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The influence of Asthma on Right Ventricular Systolic and Diastolic Function in Children according to Tissue Doppler Echocardiography

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Abstract

Introduction: Asthma is the most common chronic inflammatory condition affecting the lower airways among children. Asthma may influence right ventricular (RV) function and patients may develop right ventricular hypertrophy, pulmonary hypertension and cor pulmonale. The main objective of this study is to determine RV dysfunction in asymptomatic asthmatic children as detected by tissue Doppler echocardiography (TDE).
Methods: In this cross-sectional study, 31 cases suffering from mild intermittent asthma, and 31 age/gender-matched healthy controls were evaluated according to standard echocardiography, pulsed-wave Doppler (PWD), TDE, and pulmonary function tests on spirometry.
Results: We did not observe a statistically significant difference between cases and controls as far as RV wall, RV diameter, and ejection fraction (EF) were concerned. PWD indices of both ventricles were not significantly different between the two groups. TDE evaluation of RV diastolic function revealed that annular peak velocity early diastole (E'), annular peak velocity late diastole (A'), and E'/A' ratio had significant differences between the two groups (P = 0.001, respectively). Isovolumic relaxation time (IVRT) and myocardial performance index (MPI) of the lateral tricuspid annulus differed significantly in asthmatic children compared to healthy children (p = 0.002 and p = 0.001, respectively). There were no significant differences in regard to PEF, FVC, and FEV1/FVC between the two groups.
Conclusion: Despite normal clinical and standard echocardiographic findings, subclinical diastolic impairment of right ventricular function was determined. The findings of this study suggest that assessment, detection, and monitoring of RV diastolic function play an important role among well-controlled, mild intermittent asthmatic patients.

Introduction

Asthma is the most common chronic inflammatory disease among children. The global asthma prevalence ranges from 1–18% worldwide (1). Unfortunately, the number of patients suffering from asthma has increased over the past two decades. Exposure to hypoxia combined with hypercarbia occurs recurrently in patients. Pulmonary vasoconstriction and narrowing of the pulmonary vasculature arise from the release of various inflammatory mediators and cytokines into the pulmonary tissue (2,3), eventually leading to pulmonary hypertension in later stages of the disease. The factors effective in the development of these complications and increased mortality include distortion of pulmonary vessels, increased blood viscosity secondary to sustained and recurrent hypoxia, increased RV afterload and intra-thoracic pressure. In extreme conditions, patients may develop right heart enlargement with ventricular hypertrophy (4).

The severity of RV diastolic dysfunction depends on the degree of RV hypertrophy and pulmonary vascular resistance (1,5).

RV dysfunction in children suffering from severe asthma was documented by using standard echocardiography (6,7). PWD and TDE are optimal techniques and provide a quantitative measure of regional myocardial function (8,9). PWD and TDE parameters can detect subclinical RV dysfunction in the early stages of the disease even when routine echocardiography parameters are normal. TDE is evidently the best non-invasive method to assess ventricular diastolic dysfunction, and the tricuspid lateral annulus is supposedly the most desirable site for RV function assessment in asthmatic patients (10,11). The aim of this study was to evaluate subclinical RV dysfunction by using PWD and TDE on well-controlled, mild intermittent asthmatic children.

Materials and Methods

In this cross - sectional study, thirty-one asthmatic children were designated as cases and thirty-one age/gender-matched healthy children were designated as controls. The Pediatric Allergy Clinic referred children aged between 5-15 years that were in remission for at least 8 months over a 12 month period from Sep2015-Oct2016. All asthmatic patients suffered from intermittent or mild asthma according to the Global Initiative for Asthma (GINA) report (10). The research was approved by the Research Ethics Committee of Arak University of Medical Sciences.

History-taking, a comprehensive physical examination, and spirometry testing were performed according to the European Respiratory Society consensus standards. In both groups, anthropometric parameters including height, weight, body mass index, heart rate, respiratory rate and blood pressure (BP) were measured.

Pulmonary function testing was carried out for all study subjects via spirometry testing (peak expiratory flow [PEF] forced expiratory volume 1 [FEV1], forced vital capacity [FVC], and the ratio of FEV1 to FVC). Patients with moderate/severe persistent asthma, acute or chronic pulmonary disease, recent respiratory infection during the last 4 weeks, obesity, acute asthma attack during the last 8 weeks, use of oral steroids during the last 8 weeks, and those with a previous history of clinical cardiac disease or any other systemic disorders were excluded from this study.

