ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Cardiac Mechanics in Asthmatic Female Patients During Exacerbation and After Stabilization: A Speckle-tracking Echocardiography Study

Astımlı Kadın Hastalarda Alevlenme Sırasında ve Stabilizasyon Sonrası Kalp Mekaniğinin Değerlendirilmesi; Speckle-tracking Ekokardiyografi Çalışması

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ABSTRACT

Aim: *There is a complex relationship between asthma and cardiac functions. According to speckle-tracking echocardiography studies, asthma, especially severe asthma, was associated with left and right ventricular subclinical dysfunction. The literature lacks data comparing the cardiac functions during exacerbations and stable periods in patients with asthma. In this study, we aimed to investigate cardiac functions using speckle-tracking echocardiography during exacerbations and in the stable phase in female patients with asthma.*

Material and method: *A total of 51 female adult asthma patients who were admitted to our center due to asthma exacerbations were included in this study. All participants had a previous diagnosis of asthma. Transthoracic echocardiography was performed both during hospitalization and after the asthma exacerbation was stabilized. Echocardiographic findings, including left ventricular longitudinal strain, in the two periods were compared. All patients were discharged in good condition after their asthma attacks stabilized.*

Results: *White blood cell count (WBC) and C-reactive protein (CRP) levels were significantly higher during exacerbation than in the stable phase. Regarding echocardiographical findings, isovolumetric contraction time (IVCT) was significantly longer and left ventricular global longitudinal strain (LVGLS) was significantly lower during exacerbation compared to the stable phase [median (IQR), 70 (61–76) msec vs. 66 (57–72) msec, p=0.011 and -12.9 (-13.8 – -12.1) vs. -14.2 (-14.8 – -13.2), p<0.001, respectively]. According to the multivariate analysis, IVCT, LVGLS, and WBC were independently associated with asthma exacerbation.*

Conclusion: *Our study showed that asthma exacerbations might have an oppressive and adverse impact on cardiac functions, particularly when analyzed by STE.*

Keywords: asthma; *asthma exacerbation; heart function; left ventricular longitudinal strain*

ÖZET

Amaç: *Astım ve kardiyak fonksiyonlar arasında karmaşık bir ilişki vardır. Yapılan speckle-tracking ekokardiyografy araştırmalarına göre, astım, özellikle şiddetli astım, sol ve sağ ventrikül subklinik disfonksiyonu ile bağlantılı olduğu tespit edilmişitir. Astımlı hastalarda alevlenme ve stabil dönemlerde kardiyak fonksiyonları karşılaştıran bir çalışma yoktur. Bu çalışmada, astımlı kadın hastalarda alevlenme sırasında ve stabil fazda speckle-tracking ekokardiyografi ile kardiyak fonksiyonları araştırmayı amaçladık.*

Materyal ve Metot: *Astım alevlenmesi nedeniyle ardışık olarak merkezimize yatırılan toplam 51 kadın yetişkin astım hastası bu çalışmaya dâhil edildi. Tüm katılımcılarda daha önce astım tanısı mevcut idi. Hastalara hem hastaneye yatış sırasında hem de astım atağı stabilize edildikten sonra transtorasik ekokardiyografi çekildi. Bu iki ekokardiyografik bulgular karşılaştırıldı. Tüm hastalar astım atağı stabil olduktan sonra iyi hal ile taburcu edildi.*

Bulgular: *Alevlenme sırasında beyaz kan hücresi sayımı (WBC) ve C-reaktif protein (CRP) seviyeleri stabil faza göre anlamlı derecede yüksekti. Ekokardiyografik bulgulara bakıldığında, stabil faza göre alevlenme sırasında izovolümetrik kontraksiyon süresinin (IVCT) anlamlı derecede uzun olduğu ve sol ventriküler global longitudinal strain'in (LVGLS) anlamlı derecede düşük olduğu görüldü.[medyan (IQR), sırasıyla, 70 (61–76) msn'ye karşılık 66 (57–72) msn, p=0,011 ve -12,9 (-13,8 – -12,1) vs. -14,2 (-14,8 – -13,2), p<0,001]. Çok değişkenli analize göre IVCT, LVGLS ve WBC bağımsız olarak astım alevlenmesiyle ilişkiliydi.*

Sonuç: *Çalışmamız astım alevlenmesinin özellikle speckle-tracking ekokardiyografi ile analiz edildiğinde kalp fonksiyonları üzerinde baskılayıcı ve olumsuz bir etkiye sahip olabileceğini gösterdi.*

Anahtar kelimeler: *astım; astım atağı; kalp fonksiyonu; sol ventrikül longitudinal strain*

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Introduction

Asthma is one of the most common diseases associated with morbidity and mortality, worldwide[1,2]. Asthma is considered a heterogeneous disease that manifestly differs by gender. While there is a higher preponderance of asthma in male teenagers, rates are higher in adult women compared with men[3].

