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Original Article

Arterial Stiffness and Subclinical Myocardial Dysfunction in Pediatric Asthma: A Novel Approach Using Aortic Propagation Velocity

Çocukluk Çağı Astımında Arteriyel Sertlik ve Subklinik Miyokardiyal Disfonksiyon: Yeni Bir Yaklaşım Olarak Aortik Yayılım Hızının Kullanımı

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ABSTRACT

Objective: Childhood asthma is associated with systemic inflammation, airway inflammation, and cardiac adverse effects such as right ventricular (RV) failure and pulmonary hypertension. Arterial stiffness, an early marker of atherosclerosis, can be assessed using the color M-mode-derived aortic propagation velocity (APV) method. This study aims both to evaluate APV as a measure of arterial stiffness and also subclinical myocardial dysfunction using Doppler echocardiography in children with asthma.

Method: This prospective study evaluated early markers of arterial stiffness and subclinical myocardial dysfunction in children with asthma compared to a control group. The study included 44 children with asthma and 40 healthy controls. Echocardiographic measurements, including tissue Doppler imaging and color M-mode-derived APV were performed to assess ventricular function and arterial stiffness. Pulmonary function tests were also conducted for asthmatic patients.

Results: Our study did not reveal any significant differences in APV, left ventricular function, mitral valve Em/Am ratios, and left heart myocardial performance indices between the asthma group and the control group. However, we observed a significant difference in the peak systolic velocity at the anterior leaflet of the tricuspid valve (tricuspid valve Em velocity), which suggests that diastolic function of the RV performance is impaired in children with asthma.

Conclusion: This study is the first to evaluate APV in young children with asthma and has found no significant correlation between asthma and arterial stiffness or subclinical atherosclerosis. However, it has revealed that children with asthma are more likely to have RV diastolic dysfunction. Further studies are needed to investigate the potential link between childhood asthma and subclinical atherosclerosis.

Keywords: Childhood asthma, arterial stiffness, aortic propagation velocity, diastolic dysfunction, tissue Doppler imaging

ÖZ

Amaç: Çocukluk çağı astımı sistemik enflamasyon ve hava yolu enflamasyonunun yanında sağ ventrikül (SV) yetersizliği ve pulmoner hipertansiyon gibi kardiyak etkilerle de ilişkilidir. Aterosklerozun erken bir belirteci olan arteryel sertlik, renkli M-mod Doppler'den türetilmiş aortik yayılım hızı (APV) yöntemiyle değerlendirilebilir. Bu çalışmada astımlı çocuklarda arteriyel sertliğin bir ölçütü olarak APV'nin ve doku Doppler ekokardiyografi ile subklinik miyokardiyal disfonksiyonun değerlendirilmesi amaçlandı.

Yöntem: Bu prospektif çalışmada astımlı çocuklar kontrol grubuyla karşılaştırılarak arteryel sertliği gösteren erken belirteçler ve subklinik miyokardiyal disfonksiyon değerlendirildi. Çalışmaya 44 astımlı ve 40 sağlıklı kontrol olmak üzere 84 çocuk dahil edildi. Doku Doppler görüntüleme ve renkli M-mod'dan türetilen APV ile ventrikül fonksiyonları ve arteriyel sertlik değerlendirildi. Astımlılara ayrıca solunum fonksiyon testleri de yapıldı.

Bulgular: Astımlı çocuklar ve kontrol grubu arasında APV, sol kalp fonksiyonu, mitral kapak Em/Am oranı ve sol kalp miyokardiyal performans indeksi açısından anlamlı bir fark yoktu. Bununla birlikte, astımlı çocuklarda SV diyastolik disfonksiyonuna işaret eden triküspit kapak Em hızında anlamlı fark izlendi.

Sonuç: Bu çalışma astımlı çocuklarda APV'yi değerlendiren ilk çalışmadır. Küçük çocuklarda astım ile arteriyel sertlik yani subklinik ateroskleroz arasında anlamlı bir ilişki bulunamadı. Bununla birlikte, astımı olan çocukların SV diyastolik disfonksiyonuna sahip olma ihtimalinin daha yüksek olduğu ortaya kondu. Çocukluk çağı astımı ile subklinik ateroskleroz arasındaki potansiyel ilişkiyi araştırmak için daha fazla kontrollü araştırmaya ihtiyaç vardır.