Echocardiography

Echocardiography was performed by an experienced pediatric cardiologist in supine and left lateral decubitus positions. The instrument employed was a ViVid 3 ultrasound system (General Electric Medical Systems) along with 3 and 7 MHz transducers. All parameters were averaged over three consecutive cardiac cycles.

Standard echocardiography measurements were accorded with recommendations of the American Society of Echocardiography (12). LV ejection fraction (EF), free RV wall thickness, and RV end-diastolic diameter (RVEDD) were measured at the parasternal long axis view and four-chamber view, respectively.

RV free wall thickness is less than 0.5 cm normally. RV free wall thickness is measured using either M-mode or 2D imaging. RV free wall thickness can be captured from apical and parasternal long-axis views, however, measurement in the subcostal view at the peak of the R wave and the level of the tricuspid valve chordae tendinae provides less variation and closely correlates with RV peak systolic pressure (13).

Tricuspid diastolic flow velocities were measured in the apical four-chamber view by using PWD and placing the sample volume at the leaflet tips. Early diastolic peak velocity (E), late diastolic peak velocity (A), E/A ratio and E-deceleration time (E-DT) were parameters indicating ventricular diastolic function (14).

Diastolic RV function was also evaluated by TDE. Peak systolic velocity (S') and early and late diastolic velocities (E' and A'), E'/A' ratio and isovolumetric relaxation time (IVRT) were measured at the lateral tricuspid annulus in the apical four chamber view. TDE was recorded optimally by using a 2-3mm sample volume, a monitor velocity of 100 mm/s and adjusting Nyquist limits at 15–20 cm/s.

Myocardial performance index (MPI) could be assessed by combining both systolic and diastolic functions together (14,15). The pulmonary flow of RVMPI was calculated as the sum of isovolumetric contraction time (IVCT) and IVRT divided by ejection time (ET).

Statistical Analysis

Data analysis was performed using the SPSS software version 20.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics are presented as mean ± standard deviation (SD). Chi-square test was used to compare sex distribution. Two independent samples t-test was used to compare continuous variables. Pearson's correlation test was used to estimate correlations between the duration of treatment and the patient's age with spirometry parameters and echocardiographic parameters. A p-value of less than 0.05 was regarded as statistically significant.

Results

This study enrolled 31 asthmatic children (15 boys and 16 girls) with a mean age of 9.35 ± 2.39 years that were compared with 31 age-matched healthy subjects (13 boys and 18 girls) with a mean age of 8.81 ± 2.24 years. The duration of treatment was 2.27 ± 1.4 years. Demographic and clinical characteristics of the patients and healthy controls are listed in Table 1. There were no significant differences between asthmatic patients and healthy subjects in terms of age, weight, BMI, height, HR, SBP, and DBP.

Table 1. Mean comparison (±SD) of clinical characteristics in the two groups

Characteristic	Case group (n=31)	Control group (n=31)	P
Male/female	15/16	13/18	0.799
Age (years)	9.35±2.39	8.81±2.24	0.362
BMI (Kg/M^2)	17.77 ± 2.43	17.93 ± 3.61	0.838
Body weight (kg)	28.43±6.21	29.30 ± 6.32	0.587
Heart rate (beat/min)	96.67±10.07	98.41±7.32	0.439
Respiratory rate (breath/min)	15.33±5.77	14.56±4.49	0.560
Systolic BP (mmHg)	102.12±7.40	105.50±8.51	0.100
Diastolic BP (mmHg)	77.70±7.85	79.20±8.55	0.475

BMI: body mass index, BP: blood pressure, We did not find a significant difference in terms of PEF, FVC, and FEV1/FVC of the pulmonary function tests between cases and controls; however, the mean of FEV1 (80.51 ± 8.7) was significantly (p=0.048) less in the cases compared to the controls (84.92 ± 8.5). Spirometry results are summarized in Table 2.

Table 2. Mean (±SD) comparison of pulmonary function test findings in the two groups

Characteristic	Case group (n=31)	Control group (n=31)	P
PEF	80.78±6.9	83.94±7.9	0.090
FEV1	80.51±8.7	84.92±8.5	0.048
FVC	85.11±6.5	88.30±7.3	0.074
FEV1/FVC	82.81±5.8	86.61±9.7	0.066

FEV1 forced expiratory volume in 1 s; FVC forced vital capacity, PEF peak expiratory flow

Standard echocardiographic and PWD parameters are summarized in Table 3. Free RV wall thickness, RV diameter, and LVEF were not statistically different between the two groups (p=0.658, p=0.862, and p= 0.909, respectively). Asthmatic patients did not demonstrate changes in RV shape or dimension.

