	0.592
TAPSE (mm)	Mean ± std	21.88 ± 4.23	22.68 ± 4.78	22.26 ± 4.48 (min= 11.7; max= 36.9)	0.592
Mitral- E velocity (cm/s)	Mean ± std	98.08 ± 20.76	96.98 ± 15.74	97.54 ± 18.38 (min= 64; max= 154)	0.784
Mitral- A velocity (cm/s)	Mean ± std	70 ± 15.43	77.56 ± 18.02	73.69 ± 17.07 (min= 42; max= 128)	0.042*
Mitral- DT (ms)	Mean ± std	209.21 ± 51.77	205.22 ± 59.37	207.24 ± 55.35 (min= 144; max= 372)	0.745
EPm-1 (s)	Mean ± std	0.2 ± 0.08	0.19 ± 0.1	0.19 ± 0.09 (min= 0.06; max= 0.47)	0.549
PAm- 2 (s)	Mean ± std	0.07 ± 0.04	0.08 ± 0.04	0.08 ± 0.04 (min= 0.01; max= 0.29)	0.632
PAm-3 (s)	Mean ± std	0.11 ± 0.05	0.12 ± 0.05	0.11 ± 0.05 (min= 0.01; max= 0.3)	0.664
Tricuspid-E velocity (cm/s)	Mean ± std	72.79 ± 12.18	73.09 ± 16.01	72.96 ± 14.28 (min= 46; max= 104)	0.999
Tricuspid-A velocity (cm/s)	Mean ± std	54.62 ± 9.31	55.73 ± 13.15	55.25 ± 11.51 (min= 30; max: 79)	0.798
Tricuspid- DT (ms)	Mean ± std	186.35 ± 47.16	181.05 ± 57.11	183.36 ± 52.4 (min= 117; max= 306)	0.484

Table 4. Distribution of findings of CEI and TDI echocardiography among groups (continue)

Variables	Count	Group- 1 and 2 n= 46 (51.6%)	Group- 3 n= 43 (48.4%)	Total n= 89 (100%)	p¥, β
Tricuspid- DT (ms)	Mean ± std	186.35 ± 47.16	181.05 ± 57.11	183.36 ± 52.4 (min= 117; max= 306)	0.484
EPt-1 (s)	Mean ± std	0.19 ± 0.07	0.18 ± 0.09	0.18 ± 0.08 (min= 0.04; max= 0.41)	0.549
PAt-2 (s)	Mean ± std	0.07 ± 0.05	0.07 ± 0.03	0.07 ± 0.05 (min= 0.01; max= 0.33)	0.406
PAt-3 (s)	Mean ± std	0.11 ± 0.04	0.11 ± 0.03	0.11 ± 0.04 (min= 0.01; max= 0.27)	0.621

LV- Dd: Left ventricular end-diastolic diameter, LV- Sd: Left ventricular end-systolic diameter, EFT: Epicardial fat thickness, Pu- S': Pulmonary annular systolic velocity, Pu- 1: The time interval from onset of the QRS wave on the ECG to the beginning of the pulmonary systolic flow wave, Pu- 2: The time interval from the onset of the pulmonary systolic velocity wave to the end of pulmonary systolic wave (right ventricular systolic period), Pu- 3: Time interval from end of the pulmonary systolic wave(closing the pulmonary valve) to the beginning of the tricuspid early (E) diastolic flow velocity wave (opening the tricuspid valve, isovolumetric relaxation time [IVRT]), Ao- 1: The time interval from the onset of the QRS wave on the ECG to the beginning of the aortic systolic ejection wave or pre-LV ejection period or pre-aortic valve opening time (Pre-ejection period), Ao-2: The time interval from the onset of the LV ejection period to the end of LV ejection period (Total LV ejection time), Ao-3: The time interval from end of the LV ejection period (closing the aortic valve) to the beginning of the mitral early (E) diastolic flow velocity wave (opening the mitral valve, isovolumetric relaxation time [IVRT]), MAPSE: Mitral annular plane systolic excursion, TAPSE: Ticuspid annular plane systolic excursion, Mitral- E velocity: Mitral early peak (E) diastolic filling wave velocity, Mitral- A velocity: Mitral late diastolic (A) wave velocity, Mitral- DT: Deceleration time of E wave, EPm-1: The time interval from the onset of the early diastolic flow velocity (E) wave on echocardiography to the beginning of the P wave on the ECG, PAm- 2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity (A) wave, PAm- 3: The time interval from the onset of the late diastolic flow velocity (A) wave to the end of the late diastolic flow velocity (A) wave, Tricuspid- E velocity: Tricuspid early peak (E) diastolic filling velocity, Tricuspid- A velocity: Tricuspid late diastolic (A) wave velocity, Tricuspid- DT: Deceleration time of E wave, EPt- 1: The time interval from the onset of the early diastolic flow velocity wave (E) on echocardiography to the beginning of the P wave on the ECG, PAt- 2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity (A) wave, PAt- 3: The time interval from the onset of the late diastolic flow velocity (A) wave to the end of the late diastolic flow velocity (A) wave, std:standards deviation, mm: millimeter, cm/s: centimeter/second, s: second, ms: millisecond, min: minimum, max: maximum, ¥: Independent-Samples T test, β: Mann-Whitney U test.