Anahtar kelimeler: Çocukluk çağı astımı, arteriyel sertlik, aortik yayılım hızı, diyastolik disfonksiyon, doku Doppler görüntüleme

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INTRODUCTION

Childhood asthma is a prevailing chronic condition, and recent studies have indicated a rise in systemic inflammation and airway inflammation among individuals with asthma[1,2]. In children with asthma, the ventricular contractility is also influenced by the chronic inflammatory response[3]. In asthmatic patients, right ventricular (RV) failure, pulmonary hypertension, and atrial dilation are among the more frequently observed cardiac effects[4]. Atherosclerosis and asthma are both chronic inflammatory diseases. Inflammation leads to impaired endothelial cell function and chronic inflammation accelerates the development of atherosclerosis[5].

Aortic propagation velocity (APV) measurement using a color M-mode aortic practical way to evaluate the arterial stiffness in the thoracic aorta and is found to be inversely related to the extent of coronary artery disorder[6,7]. APV is more convenient for clinical use than other techniques, including pulse wave velocity, aortic distensibility, and aortic strain. Recent research has indicated that APV is similarly effective as pulse wave velocity and aortic distensibility for the evaluation of arterial stiffness, and it is also simpler to apply and replicate[8].

Asthma is characterized by chronic inflammation, which causes pulmonary vasoconstriction through the release of mediators and cytokines. Pulmonary vasoconstriction is further exacerbated by structural changes in pulmonary vessels due to parenchymal deterioriation, increased cardiac output, and blood viscosity due to hypoxia-induced polycythemia[9]. Asthmatic patients have increased intrathoracic pressure due to excessive breathing efforts, leading to RV afterload, and ultimately, to RV hypertrophy and diastolic dysfunction. RV diastolic dysfunction is a significant prognostic factor[10]. Left ventricular (LV) diastolic dysfunction, on the other hand, is related to the interventricular interaction, increased LV afterload, and decreased LV preload[10].

The use of color M-mode derived APV has not been investigated in children with asthma. Therefore, our aim was to evaluate the early signs of arterial stiffness in asthmatic children by using APV and also determine possible subclinical myocardial dysfunction using Doppler echocardiography.

MATERIALS and METHODS

Between December 2018 and July 2019, we conducted a prospective study at Kütayha Evliya Çelebi Training and Research Hospital. The study involved children who had been diagnosed with asthma at least 6 months before and were followed up at the pediatric allergy outpatient clinic. We also recruited healthy children who were matched by age and sex and visited the pediatric cardiology outpatient clinic as the control group. There were 84 children in the study, 44 in the asthma group and 40 in the control group. The parents provided the informed consent and the Kütahya Health Sciences University Ethics Committee approved the study (decision no: 2018/14-6, date: 14.11.2018). We followed the GINA Strategy 2018 guidelines to evaluate the diagnosis, treatment, and control of asthma symptoms[11].

The study excluded patients who had a respiratory tract infection or asthma attack in the previous month. Children aged 5 to 15 years who attended the pediatric cardiology outpatient clinic with heart murmurs or chest pain made up the control group. All patients underwent routine examinations. We also excluded participants who had a chronic lung disease, an atopic, rheumatologic, or autoimmune disease, were exposed to secondhand smoke, or had an asthma attack in the previous month. We carried out echocardiographic measurements for eligible participants in both groups, and pulmonary function and skin prick tests for asthmatic patients who met the study criteria.

Echocardiography

A Philips Affinity 50 echocardiography device (Philips Healthcare, Andover, Netherlands) with an S4-2 (3.4 MHz) transducer was used by the same pediatric cardiologist (R.Ö.) to perform all echocardiographic examinations. The methodology from previous guideline was applied to ensure the accuracy of all echocardiographic measurements[12]. TDI technique indices, including Em, Am, Em/Am, Sm, and myocardial performance index (MPI), were used to evaluate ventricular functions. A decreased Sm indicated impaired ventricular systolic function, while decreased Em and Em/Am ratios, as well as increased Am, indicated impaired diastolic function. An increased MPI index indicated impaired ventricular functions. We acquired suprasternal window images while the patients were lying in the supine position. We aligned a M-mode cursor with the flow direction in the aorta, using a Nyquist limit of 30-50 cm/s and an M-mode sweep rate of 200 mm/s. We adjusted the aliasing velocity to improve the velocity slope delineation, and divided the propagation slope distance by the velocity slope duration. The estimated value was defined as the APV (Figure 1).

