INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways which is associated with airway obstruction, hyper-responsiveness and characterized recurrent episodes of wheezing, breathlessness, and coughing.1 Atherosclerosis and asthma are both chronic inflammatory disorders. Asthma is not only associated with multiple markers of chronic systemic inflammation but also increased risk of atherogenesis. Several previous studies showed that arterial stiffness was increased in patients with asthma.2,3 Arterial stiffness indicates the viscoelastic properties of the vessel wall. Arterial stiffness represents vascular damage and is a measure of the degree of atherosclerosis.4 Chronic inflammation is associated with atherosclerosis, endothelial dysfunction, and arterial stiffness and subsequently adverse cardiovascular events via common inflammatory pathways.5 Cohn et al. suggested that peripheral arterial stiffness measurements were correspondent with atherosclerotic cardiovascular disease. To detect the risk of cardiovascular events and early atherosclerosis, non-invasive techniques of measuring arterial stiffness are increasingly being used.6 In patients with chronic obstructive pulmonary disease (COPD), the mean aortic pulse wave velocity, inflammatory markers and augmentation index are higher than controls and increased arterial stiffness was associated with the degree of the airflow obstruction in COPD.7 Although the most commonly used method to assess the arterial stiffness is the peripheral artery pulse wave velocity, there are more sensitive measures, of arterial stiffness (effective arterial elastance; Ea), and ventricular-arterial coupling (ratio of arterial and end-systolic ventricular elastance; Ea/Ees) which can be used in patients with asthma.8

It was hypothesized that since asthma is a chronic inflammatory disease, it could lead to the early development of atherosclerosis in childhood-onset asthma and to detect atherosclerosis arterial stiffness was used.

The aim of this study was to assess arterial-ventricular elasticity and cardiovascular coupling in asthmatic children and correlate it with pulmonary function tests. This will help to identify subjects for enrollment in clinical trials using echocardiography for assessing the impact of asthma on cardiovascular outcome.

ORIGINAL ARTICLE

Arterial and Ventricular Elastance and Ventriculo-arterial Coupling in Asthmatic Children

Esra Akyuz Ozkan1, Hashem E. Khoreshahi2, Mahmut Kilic3, U. Aliye Gecit1, Esra Domur1 and Perihan Beysel1

ABSTRACT

Objective: To compare arterial and ventricular end-systolic elastance and ventriculo-arterial coupling between asthma and healthy children and correlate these all three parameters with pulmonary function tests in subjects with asthma.

Study Design: A cross-sectional analytical study.

Place and Duration of Study: Department of Pediatrics, Bozok University Medical Faculty, Yozgat, Turkey, from January 2012 to November 2014.

Methodology: Transthoracic and Doppler echocardiography and pulmonary function tests in patients with asthma aged 7 - 12 years and control subjects. Forty stable asthma patients on prophylactic inhaled corticosteroids and 97 healthy subjects were investigated. Both groups were matched for age, gender, blood pressure, heart rate, body surface area, echocardiographic parameters and pulmonary function tests.

Results: There was no difference regarding left ventricular elastance at end-systole derived by single beat/body surface area (Ees(sb)/BSA) between asthmatic patients and healthy children (2.59 ±1.29 mmHg/ml/m², 2.43 ±1.28 mmHg/ml/m² respectively, p=0.504), arterial elastance/BSA (Ea/BSA) (2.10 ±0.97, 1.75 ±0.89 respectively, p=0.041), and ventriculo-arterial coupling (VAC) (0.83 ±0.13, 0.74 ±0.13, respectively, p < 0.001) were higher in asthmatic group than controls. There was no correlation between Ea, Ees (sb), VAC and pulmonary function tests.

Conclusion: Arterial elastance increase and stiffness decrease in asthmatic patients. This may be due to using prophylactic inhaled corticosteroids. Using inhaled corticosteroids have protective effects against atherosclerosis. As a result of this higher arterial elastance, asthmatic children had higher VAC resulting in less efficient cardiovascular function.

Ventriculo-arterial coupling in asthmatic children

METHODOLOGY

This case-control study was carried out at pediatrics outpatient clinic, Medical Faculty of Bozok University from January 2012 to November 2014. Inclusion criteria include all patients met the criteria for bronchial asthma. The patients with comorbid diseases, such as upper or lower respiratory infection, allergic rhinitis, gastro-esophageal reflux or obesity, chronic cardiovascular or pulmonary diseases, acute asthma attack during the last 4 weeks were excluded. The control group was selected from healthy children. Ethics Committee of the Institution approved the study and informed consent forms, signed by the parents, were obtained.