(millimeter) has been associated with greater RV systolic dysfunction (% area change, 24% vs. 33%) (19). As cut-off level of MAPSE, it was determined as >12 mm according to a previous report. MAPSE> 12 mm was found to be correlated with RA dyssynchrony (p< 0.0001) (25). Mean MAPSE and TAPSE levels were higher than previously determined cut-off level in our study (22). Also, t-S' was not different among groups (p> 0.05). Investigation of time intervals of both of e' and a' from the mitral lateral, septal and tricuspid lateral annulus showed significantly differences at Pa'm-3 and Pa's-3 intervals between groups on TDEI. It means only intervals of intra-LA diastolic functions were found to be more affected in severe asthmatic group (p= 0.027; p= 0.033; respectively). So, total LA late kicking time was found to be different between groups. Along with these results, investigation of the LA volumes revealed only LA-Vmax was higher in severe asthmatic group (p= 0.035). Additionally, as a novel parameter, EMCD revealed that parameters would be identified as indicator of arrhythmias and other cardiac disease like systolic and diastolic HF, PAF (4-7). Diastolic dysfunction is generally caused by increased of LV filling pressure which may causes atrial fibrosis. Ultimately this is a contributing factor to lead lengthening of atrial activation time and changes atrial volumes or functions w/out increased atria dimensions. Finally, this pathological process may cause deterioration of atrial electrical activity. This electrical disruption can cause intra or inter-atrial EMCD or dyssynchrony (7). It has been reported that this kind of electrocardiographic abnormalities are not rare in asthmatic patients (23). In a study, intra-atrial and inter-atrial dyssynchrony has been found to be significant predictor of mortality (p= 0.025, p= 0.017; respectively) (23-25). However, this atrial EMCD calculation pronounced only late diastolic interval or evaluated late atrial contractile force in the literature (23-25). However, it has been known that both atriums have three functional phases including a reservoir, conduit, and active contractile function (24). In another similar study, it has been determined that structural and functional changes of the LA were related to various cardiovascular diseas-

Table 5. Distribution of other findings of CEI and TDI echocardiography among the groups

