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 a 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 ranges1. 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 be occured1-3. 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). The atrial 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 TDIE4,8. 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 fraction2. 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 ECG9. The QT interval is another measurement method for depolarization-repolarization dispersion of myocardial tissue. The 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, the Tp-Te value was found to be generally more than 100 milliseconds (ms)10. Based on these 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 severeity of asthma and cardiovascular functions11.

Materials and methods

Study population

This cross-sectional study consisted of 89 patients (63 female [%70,8] and 26 male [%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 Ethics Committee at Kirsehir Ahi Evran University (No: 2019-02-17, date: 29-01-2019) and the informed consent was obtained from each patient.

Inclusion criteria: Patients between 18 and 40 years old 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 patients12. We categorized patients into three groups based on asthma severity in accordance with the GINA 2016 guidelines as mild, moderate, and severe asthma12.

Exclusion criteria: Exclusion criteria was 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 4 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), waist, neck, chest and mid-upper arm circumference (WC, NC, CC and MUAC, respectively) were recorded. We compared these variables for three groups. WC (centimeter [cm]) was horizontally measured at midpoint between the costal margin and iliac crest. The NC (cm) was measured in a horizontal plane as possible at a point just below the larynx (thyroid cartilage) and perpendicular to the long axis of the neck13. MUAC (cm) values were measured on the upper left arm (halfway between the acromion and the olecranon process)14. CC values were obtained as nipple chest circumference15.

Pulmonary function test: Pulmonary function tests were performed according to the American Thoracic Society Guide¬lines by a single physician using a spirometer (SensorMed¬ics Vmax spectra 229; Bilthoven, The Netherlands) to deter¬mine forced expiratory volume in one second (FEV1), forced vital capacity (FVC) in estimated percentage for both and FEV1/FVC ratio12. The Asthma Control Test (ACT®) and Childhood Asthma Control Test (C-ACT®) were used to assess asthma examination. Based on the American Thoracic Society Guide¬lines, 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 control16.

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 interval10.

Echocardiography: We used Vivid 5 pro echocardiographic unit (GE Healthcare, GE, USA) including 3,5 MHz probe for echocardiographic assessment. All test sub¬jects were evaluated by a standard two-dimensional and Doppler evaluation according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging by a single experienced cardiologist who was blinded to the test subjects and all clinical findings12. 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 vis¬ceral stratum of the pericardium12. 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 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 was 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 patients5,17.

Another investigation time intervals to find differences of EMCD of where were obtained from both atrium and ventricule were listed below. 1: The time intervals of diastolic filling velocities where 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 (Figure-2): 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 the late diastolic flow velocity (a') wave. 3: The time intervals of ventricular outflow systolic velocity recordings where 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 by one operator who was blind¬ed to subjects at twice 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 were shown in Table 1. The baseline characteristics of the groups were shown in Table 2. The ECG results were summarized in Table 3 and echocardiographic results were listed in Table 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 is no significant difference among the groups with respect to age, gender and anthropometric data (P> 0,05) and no difference was detected between groups with regard to indices of TDR in ECG results (P> 0,05) (Table 3). Results of CEI and TDIE parameters were 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 groups (3,42±1,72 vs. 4,05±2,27, P: 0,197). All time intervals obtained from both of ventricular outflow systolic velocity recordings at the just proximal to the aortic and pulmonary valve were found to be similar (P> 0,05). MAPSE 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 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 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 significantly difference between 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 were reflecting 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).