All of the children included in the study were subjected to full history-taking and complete physical examination performed by the same physician. Body height, body weight, heart rate, and blood pressure (BP) of all children were recorded. Mostor formula, $[\text{height (cm)} \times \text{weight (kg)}] / 3600]^{0.5}$ was used to calculate body surface area (BSA). Color Doppler transthoracic echocardiography applied by a single experienced pediatric cardiologist.

Brachial systolic (Ps) and diastolic (Pd) blood pressures were recorded using bilateral triplicate measurements on a rested subject using a validated oscillometric device in supine position.

Ejection fraction (EF) was calculated using the standard dimension cubed formula $\text{EF} = (\text{LVDD}^3 - \text{LVDS}^3) / \text{LVDD}^3$, where LVDD and LVDS stands for left ventricular dimension in diastole and systole, respectively. LV outflow tract (LVOT) diameter was measured at the base of aortic leaflet at parasternal long axis view in echocardiography. Time velocity integral for aortic valve (VTIAo) were obtained with continuous wave Doppler immediately below the aortic valve in the apical long axis view. Using LVOT and VTIAo, the stroke volume (SV) were calculated as: $\text{SV} = (\text{LVOT} / 2) \times \text{VTIAo} \times 3.141$. To compute Ees(sb), the equation developed by Chen adjusted by BSA in both groups was used: $\text{Ees(sb)} = \text{Ea} \times \text{BSA}$. Ea and Ees(sb) measurements were calculated as: $\text{SV} = \text{VTIAo} \times 3.141$. The correlation between spirometric findings and arterial and echocardiographic findings were performed by the same physician.

Table I: Comparison (mean ± SD) of clinical characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthmatic children</th>
<th>Healthy children</th>
<th>p-value*</th>
<th>Levene's test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>9.55±2.53</td>
<td>10.59±3.16</td>
<td>0.066</td>
<td>0.078</td>
</tr>
<tr>
<td>Male/female</td>
<td>22/18</td>
<td>45/52</td>
<td>0.314</td>
<td>&amp;</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>142.8±12.2</td>
<td>144.5±12.4</td>
<td>0.120</td>
<td>0.524</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>26.6±12.5</td>
<td>29.8±13.1</td>
<td>0.480</td>
<td>0.772</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>84.68±14.93</td>
<td>86.42±10.87</td>
<td>0.537</td>
<td>0.085</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>104.74±8.94</td>
<td>103.78±9.47</td>
<td>0.345</td>
<td>0.682</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>64.02±5.88</td>
<td>61.38±9.63</td>
<td>0.175</td>
<td>0.065</td>
</tr>
</tbody>
</table>

*Student's t-test, & Chi-square test, Levene's Test for equality of variances (p < 0.05), SD: Standard deviation.

Table II: Comparison (mean ± SD) of echocardiographic findings.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthmatic children</th>
<th>Healthy children</th>
<th>p-value*</th>
<th>Levene's test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ea/BSA (mmHg/ml/m²)</td>
<td>2.10±0.97</td>
<td>1.75±0.89</td>
<td>0.041</td>
<td>0.124</td>
</tr>
<tr>
<td>Ees(sb)/BSA (mmHg/ml/m²)</td>
<td>2.59±1.29</td>
<td>2.43±1.28</td>
<td>0.504</td>
<td>0.962</td>
</tr>
<tr>
<td>VAC</td>
<td>0.83±0.13</td>
<td>0.74±0.13</td>
<td>&lt;0.001</td>
<td>0.428</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>43.01±14.36</td>
<td>50.22±13.10</td>
<td>0.008</td>
<td>0.236</td>
</tr>
<tr>
<td>VTIAo (cm)</td>
<td>22.05±4.28</td>
<td>22.42±3.32</td>
<td>0.703</td>
<td>0.563</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.65±0.098</td>
<td>0.71±0.094</td>
<td>&lt;0.001</td>
<td>0.628</td>
</tr>
</tbody>
</table>

*Student's t-test, *Statistically significant (p < 0.05), Levene's Test for equality of variances (p=0.05). Ea: Arterial elastance, Ees(sb): Left ventricular elastance at end-systole derived by single beat, VAC: Ventriculo-arterial coupling, SV: Stroke volume, VTIAo: Time velocity integral for aortic valve, EF: Ejection fraction.