Variables	Count	Group 1 and 2 n= 46 (51.6%)	Group- 3 n= 43 (48.4%)	Total n= 89 (100%)	p¥, β
Mitral-e'- velocity (cm/s)	Mean ± std	86.68 ± 32.54	86.03 ± 26.04	86.36 ± 29.41 (min: 19.3; max: 159)	0.920
Mitral-a'- velocity (cm/s)	Mean ± std	60.63 ± 22.26	64.14 ± 21.73	62.32 ± 21.94 (min= 9.8; max= 128)	0.464
Mitral- dt' (ms)	Mean ± std	86.92 ± 22.03	87.77 ± 24.01	86.98 ± 31.23 (min: 24; max: 157)	0.895
e'Pm-1 (s)	Mean ± std	0.19 ± 0.11	0.18 ± 0.09	0.19 ± 0.1 (min= 0.03; max: 0.44)	0.809
Pa'm-2 (s)	Mean ± std	0.05 ± 0.01	0.06 ± 0.03	0.06 ± 0.02 (min= 0.03; max= 0,13)	0.292
Pa'm-3 (s)	Mean ± std	0.11 ± 0.02	0.1 ± 0.02	0.1 ± 0.02 (min= 0.03; max= 0.16)	0.027*
e'Ps-1 (s)	Mean ± std	0.17 ± 0.08	0.17 ± 0.11	0.17 ± 0.09 (min= 0.03; max= 0.37)	0.787
Pa's-2 (s)	Mean ± std	0.05 ± 0.02	0.06 ± 0.03	0.05 ± 0.02 (min= 0.01; max= 0.12)	0.524
Pa's-3 (s)	Mean ± std	0.12 ± 0.01	0.1 ± 0.02	0.11 ± 0.02 (min= 0.05; max: 0.13)	0.033*
e'Pt-1 (s)	Mean ± std	0.19 ± 0.08	0.18 ± 0.08	0.18 ± 0.08 (min= 0.05; max= 0.4)	0.894
Pa't-2 (s)	Mean ± std	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.02 (min= 0.01; max= 0.09)	0.211
Pa't-3 (s)	Mean ± std	0.14 ± 0.02	0.12 ± 0.03	0.13 ± 0.02 (min= 0.06; max= 0.16)	0.164
t-S'- velocity (cm/s)	Mean ± std	17.42 ± 5.7	18.82 ± 4.77	18.07 ± 5.29 (min= 2.6; max= 31.7)	0.264
LA Vmax (mm^3)	Mean ± std	12.49 ± 3.64	14.59 ± 5.37	13.49 ± 4.64 (min= 6.7; max= 27.4)	0.035*
LA VpreA (mm^3)	Mean ± std	9.84 ± 5.96	10.9 ± 4.49	10.35 ± 5.3 (min= 4.7; max= 44)	0.107
LA Vmin (mm^3)	Mean ± std	8.25 ± 6.89	8.46 ± 3.46	8.35 ± 5.54 (min= 2.4; max= 50)	0.228

Mitral-e'- velocity: TDI echocardiographic mitral lateral annulus diastolic peak early (e') filling wave velocity, mitral-a'- velocity: TDI echocardiographic mitral lateral annulus diastolic late (a') velocity, mitral- dt': TDI echocardiographic mitral lateral annulus deceleration time of e' wave, e'Pm-1: The time interval from the onset of the early diastolic flow velocity wave (e') on TDI echocardiography to the beginning of the P wave on the ECG, Pa'm-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity wave (a') wave on TDI echocardiography, Pa'm-3: The time interval from the onset of the late diastolic flow velocity wave (a') wave to the end of the late diastolic flow velocity (a') wave on TDI echocardiography, e'Ps-1: the time interval from the onset of the early diastolic flow velocity wave (e') on TDI echocardiography to the beginning of the P wave on the ECG, Pa's-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity wave (a') wave on TDI echocardiography, Pa's- 3: The time interval from the onset of the late diastolic flow velocity wave (a') wave to the end of the late diastolic flow velocity (a') wave on TDI echocardiography, e'Pt- 1: The time interval from the onset of the early diastolic flow velocity wave (e') on TDI echocardiography to the beginning of the P wave on the ECG, Pa't-2: The time interval from the onset of the P wave on the ECG to the beginning of the late diastolic flow velocity wave (a') wave on TDI echocardiography, Pa't-3: The time interval from the onset of the late diastolic flow velocity wave (a') wave to the end of the late diastolic flow velocity (a') wave on TDI echocardiography, t-S'- velocity: TDI echocardiographic tricuspid lateral annulus systolic velocity, LA Vmax: End-systolic volume was measured just before the opening of the mitral valve, LA VpreA: Pre-atrial contraction volume was measured at the onset of the P wave,on the ECG, LA Vmin: end-diastolic volume was measured at the closure of the mitral valve, std:standard deviation, cm/s: centimeter/second, s: second, ms: millisecond, ml: milliliter, min: minimum, max: maximum, ¥: Independent-Samples T test, β: Mann-Whitney U test.