Table 3. Mean (±SD) comparison of of PWD echocardiographic measures in the two groups

Characteristic	Case group (n=31)	Control group (n=31)	P
LVEF (%)	64.90±3.24	65.4± 6.20	0.909
Free RV wall thickness mm)	5.25±1.32	5.12±0.99	0.658
RV diameter (mm)	23.45±2.33	23.34±2.47	0.862
Tricuspid E (cm/s)	86.67±9.37	91.58±13.10	0.095
Tricuspid A (cm/s)	55.24±9.95	52.63±10.95	0.331
Tricuspid E/A	1.68±0.25	1.77±0.27	0.178
Tricuspid E- DT (ms)	128.58±17.39	126.77±15.81	0.670

A peak velocity late diastole, DT deceleration time, E peak velocity early diastole, EF ejection fractional of the left ventricle

Pulse-wave Doppler index of both ventricles did not significantly differ between cases and controls. Asthmatic patients did not demonstrate diastolic dysfunction according to PWD findings.

TDE parameters are summarized in Table 4. Tricuspid annular peak velocities of early diastole (E') (p=0.001), late diastole (A') (p=0.001) and E'/A' ratio (p=0.001) differed significantly between patients with asthma and healthy subjects; however, no significant difference was found with regard to peak systolic velocities of tricuspid annulus. (p=0.180). IVRT of the lateral tricuspid annulus was significantly different between the two groups (p=0.002) and right ventricular myocardial performance index (RVMPI) was also significantly greater for patients with asthma compared with healthy children (p=0.001). (Table 4)

Table 4. Mean (±SD) comparison of TDE indices in tricuspid annular in the two groups

Characteristic	Case group (n=31)	Control group (n=31)	P
E' (cm/s)	15.51±0.91	13.58±1.09	0.001
A' (cm/s)	4.40±0.69	7.68±0.24	0.001
E'/A'	3.56±0.46	1.73±0.11	0.001
S' (cm/s)	10.21±2.59	9.45±1.67	0.180
IVRT (ms)	50.74±7.58	45.00±6.00	0.002
RVMPI (%)	0.39±0.02	0.34±0.02	0.001

Discussion

In this study, standard echocardiographic parameters of asthmatic patients such as, left ventricular EF, RV free wall thickness and RV diameter were similar to the controls. The findings of normal RV wall thickness and normal RV diameter in well-controlled asthmatics were desirable. Despite the fact that TDE demonstrated RV diastolic impairment in asymptomatic asthmatics; however, systolic dysfunction was not identified in the asthmatics.

A previous study on moderate to severe asthmatic patients showed some evidence of RV diastolic dysfunction (6,7). The degree of RV diastolic dysfunction was the resultant of RV hypertrophy and pulmonary hypertension and resistance (2,5).

In this study, asthmatic patients suffered from a mild intermittent disease; therefore, RV diastolic function was important to be readdressed. In addition to RV shape or geometry; there may be other causes that influence RV function. Various mediators and cytokines are produced during the disease, which are potent depressants of cardiac contractility(16).

Unfortunately, previous research has failed to address right ventricular diastolic function by Tissue Doppler Echocardiography in asthmatics; even though it appears that right ventricular diastolic dysfunction has already occurred and provoked its deleterious effects. In the present study, TDE findings demonstrated subclinical RV dysfunction.

Zeybek et al. showed that standard echocardiographic parameters of mild asthmatic patients were similar to the normal population. Standard echocardiographic indices have not been appropriate to assess early diastolic ventricular dysfunction in asthmatic patients. It was also found that tricuspid lateral annular velocities and IVRT were significantly different between mild asthmatic patients and healthy subjects (11).

Shedeed showed a greater RV free wall thickness in asthmatic patients, despite other RV echocardiographic dimensions. It was also observed that E'/A', IVRT, IVCT, and MPI parameters were significantly greater in asthmatic children; however, E', A', and S' were significantly lower in the asthmatics (10). Eventually, they reached the conclusion that asthmatic patients have increased RV dysfunction and TDE may help determine RV diastolic and systolic dysfunction at early stages.