Although there is plenty of data investigating the relationship and intercourse between chronic obstructive pulmonary disease (COPD) and cardiovascular disease, little is known about the interaction between asthma and cardiovascular disorders[4,5]. Some studies are showing biventricular subclinical dysfunction in asthma patients[5,6]. However, the literature lacks research comparing cardiac functions during exacerbations and stable periods, in patients with asthma. In our study, we aimed to investigate cardiac functions using conventional and speckle-tracking echocardiography (STE) measurements during exacerbation and in the clinically stable phase, in female patients with asthma.

Material and Method

A total of 51 female adult (>18 years) asthma patients hospitalized for asthma exacerbations were included in this observational case-control study between December 2019 and January 2021. All participants had a previous diagnosis of asthma. The admission hemogram and biochemical blood parameters of the patients were analyzed. Transthoracic echocardiography was performed within 12 hours of hospitalization and after the asthma exacerbation was stabilized. The initial (during asthma exacerbation) and follow-up (after clinical stability) echocardiographic findings were compared. All subjects received bronchodilator medications, including budesonide, ipratropium bromide, and salbutamol, as well as prednisolone. Those with heart failure (left ventricular ejection fraction <50), congenital heart disease, moderate or advanced heart valve disease, arrhythmia, renal failure (estimated glomerular filtration rate <60), malignancy, and thyroid dysfunction were excluded from the study.

Standard two-dimensional and Doppler echocardiographic evaluation

Philips HD 11 XE ultrasound machine (Andover, MA, USA) was used for echocardiography measurements. Left ventricle (LV), left atrial (LA), right ventricular (RV), and aortic root dimensions and LV wall thickness were measured according to the American Society of Echocardiography 2015 guideline[7]. Early (E) and late (A) wave velocities were measured from the mitral inflow profile. E/A values were calculated by dividing E to A. Tissue Doppler imaging (TDI) measurements were assessed in the apical four-chamber view. The myocardial systolic (s'), early diastolic (e'), and late diastolic (a') velocities were recorded at the lateral and septal mitral annulus by TDI in 3 consecutive beats. Mitral annular isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) were also calculated. Modified Simpson's rule was utilized to calculate left ventricular ejection fraction (LVEF)[8].

2D-speckle tracking strain echocardiography

Analysis of STE was carried out per the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[9]. Speckle-tracking echocardiography analysis was performed per the Consensus Document of the EACVI/ASE/Industry Task Force to Standardize RV and LV myocardial Deformation Imaging[10]. Qlab13 (Philips Healthcare, Andover, Massachusetts) software was utilized for the calculation of LVGLS. End-diastole was specified as the peak R wave of the electrocardiogram and the end-systole was determined as aortic valve closure. The average of peak global longitudinal strain (GLS) values from apical two-chamber, apical three-chamber, and apical four-chamber images was estimated as left ventricular global longitudinal strain (LVGLS). During the end-systole, endocardial borders were detected automatically. Manually corrected when needed. left ventricular global longitudinal strain (LVGLS) change was expressed as percentages (%). Negative values of LVGLS represent myocardial contractility ability (the less negative value, the worse the LV systolic performance).

Statistical analyses

IBM Statistical Package for Social Sciences (SPSS) program version 20 (IBM Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables were represented as mean ± standard deviation (SD) or median [25–75 interquartile range (IQR)] according to normality and distribution characteristics. Comparisons were carried out using the student's *t*-test, or Mann–Whitney U-test. Categorical variables were shown with numbers and percentages. Categorical variables were compared using the χ^2 test or Fisher's exact test. A multivariate analysis was performed to indicate variables those are independently associated with asthma exacerbations. p-value under 0.05 was considered significant.