Pulmonary Function Tests

Spirometric evaluations were done using Spirobank G USB spirometer (Rome, Italy). The patients were sitting and had a clip on their nasal airways during the tests, which were done at room temperature. The parameters of FEV1, FVC, FEV1/FVC ratio, PEF, and FEF 25-75 were used by experienced technicians to perform all pulmonary function tests as recommended[13].

Statistical Analysis

The study data were analyzed using the Statistical Package for the Social Sciences program (version 15.0, Chicago, Illinois, USA). The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the normality of all data distributions. The variance homogeneity was determined using the Levene test. The group comparisons were evaluated using the Student t-test for parametric parameters and the Mann-Whitney U test for non-normally distributed data. The parametric parameters evaluated using the Student t-test were presented as meanstandard deviation, and the parameters evaluated using the Mann-Whitney U test were presented as median (interquartile range). The level of statistical significance for all data was p<0.05.

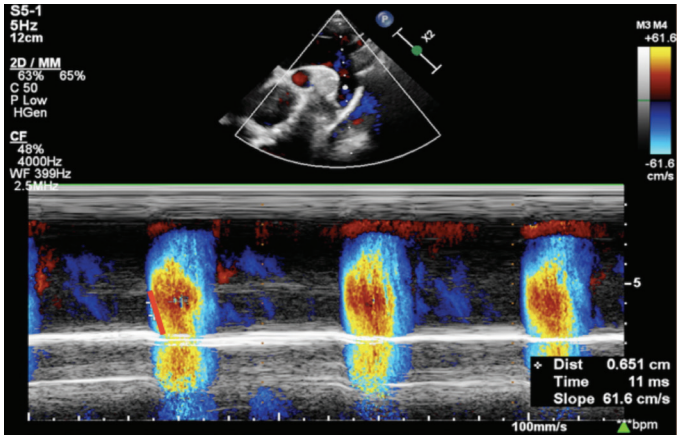

Figure 1. Aortic propagation velocity in a patient. The red line shows time slope

RESULTS

The study group had a mean age of 8.3±3.1 years, with no statistically significant difference compared to control group (p>0.05, Table 1). The mean Em/Am ratios of the mitral valve were 1.55±0.96 in the study group and 1.57±0.73 in the control group (p=0.72). The mean Em/Am ratios of the tricuspid valve were 1.25±0.43 in the study group and 1.13±0.33 in the control group (p=0.15). The mean mitral valve MPIs derived from tissue Doppler were 41±6 in the study group and 40±7 in the control group (p=0.91). The mean tricuspid valve MPIs derived from tissue Doppler were 45±9 in the study group and 44±6 in the control group (p=0.72). The mean Em velocities of the mitral valve were 0.15±0.03 m/s in the study group and 0.16±0.04 m/s in the control group (p=0.67). The mean Em velocities of the tricuspid valve were 0.15±0.032 m/s in the study group and 0.14±0.022 m/s in the control group (p=0.02) (Table 2). No statistically significant differences were detected between the groups for Am, Sm, Em, Em/Am ratio, and left heart MPI values obtained from the mitral lateral annulus in LV echocardiography (p=0.56, p=0.89, p=0.67, p=0.72, and p=0.91, respectively) (Table 2). Similarly, no statistically significant differences were seen between the groups for Am, Sm, Em/Am ratio, and right heart MPI parameters obtained from the tricuspid lateral annulus in RV echocardiography (p=0.95, p=0.8, p=0.15, and p=0.72, respectively). However, there was a statistically significant difference between the groups for measurements indicating the diastolic function of right cardiac performance, with tricuspid valve mean Em (m/s) being 0.15±0.032 in the study group and

Table 1. Characteristics of patients with asthma and spirometry findings

	Minimum	Maximum	Mean	SD
Age (year)	2.5	16	8.3	3.1
Weight (kg)	15	60	31.1	12.7
Height (cm)	95	160	129.4	16.9
FVC (cm^3)	52	123	82.2	13.5
FEV1 (L)	54	126	86.6	14.5
FEV1/FVC	87	117	104.1	8.3
PEF (L/min)	38	103	68.2	15.5
FEF 25/75	39	144	81.7	20.1

SD: Standard deviation, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, PEF: Peak expiratory flow, FEF 25/5: Forced expiratory flow over the middle one-half of the FVC

0.14±0.022 in the control group (p=0.02). The mean APVs (cm/s) were 60±13.2 in the study group and 64±13 in the control group without any statistically significant intergroup difference (p=0.27). LV conventional M mode measurements did not differ statistically significantly between groups (Table 2).