Discussions

Anthropological data and asthma: Asthma is a chronic recurrent disease which can cause pulmonary hypertension. At the same time, it has been known that obesity is able to increase incidence and severity of asthma. It is believed that the suggested mechanisms of this relationship is primarily systemic inflammation and hormonal dysregulation like higher Leptin levels and other mediators like interleukins (IL-6, IL-17, IL-4, IL-13 and IL-8) which have been found to play role in occurrence of asthma18. Therefore, patients involved in this study were mainly overweight asthmatic patients (mean BMI: 26,56±5,33) and the mean BMI were similar in groups and there was not differences between groups (P: 0,540). Other indicators of obesity or distribution of adipose tissue like visceral obesity are WC, NC, MUAC and CC. It has been found that higher WC (≥ 100 cm for male, ≥ 95 for female) was significantly related to the incidence of asthma in both sexes (Hazard Ratio (HR) for male: 1.34, 95% CI: 1,16–1,57 and HR for female: 1.19, 95% CI: 1,03–1,37) 13,19-21. When it was compared our patients' mean WC and NC levels with previously determined cut-off levels (cut-off values for WC: 84,25±1,76 cm and 80,75±4,71 cm and cut-off values for NC: 35,75±0,49 cm and 32,21±0,97 cm in males and females, respectively), it was determined that there was no significant difference between groups for WC and NC levels (P: 0,202 and 0,054; respectively)13 (Table-2). MUAC which has been widely used for the screening central obesity is a novel anthropometric measurement. It has been suggested that low MUAC value (<23,5 cm) could help to predict mortality risk in patients with chronic obstructive pulmonary disease (COPD) (HR: 3,09; 95% CI: 1,30–7,38) 24 22. In this study, our mean MUAC level (27,39±3,53 cm) was higher than the threshold value of MUAC according to the previous report22. Another rarely used indicator to determine the distribution of adipose tissue is CC15. Up to now, the relationship between asthma severity and CC has never been investigated. It is the first time, we investigated this relationship and found that there was no significant difference between groups (P: 0,897). So, this is the first study showing the comparision of WC, MUAC and CC levels in different severity of adult asthmatic groups.

ECG results for Asthma Patients: The pathogenesis of cardiac arrhythmias in asthma patients has not been fully explained. Adverss effects of B2-mimetics may play a role in this pathogenesis, however we know that VA and SCD risks may not be increased in asthmatic patients23-24. In a cross-sectional study performed with 158 asthma patients, it has been shown that tachycardia and premature ventricular contractions (PVC) were more prevalent in asthma patients (P<0,001, P= 0,03, respectively). In that study, it has been found that the

prevalence of QTc interval prolongation was similar between groups. They found that tachycardia and PVCs were more common in patients treated with B2-mimetics25. In another study, it has been shown that the risk for developing atrial fibrillation (AF) was increased with asthma comparing to control group23. On the surface ECG, Tp-Te interval has been considered of a measure of TDR and prolongation of Tp-Te, QTc interval and Tp-Te/QT ratio have been found of risk factors to develop cardiac arrhythmia and SCD in various cardiac disease as well as normal healthy individuals10. In groups of patients with increased risk of VA, the Tp-Te was often more than 100 ms in various clinical scenarios10. In our study, it was determined that there is no significant difference between mild/modarete 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 groups (74,98±15,72 ms vs. 76,71±15,44 ms; P: 0,610).

Echocardiographic parameters of patients: RV-DD is important determinant of prognosis in long-stage asthmatic patients due to the risk of progression to the PHT. There is an interaction between the RV dysfunction and LV functions which is related to increased LV afterload and decreased LV preload, and thus LV dysfunction26. CEI and TDIE parameters were given in Table 4. LV-DD and RV-DD were indifferent between groups, except for LV late diastolic A wave velocity which was higher in the severe asthmatic group in that 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 didn't 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 3,11,27-28. 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 another examinations of CEI. In a cohort study, a TAPSE of less than 18 mm (millimeter) was associated with greater RV systolic dysfunction (% area change, 24% vs. 33%)26. 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)29. Mean MAPSE and TAPSE levels were higher than previously determined cut-off level in our study29. 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 that 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, PAF4-7. 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 dyssynchrony7. It was reported that this kind of electrocardiographic abnormalities are not rare in asthmatic patients30. In a study, intra-atrial and inter-atrial dysynchrony were found to be significant predictor of mortality (P: 0,025, P: 0,017; respectively)30-32. However, this atrial EMCD calculation pronounced only late diastolic interval or evaluated late atrial contractile force in the literature30-32. However, it has been known that both atriums have three functional phases including a reservoir, conduit, and active contractile function31. In another similar study, it was determined that structural and functional changes of the LA were related to various cardiovascular diseases such as stroke and T2DM (Type-2 Diabetes Mellitus) 33-35. In the literature, it was shown that LA diameter and LA-Vmax index, IVRT and mitral-A velocity were found to be higher in T2DM patients34. The LA functional indexes were proposed to be more sensitive risk indicators for cardiovascular diseases33. However, it is now unclear that these indexes could be a sensitive risk indicator for asthma severity or not? Therefore, we evaluated all intervals or elec¬trical activities of atrial tissue and atrial functions detailedly. 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 reached the significance level (P> 0,05).