Results

The mean age of the patients was 53.33 (standard deviation 12.42). While 6 (11.7%) of the patients were smokers, 12 (23.5) were diagnosed with hypertension and 7 (13.7) were diagnosed with diabetes. The demographics, and laboratory findings of the patients during hospitalization (asthma exacerbation) and follow-up (after clinical stability of asthma exacerbation) are shown in Table 1. Levels of white blood cell count (WBC) and C-reactive protein (CRP) were significantly higher during exacerbation than in the stable phase.[median (IQR), 12.21 (9.22–13.77) vs. 10.41 (7.14–11.67), p=0.002 and 15 (3.03–36) vs. 4.26 (2.4–9.8), p=0.016, respectively]. The initial (during asthma exacerbation) and follow-up (after clinical stability of asthma exacerbation) echocardiographic evaluations of the study population are listed in Table 2. Isovolumetric contraction time was significantly longer during exacerbation than during the stable phase [median (IQR), 70 (61–76) msec vs. 66 (57–72) msec, p=0.011] (Fig. 1a). However, IVRT was similar in both recordings [median (IQR), 65 (60–69) vs. 66 (60–69), p=0.540]. Left ventricular global longitudinal strain by STE was significantly worse during the exacerbation than during the stable phase.[median (IQR), -12.9 (-13.8 – -12.1) vs. -14.2 (-14.8 – -13.2), p <0.001] (Fig. 1b). There was no significant difference in left ventricular end-diastolic, left ventricular end-systolic, septal thickness, posterior wall thickness, left atrial, right ventricular, and right atrial diameters. Left ventricular ejection fraction was similar between the first and second measurements. In addition, diastolic function parameters measured by echocardiography showed statistically similar values. Moreover, there was no significant difference in right ventricular systolic function measured by tricuspid annular plane systolic excursion (TAPSE) and tricuspid

Table 1. *Demographic, clinical, and laboratory characteristics*

	n=51
Age (years), mean ± SD	53.33±12.42
Smoking	6 (11.7)
Hypertension, n (%)	12 (23.5)
Diabetes, n (%)	7 (13.7)
Laboratory findings at admission	
Hgb (g/dL), median [IQR]	14.4 [13.1–15.1]
WBC (× 103/µL), median [IQR]	12.21 [9.22–13.77]
PLT (× 103/µL), median [IQR]	264 [212–325]
Albumin (mg/dL) median [IQR]	44.8 [39.5–46.2]
CRP (mg/L), median [IQR]	5.86 [2.96–12.3]
Creatinine (mg/dL), mean ± SD	0.64±0.14
Lymphocyte (× 103/µL), mean ± SD	2.45±1.01
Neutrophil (× 103/µL), mean ± SD	8.23±2.76

Hgb: hemoglobin; WBC: white blooc count; PLT: platelet; CRP: C-reactive protein

Table 2. *Comparison of echocardiographic characteristics during asthma exacerbation and after clinical stability*

Echocardiography features	During Exacerbation	After Stabilization	
LVDD (mm), mean ± SD	39±0.5	39±0.5	0.916
LVSD (mm), median [IQR]	28 [26–30]	27 [26–31]	0.898
IVS (mm), median [IQR]	9 [8–10]	9 [8.5–10]	0.756
PW (mm), median [IQR]	8 [7.2–8]	8 [7–8]	0.994
LA (mm), median [IQR]	31 [28.5–35]	30 [26.5–35]	0.793
RV (mm), median [IQR]	34 [31–37]	35 [31–37]	0.812
RA (mm), median [IQR]	30 [26–32]	28 [26–32]	0.783
Ejection Fraction (%), mean ± SD	60±6	60±5	0.856
E, mean ± SD	72.6±17.5	71.4±17.2	0.725
A, median [IQR]	80 [70–90]	77 [70–90]	0.234
E/A, median [IQR]	0.87 [0.79–1.13]	0.82 [0.70–1.01]	0.144
e’	8 [7–8.5]	7 [6–9]	0.095
E/e’, mean ± SD	9.25±2.60	10±2.73	0.161
TAPSE, median [IQR]	24 [19–25]	21 [19–25]	0.407
S’, mean ± SD	3.21±5.81	2.96±5.52	0.824
PASB (mmHg), median [IQR]	16.7 [15–18]	17 [15–20]	0.325
IVCT (ms), median [IQR]	70 [61–76]	66 [57–72]	0.011
IVRT (ms), median [IQR]	65 [60–69]	66 [60–69]	0.540
LVGLS, median [IQR]	-12.9 [-13.8 – -12.1]	-14.2 [-14.8 – -13.2]	<0.001

LVDD: left ventricle end-diastolic diameter; LVSD: left ventricle end-systolic diameter; IVS: interventricular septum thickness; PW: left ventricular posterior wall thickness; LA: left atrium diameter; RV: right ventricle diameter; RA: right atrium diameter; E: maximum flow velocity during early LV diastolic filling; A: maximum flow velocity during late diastolic LV filling; e’: mitral annulus systolic velocity; TAPSE: tricuspid annular plane systolic excursion; S’: tricuspid annulus systolic velocity; PASP: pulmonary arterial systolic pressure; IVCT: isovolumetric contraction time; IVRT: isovolumetric relaxation time; LVGLS: left ventricle global longitudinal strain.