DISCUSSION

Although publications have indicated cardiac involvement and impairment of ventricular function in bronchial asthma, the evaluation of aortic flow velocity using Doppler echocardiography have not been reported previously. In this study, we found that Em, a right ventricular diastolic function parameter, was affected in children with asthma. Myocardial performance indices of right and left ventricles were higher in asthmatic patients without any statistically significant inter-ventricular difference. The APV, which was investigated for the first time, was similar in both groups. Conflicting results have been shown by studies evaluating the right and LV functions in asthmatic patients, but it has been shown that RV function may be impaired in the early stage of the disease[14-17]. In the study of Abdalla and El Azeem[16], LV diastolic function was impaired in young adult asthmatic patients while RV diastolic function was unaffected. In the same study, it was found that LV MPI parameters impaired in study group, while RV MPI parameters did not demonstrate any significant intergroup difference. Similarly, in our study, RV MPI values did not show any deterioration. However, in our study, LV diastolic function was not statistically different between the asthmatic cases and the control group. In our study, only Em parameter of RV diastolic function was found to be affected in asthmatic children. In a study of Ozde et al.[18], the tricuspid Em was lower in the control group. However, Ozdemir et al.[14] showed that the tricuspid Em value was higher in the asthmatic children. We also found that Em was higher in asthmatic patients when compared to healthy subjects. These discrepancies may be explained by the younger age of our study participants and their response to treatment. Accordingly, our study participants were younger than those in the other two studies. In the study by Shedeed[4], RV diastolic functions worsened as the severity of asthma increased, and diastolic functions improved thanks to the reduction of RV afterload by treatment. As inflammation is involved in all stages of the atherosclerotic process[19], atherosclerosis is commonly recognized as a chronic

Table 2. Ventricular tissue Doppler and conventional echocardiographic measurements in patient and control groups

Variables	Patients (n=44)	Control subjects (n=40)	p-values
Mitral lateral annulus TDI			
Sm (m/s), median (IQR)	0.1 (0.02)	0.1 (0.03)	0.89
Em (m/s), mean ± SD	0.15±0.03	0.16±0.04	0.67
Am (m/s), median (IQR)	0.1 (0.03)	0.09 (0.03)	0.56
Em/Am, median (IQR)	1.55 (0.96)	1.57 (0.73)	0.72
LV MPI, mean ± SD	41±6	40±7	0.91
Tricuspid lateral annulus TDI			
Sm (m/s), mean ± SD	0.13±0.019	0.13±0.017	0.8
Em (m/s), mean ± SD	0.15±0.03	0.14±0.02	0.02
Am (m/s), median (IQR)	0.13 (0.06)	0.13 (0.06)	0.95
Em/Am, mean ± SD	1.25±0.43	1.13±0.33	0.15
RV MPI, mean ± SD	45±9	44±6	0.72
Aortic propagation velocity			
(cm/s), mean ± SD	60±13.2	64±13	0.27
M-mode parameters			
LVEDd (cm), mean ± SD	4.21±0.46	4.32±0.72	0.81
IVSDd (cm), mean ± SD	0.807±0.14	0.81±0.16	0.72
LVPWd (cm), mean ± SD	0.86±0.15	0.88±0.12	0.68
Fractional shortening (%), mean ± SD	40.1±6.2	42±3.8	0.59

IQR: Interquartile range, Sm: Systolic myocardial velocity, Em: Early diastolic myocardial velocity, Am: Late myocardial velocity, LV: Left ventricle, RV: Right ventricle, MPI: Myocardial performance index; LVEDd: Left ventricular end-diastolic diameter, IVSDd: Interventricular septal diameter in diastole, LVPWd: Left ventricular posterior wall thickness in diastole

inflammatory disease[20]. Inflammation serves as a shared underlying mechanism for the physiological and pathological modifications occurring during the onset and progression of atherosclerosis. It is well known that atherosclerosis affects both medium-sized and larger vessels, including the thoracic aorta.