es such as stroke and T2DM (Type-2 diabetes mellitus) (26-28). In the literature, it has been shown that LA diameter and LA-Vmax index, IVRT and mitral-A velocity were found to be higher in T2DM patients (23). The LA functional indexes were proposed to be more sensitive risk indicators for cardiovascular dis-

Table 6. Comparison between mild-moderate and severe asthma groups

	AUC	%95 CI		p
Mitral-A velocity	0.558	0.435	0.682	0.359
Pa'm-3	0.507	0.298	0.716	0.950
Pa's-3	0.409	0.187	0.630	0.405
LA-Vmax ROC curve	0.590	0.467	0.713	0.151

AUC: Area under the curve, CI: Confidence interval, ROC: Receiver operating characteristic. AUC values of Mitral-A velocity, LA-Vmax, Pa'm-3, Pa's-3. Mitral- A velocity: Mitral late diastolic (A) wave velocity, LA Vmax: End-systolic volume was measured just before the opening of the mitral valve, Pa'm-3: The time interval from the onset of the late diastolic flow velocity wave (a') wave to the end of the late diastolic flow velocity (a') wave on TDI echocardiography.

eases (26). However, it is now unclear whether these indexes could be a sensitive risk indicator for asthma severity or not. Therefore, we evaluated all intervals or electrical activities of atrial tissue and atrial functions in detail. We also assessed the EMCD of total intervals for both atrial waves on CEI. But we found that there was no significant difference between groups (p= 0.042). Interestingly, only LA kicking functional intervals (at mitral lateral and interatrial septal wall annulus, p= 0.027; p= 0.033, respectively) were found to be different between groups based on TDEI study. Also, EMCD for the interventricular systolic outflow velocities at aortic and pulmonary valves were also not different between groups (p> 0.05 for all) on CDEI study. So, total LA late kicking time was found to be different between groups. Finally, to find best cut-off level for mitral-A velocity, LA-Vmax, Pa'm-3, Pa's-3, ROC analysis did not reach the significance level (p> 0.05).

Limitation of the Study

The study was conducted in a relatively small hospital. This may have caused some bias on patient selection and therefore, it might not represent for the entire spectrum for asthmatic patients. The patients with acute asthma attack which may give more detailed information about RV, LV functions and atriums EMCD were not involved in the study. Since the design of the study was cross-sectional, patients could not be followed up for long-term cardiac arrhythmia. The other limitation of our study was that conduction times were determined with TDIE manually, and the gold standard technique, electrophysiological study or computer-assisted calculating system, was not performed. Lastly, in order to support our hypothesis, there is a need for studies including a large number of subjects and long-term follow-up.

CONCLUSION

This study showed that the LA mechanical functions, and intra-atrial LA electromechanical durations were impaired in severe asthmatic patients. These results may suggest that asthma may lead to atrial electrical remodeling and prospective risk assessment of asthma via functions and EMCD features of LA. Large-scale and long-term follow-up prospective studies are required to establish the predictive value of atrial conduction parameters for the future development of cardiac outcomes in patients with asthma. Additionally, central or visceral obesity screening measurements (WC, NC, MUA) may be considered to use for prospective clinical follow-up in patients with asthma.

Learning Points

Left atrium mechanical functions, and intra-atrial LA electromechanical durations were impaired in severe asthmatic patients.

Ethical Committee Approval: This study approval was obtained from Kırşehir Ahi Evran University Clinical Researches Ethical Commitee (Decision no: 2019-02/17 Date: 29.01.2019).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: DZ, YB

Analysis/Interpretation: DZ, YB

Data acqusition: DZ, YB

Writing: DZ, YB

Clinical Revision: All of authors

Final Approval: All of authors

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