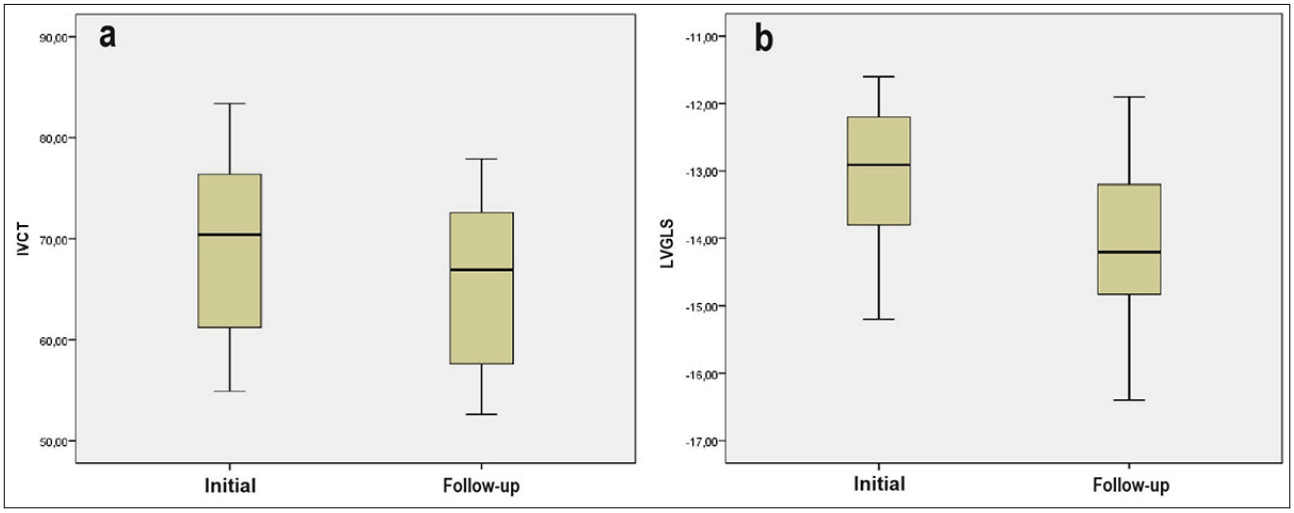

Figure 1. a, b. *Distribution of IVCT* ***(a)*** *and LVGLS* ***(b)*** *during asthma exacerbation (initial) and after stabilization (follow-up)(IVCT, isovolumetric contraction time; LVGLS, left ventricular global longitudinal strain).*

Table 3. *Univariate and multivariate regression analysis*

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
IVCT	0.942 (0.898-988)	**0.013**	0,914 (0.848-0.986)	**0.019**
LVGLS	0.358 (0.226-0.568)	**<0.001**	0,194 (0.087-0.428)	<0.001
CRP	1.016 (1.001-1.031)	**0.042**	1,005 (0.984-1.026)	**0.634**
WBC	1.324 (1.111-1.577)	**0.002**	1,450 (1.144-1.839)	**0.002**

CI, confidence interval; CRP, C-reactive protein; IVCT, isovolumic contraction time; LVGLS, left ventricular global longitudinal strain; OR, odds ratio; WBC, white blood count

annular systolic velocity (S') between the initial and follow-up recordings [median (IQR), 24 (19–25) vs. 21 (19–25), p=0.407 and (avarage ± SD), 3.21±5.81 vs. 2.96±5.52, p=0.824, respectively]. Pulmonary artery systolic pressure (PASB) measured from tricuspid valve regurgitation was also similar between initial and follow-up recordings [median (IQR), 16.7 (15–18) vs. 17 (15–20), p=0.325]. According to the multivariate analysis, IVCT, LVGLS, and WBC were independently associated with asthma exacerbation [OR (95% CI), 0.914 (0.848–0.986), p=0.019, 0.194 (0.087–0.428), p<0.001 and 1.450 (1.144–1.839, p=0.002, respectively] (Table 3).