Endothelial dysfunction serves as an early sign of vascular damage and subclinical atherosclerosis[21]. Moreover, endothelial damage causes vascular fibrosis in larger arteries, leading to reduced arterial elasticity[22]. Recently, the link between systemic inflammation and asthma has attracted increasing attention. A notable study by Wood et al.[1] demonstrated that a subset of asthmatic patients with airway inflammation had worsened systemic inflammation, as evidenced by elevated levels of IL-6 and high-sensitivity C-reactive protein. In addition, this systemic inflammation was associated with poorer clinical outcomes. Therefore, we aimed to evaluate subclinical atherosclerosis in asthmatic children using a novel method namely color M-mode-derived propagation velocity of the descending aorta (APV). The color M-mode propagation velocity is an effective tool for generating spatiotemporal maps of blood flow velocities within the arterial lumen which is currently used for noninvasive evaluation of aortic distensibility. Various studies have explored the correlation between APV and endothelial dysfunction and carotid intima-media thickness (CIMT) has been closely linked with APV[7,23]. Several studies have been conducted to examine the correlation between systemic inflammation and arterial stiffness[24,25]. One such study by Demiralp et al.[25] explored changes in aortic elasticity in patients with ankylosing spondylitis. The study showed that these patients had reduced aortic elasticity, irrespective of how long they had the disease, and their average aortic stiffness index was higher than the control group.

The development of atherosclerosis is thought to mediate these arterial wall changes, which can be explained by the adverse effects of inflammation. A study conducted by Karaman et al.[24] observed that patients diagnosed with Familial Mediterranean Fever (FMF) had lower APV values compared to control subjects. Moreover, a correlation was found between APV and mean CIMT values, with APV being identified as an independent predictor of FMF. The researchers proposed that the lower APV values may be linked to endothelial dysfunction and may indicate the presence of subclinical inflammation in FMF patients who had not cardiovascular involvement. Our study has revealed that asthmatic children had lower APV values compared to the control group. However, there was no significant statistical difference between both groups. Previous studies have explored the relationship between asthma and CIMT in both children and adults[26,27]. Cakmak et al.[26] demonstrated that CIMT values were significantly higher in asthmatic children compared to the control group. This increase is known to be correlated with the progression of atherosclerosis seen in adult patients with inflammation. Furthermore, the patient group had a significant increase in oxidative stress, which was positively correlated with CIMT. The findings of the current study do not support the results of Cakmak et al.'s [26] study. This discrepancy might be explained by our younger study population, different treatment strategies used and severity of asthma. One potential explanation could be linked to the diverse range of pathophysiological mechanisms associated with asthma. Liang et al.[28] found higher levels of systemic inflammation markers including leptin and vascular endothelial growth factor in asthmatic subjects. An adult study found that women with adult-onset asthma had thicker far (deeper) wall intima-media thickness, indicating carotid atherosclerosis, compared to non-asthmatic counterparts[27]. This difference in CIMT values was also detected between smoking and non-smoking women in the cohort which was partially explained by smoking, physical activity, pulmonary function, and other confounding factors. There was no significant difference in APV values among male and female asthmatic patients, according to our study. Childhood-onset asthma and asthma in men were not associated with carotid atherosclerosis[28].

Study Limitations

First limitation that deserve attention is the absence of data regarding the occurrence of systemic inflammation in the population under investigation. Another study limitation is that the color M-mode echocardiography method used for the assessment of APV based on aortic flow propagation velocity may be subject to errors. Careful attention is required in identifying the starting and ending points of the propagation slope, as even small placement errors can result in significant calculation errors. Secondly, the statistical power of the study may have been compromised due to the limited number of patients included in the analysis. Although our study provides valuable insights, since it was conducted at a single center, our findings require validation through prospective, multi center studies with long-term follow-up.

CONCLUSION

Assessment of APV for the first time in children with asthma have shown that asthma in small children is not significantly associated with arterial stiffness or subclinical atherosclerosis. This research study has also shown that children with asthma have RV diastolic dysfunction. Further research studies with control groups should be conducted to elucidate the association between asthma and subclinical atherosclerosis in asthmatic children.

Ethics

Ethics Committee Approval: The Kütahya Health Sciences University Ethics Committee approved the study (decision no: 2018/14-6, date: 14.11.2018).

Informed Consent: The parents provided the informed consent.

Peer-review: Externally and internally peer reviewed.

Author Contributions

Concept: R.Ö., A.T, Design: R.Ö., B.G., Data Collection and/or Processing: H.B.İ, D.G., Analysis and/ or Interpretation: B.G, D.G, Literature Search: R.Ö., B.G., H.B.İ., D.G., Writing: R.Ö., B.G.

Conflict of Interest: The authors have no conflict of interest to declare.

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