Results of our study showed no significant difference between cases and controls in terms of RV free wall thickness and/or RV diameter. In the study by Shedeed, patients were moderately and severely asthmatic (10); however, our study was conducted on patients with the mild and intermittent disease.

Ozdemir et al. also revealed that the RV wall was significantly thicker among asthmatics; however, RV dimensions and LV function were similar to healthy subjects. It was also found that E', A', E'/A', and IVRT of the lateral tricuspid annulus were significantly different between asthmatics and healthy subjects, and RV systolic function indicated as S' velocities had resemblance in both groups. Furthermore, it was also found that right ventricular MPI was significantly greater in the asthmatics compared to the healthy controls (15). These findings were in line with the results of our study which also found no difference in terms of RV shape or geometry between the two groups.

It is determined that prolonged MPI and IVRT confirm ventricular diastolic dysfunction. Therefore, subclinical RV diastolic dysfunction was shown in this study and in recently published studies (11,15).

The retrosternal location of the right ventricle, complex geometry, and hyperinflated lungs are factors responsible for making conventional echocardiography incompetent for RV assessment in patients with asthma (9,11). By standard methods, estimation of RV function depends on preload and afterload (9). Therefore, this paper supports the opinion that standard echocardiography is not appropriate to accurately assess RV function (11). Consequently, TDE is more appropriate for precise assessment of subclinical RV systolic and diastolic function and measurement of regional myocardial velocities (8,9). Nowadays, TDE is considered favorable for identifying RV dysfunction in comparison to standard echocardiography and is strongly correlated with pulmonary function tests (PFT) in patients suffering from chronic obstructive lung disease (17).

In a previous study conducted by Ghaderian et al. conventional echocardiography revealed no significant difference between the cases and controls which was in contrast with TDE that demonstrated a significant difference. E', A', E'/A' ratio and S' in the lateral and medial aspects of the tricuspid annulus were significantly different between the cases and controls. IVRT, IVCT and mean MPI were greater in asthmatics. There was no difference in terms of E-DT between the two groups (18). In this study, systolic dysfunction was not detected by TDE and no significant difference was found in terms of S'.

Akyüz Özkan E et al., found lower E'/A' ratio, tricuspid annular peak systolic velocities(S') and early diastolic tricuspid velocities (E') in asthmatics. The FEV1 was positively correlated with IVRT and mitral ET. The PEF was negatively correlated with the RV and LV work indices (19). These findings may be associated with disease duration and severity in other studies. In this study, patients were intermittently and mildly asthmatic, and disease duration was not evaluated. Our results are in line with previous studies conducted by Ghaderian et al. and Akyüz Özkan et al. (18,19).

MPI is used to evaluate cardiac effects of multiple chronic systemic diseases. Measurement of MPI by TDE serves as a useful and practical indicator of global ventricular function, while independent of ventricular geometry and HR. If subclinical RV dysfunction occurs, MPI of the ventricle measured by TDE will be greater than normal. It must be emphasized that MPI reflects global cardiac effects of chronic disease.

The best predictors of severity in children suffering from asthma are pulmonary function tests including FEV1, FEV1/FVC, and PEF (20). In some studies, results showed a significant correlation between the TDE parameters and spirometry testing in asthmatic children (10,11). Contrary to our expectations, we did not find a significant correlation between PFT and standard echocardiography, PWD, and TDE.

Three hypotheses are found responsible for why PFTs do not correlate with TDE findings in this study. The first is a small sample size and the limited number of study subjects. The second is a lower severity of disease and the last may be the well-controlled condition in patients. PFTs reflect disease severity which revealed no significant difference between the two groups in this study, except for FEV1, which showed the asthmatic disease in the cases.

Finally, a number of potential shortcomings need to be considered. First, a relatively small sample size, second, the fact that radionuclide ventriculography was not employed to confirm ventricular function along with TDE. However, TDE is considered as a favorable and valid method for the assessment of ventricular function. Itis recommended that this study be conducted with a larger sample size, monitoring, and longer follow-ups.

Conclusion

Based on the results, it can be concluded that RV diastolic dysfunction in children suffering from asthma had occurred despite normal standard echocardiographic findings. Therefore, these findings highlight the importance of employing TDE for detection or assessment in the early stages of asthma and for patients being monitored in the later stages of the disease.

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Conflict of interest

Authors declare that they have no conflict of interest.

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