Limitation of the study: The study was conducted in a relatively small hospital. This may has 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 by 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

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

Abbrevations: RV: Right ventricular, PV: Pulmonary vasoconstriction, PHT: Pulmonary hypertension, TDIE: Tissue doppler imaging echocardiography, CEI: Conventional Echocardiographic Imaging, LV-DD: Left ventricular diastolic dysfunction, LV-SD: Left ventricular systolic dysfunction, RV-DD: Right ventricular diastolic dysfunction, LA: Left atrium, EMCD: Eletromechanical conduction delay, HF: Heart failure, PAF: Paroxysmal atrial fibrillation, ECG: Electrocardiography, TAPSE: Tricuspid annular alane systolic

excursion, **MAPSE:** Mitral annular plane systolic excursion, TDR: Transmural dispersion of repolarization, VA: Ventricular arrhythmia, SCD: Sudden cardiac death, BMI: Body-Mass index, WC: Waist circumference, NC: Neck circumference, MUAC: Mid-Upper arm circumference, CC: Chest circumference, FEV1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, ACT: Asthma control test, QT: Time interval from the onset of the QRS complex to the end of the T wave, QTc: Heart rated corrected form of QT interval, Tp-Te: Time interval from T wave peak point to end point, LV-Dd: Left Ventricular end diastolic dimension, LV-Sd: Left Ventricular end systolic dimension, LVEF: Left ventricular ejection fraction, PVC: Prematüre ventricular contractions, AF: Atrial fibrillation, E: Early peak diastolic wave on CEI, A: Late diastolic wave on CEI, DT: Deceleration time, IVRT: Isovolumetric relaxation time, e': Early peak diastolic wave on TDIE, a': Late diastolic wave on TDEI, EFT: Epicardial fat thickness, t-S': Systolic velocity of tricuspid lateral annulus on TDEI, Pu-S': Pulmonary annular systolic velocity on TDEI, LA-Vmax: The maximal volume of left atrium, LA-VpreA: Pre-atrial contraction left atrial volume, LA-Vmin: Minimal left atrial volume, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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 openning 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 (clossing the aortic valve) to the beginning of the mitral early (E) diastolic flow velocity wave (openning the mitral valve, isovolumetric relaxation time [IVRT]), 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 (clossing the pulmonary valve) to the beginning of the tricuspid early (E) diastolic flow velocity wave (openning the tricuspid valve, [IVRT]), IL: Interleukin, COPD: Chronic Obstructive Pulmonary Disease.

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Tables

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

Table 1	**Individual distribution of groups**	
Groups	**Count**	**Total n: 89 (100%)**
Group- 1 (Mild Asthma)	**(count & percent in total)**	**n: 4 (4,5%)**
Group- 2 (Intermediate Asthma)	**(count & percent in total)**	**n: 42 (47,2%)**
Group- 3 (Severe Asthma)	**(count & percen in total)**	**n: 43 (48,3%)**

Table 2: Distribution of baseline demographic and anthropometric features of groups.

Table 2	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
Left Arm Circumference (cm)	Mean ± std	27,09 ± 3,28	27,7 ± 3,78	27,39 ± 3,53 (min: 19; max: 35)	0,422
Neck Circumference (cm)	Mean ± std	34,62 ± 3,39	36,14 ± 3,89	35,36 ± 3,7 (min: 25; max: 44)	0,054
Waist Circumference (cm)	Mean ± std	87,38 ± 13,59	91,28 ± 14,85	89,28 ± 14,27 (min: 55; max: 139)	0,202
Chest Circumference (cm)	Mean ± std	91,51 ± 8,5	91,23 ± 11,43	91,38 ± 9,98 (min: 53; max: 120)	0,897
Gender					
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 amoung groups.

Table 3	Distribution of ECG findings amoung 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:standart 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.

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

Table 4	Distribution of other findings of CEI and TDI echocardiography amoung 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
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(clossing the pulmonary valve) to the beginning of the tricuspid early (E) diastolic flow velocity wave (openning 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 openning 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 (clossing the aortic valve) to the beginning of the mitral early (E) diastolic flow velocity wave (openning 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:standart deviation, mm:millimeter, cm/s: centimeter/ second, s: second, ms: millisecond, min: minimum, max: maximum, ¥: Independent-Samples T test, β: Mann- Whitney-U test.

Table 5: Distribution of other findings of CEI and TDI echocardiography amoung groups.