Discussion

In our study, we compared conventional and STE examinations during asthma exacerbation and clinically stable periods, in female patients with asthma. The main findings were as follows: The IVCT of the left ventricle was prolonged during asthma exacerbation compared to the clinically stable period. More importantly, based on the STE measurements the left ventricular systolic function during asthma exacerbation was more impaired than during the stable period. To the best of our knowledge, it is the first time the current study established a comparison of cardiac function during asthma exacerbation and stable phase in patients with asthma.

Previous studies showed a variety of cardiac dysfunction in patients with asthma[5,6,11]. De-Paula et al. found lower pulmonary acceleration time and higher PSAP in asthma children and adolescents compared to age-matched healthy control[6]. Another study showed that asthma was associated with an increased occurrence of subclinical biventricular dysfunction[5]. However, the literature lacks data investigating the comparison of cardiac functions during exacerbation and stable phase in asthma patients. The current study aimed to address this gap.

According to previous reports, IVCT was significantly associated with heart failure (HF) and provides important prognostic information for the risk of future HF in the general population[12,13]. According to Alhakak et al., the risk of HF increased by 24% per 10 msec increase in IVCT (per 10 msec increase: HR 1.24;

95% CI (1.14–1.36), p<0.001)[12]. Myocardial fibers start to contract during the IVCT, increasing LV pressure without changing ventricular volume[14]. Thus, no blood is ejected and only internal work is performed. The cardiac efficiency is zero. However, during the ejection, external work is performed and cardiac efficiency improves. As myocardial function deteriorates, the IVCT is prolonged, increasing the internal work. Furthermore, the ejection time is shortened, decreasing the external work[15]. In a study consisting of mild-to-moderate HF patients, the ejection time was dramatically reduced and the IVCT was significantly extended[16]. Similarly, we found longer IVCT during exacerbation compared to the stable period. Mentioned phenomena could explain the prolongation of IVCT during asthma exacerbations. This prolongation possibly indicates that asthma exacerbation implements additional oppression on cardiac functions through varied substances produced during the exacerbation. It should be kept in mind that bronchodilator treatment also might have deteriorated the cardiac function. We also examined IVRT, which may be prolonged in HF and some diseases[14,17]. No significant prolongation of IVRT was observed during exacerbation in asthma patients compared to the stable period.

LVGLS, a measure of systolic myocardial deformation over the longitudinal axis, has proven effective in detecting subtle LV systolic dysfunction when LV ejection fraction is still preserved. Furthermore, it does not only reveal the subclinical LV systolic dysfunction but also predicts worse outcomes in many diseases[18]. Tuleta et al. investigated the LVGLS in mild-to-severe asthma patients[5]. Left ventricular global longitudinal strain values were reduced significantly in severe and mild-to-moderate asthma patients compared to the control group [avarage ± SD, -12.91±0.84% and -13.92±1.55%, p<0.05). Özkan et al. showed the adverse impact of asthma on ventricular contractility and that cardiac systolic function was impaired, in children with asthma[19]. In our study, according to the STE measurements left ventricular systolic function during asthma exacerbation was more impaired than during the stable period. The deterioration of LV systolic function during an asthma exacerbation is presumably due to some non-cardiac circumstances that implement oppression on cardiac function.

Asthma is mostly characterized by reversible obstruction of proximal and distal airways in response to various triggers. When compared to COPD, oxidative stress, neutrophil dominancy, and traditional systemic inflammation with specific pro-inflammatory mediators like tumor necrosis factor-alpha, interleukin-8, etc. —generally seem to be less prominent in the context of asthma[20]. Conversely, asthma is essentially defined by mast cells and eosinophils in the airways, which produce particular bronchoconstrictor chemicals such as histamine. Nevertheless, there is probably some overlap between the eosinophilic and neutrophilic pathways in these two situations[21]. During an asthma exacerbation, not only a variety of non-cardiac clinical scenarios such as hypoxemia, tachycardia, and bronchodilator therapy but also pro-inflammatory mediators might account for the depression of cardiac functions.

Conclusion

Our study showed that asthma exacerbation might have an oppressive and adverse impact on cardiac functions, particularly when analyzed by STE. Therefore, maximum efforts should be made to prevent asthma attacks and treat exacerbations without delay. Prospective studies with a larger number of patients are needed in this area.

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Authors' Contribution

The authors share the responsibility for the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no potential conflicts of interest regarding this article.

Disclaimer

The content is solely the responsibility of the authors.

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