Table 5	Distribution of other findings of CEI and TDI echocardiography amoung 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

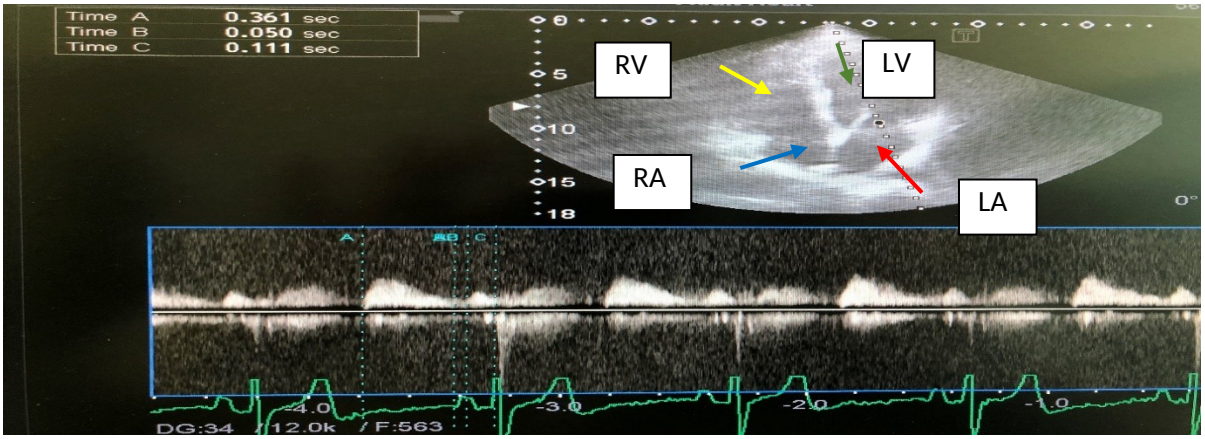
Mitral-e'- velocity: TDI echocardiographic mitral lateral annulus diastolic peak early (e') filling wave velocity, mitral-a'- velocity: TDI echocardiographic mitral lateral annulus diastolic late (a') velocity, mitral- dt': TDI echocardiographic mitral lateral annulus deceleration time of e' wave, *e'Pm- 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:standart deviation, cm/s: centimeter/second, s: second, ms: millisecond, ml: milliliter, min: minimum, max: maximum, ¥: Independent-Samples T test, β: Mann-Whitney-U test.

Tablo 6: Compared 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

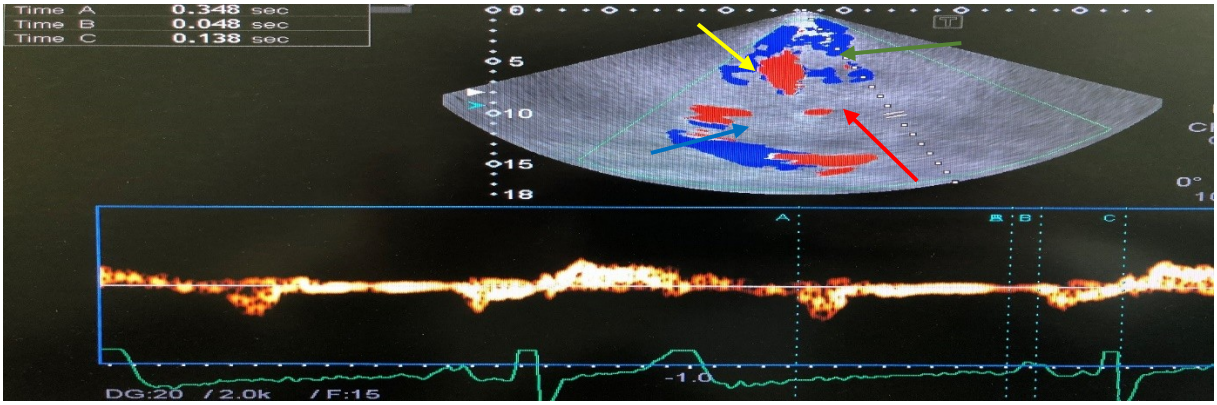
Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic. AUC values of Mitral-A velocity, LA-Vmax, Pa'm- 3, Pa's- 3.

Figure 1: The time intervals of diastolic filling velocities where were obtained from the tips of mitral leaflets by CEI.



Green Arrow: Left ventricule (LV), red arrow: left atrium (LA), blue arrow: right atrium (RA), yellow arrow: right ventricule (RV).

Figure 2: The time intervals of TDIE diastolic velocities where were obtained from the mitral lateral wall annulus.



Green Arrow: Left ventricule, red arrow: left atrium, blue arrow: right atrium, yellow arrow: right ventricule.