Table III: The correlation between spirometric findings and arterial and ventricular elastance in asthmatic children.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ea (mmHg/ml)</th>
<th>Ees(sb) (mmHg/ml)</th>
<th>FEV1</th>
<th>FVC</th>
<th>FEV1 / FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pb</td>
<td>-0.102</td>
<td>-0.057</td>
<td>0.418*</td>
<td>0.014</td>
<td>0.584**</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed). Pearson's correlation analyses (r = correlation coefficient), FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, PEF: Peak expiratory flow, Ea: Arterial elastance, Ees(sb): Left ventricular elastance at end-systole derived by single beat.

RESULTS

Forty pediatric patients (22 males and 18 females, (aged 7 - 12 years) selected randomly from those with bronchial asthma and 97 (aged 7.5 - 13.5 years) healthy subjects. The characteristics of the patients and the healthy subjects are shown in Table I. Blood pressure, heart rate, age, body height and weight were all nearly similar in both groups.

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Ea/BSA and ventriculo-arterial coupling (VAC) were higher in asthmatic children (p=0.041, p < 0.001, respectively), whereas Eesb/BSA was similar. SV and EF were lower in asthmatic group than healthy children (p=0.008, p=0.001, respectively). There was no difference regarding VTIao (Table II). There was no correlation between arterial and ventricular elastance and spirometric findings in asthmatic children (Table III).

DISCUSSION

Asthma is the most common cause of respiratory disorder among children and may affect many organs including the heart. The aim of the current study was to determine non-invasively the impact of asthma on cardiovascular status of the children. We previously showed that the arterial and LV elasticity decrease and stiffness increase by increasing the age of the healthy children and adolescents.12

All three parameters (Ea, Ees and VAC) reflect different aspects of left ventricle hemodynamic, and should be used in LV performance assessment, accordingly. Left ventricular end-systolic elastance (Ees) is a major determinant of cardiac systolic function reflecting LV contractility. This study results did not find any relation which may exist between the severity and the duration of the disease and Ees.

Ea, as representative of arterial loading properties, is a more accurate parameter to assess arterial load on ventricular performance.11 Ea reflects afterload and sensitive to any kind of afterload changes such as blood pressure. In this study, Ea was increased among the asthmatic children adjusted by BSA which means that arterial stiffness was decreased in these individuals. It is known that Ea decreases with increasing age and BSA. Therefore, Ea was calculated after adjusting age and BSA.

Ea/Ees ratio is used as an index for assessment of cardiovascular performance and represents left ventricular efficiency.13 It was found that mean arterial elastance was significantly higher in the asthmatic children compared with controls. As a result of this higher arterial elastance, asthmatic children had higher Ea/Ees ratios, potentially suggesting a less favourable ventricular-arterial coupling resulting in less efficient cardiovascular function. The examination of the alterations in VAC with disease can yield mechanistic insights into the pathophysiology of the conditions and help increase the effectiveness of ongoing therapeutic interventions.14 SV and EF are used to calculate the VAC ratio and both these parameters were lower in asthmatic children.

In contrast to this study, Steinman et al. found that arterial stiffness increased in asthmatic children who expressed arterial stiffness as carotid-femoral pulse wave velocity.2 The authors could not find any correlation between arterial and left ventricular elasticity and pulmonary function among asthmatic patients. In a previous study, it was shown that increased arterial stiffness was correlated with the degree of the airflow obstruction in COPD patients.7 Weiler et al. studied arterial stiffness from peripheral large and small arteries; they did not find any difference between asthmatic and healthy subjects and there was positively a correlation between small arteries elasticity index and forced expiratory volume in 1 s (FEV1) in asthmatic adults.15 Sun et al. evaluated arterial stiffness by using brachial-ankle pulse wave velocity and they reported that arterial stiffness was elevated in stable asthma compared with control subjects in adults. There was a negative correlation between brachial-ankle pulse wave velocity and FEV1.3 Recently, Ulger et al. found any difference between asthmatic children and control group with regard to aortic stiffness parameters.16 Reduced lung function is associated with an increased incidence of cardiovascular disease, even after adjustment for the effects of traditional cardiovascular risk factors, particularly smoking.17 Ayer et al. suggested that lower lung volumes are associated with increased arterial stiffness in early childhood.18

The others have shown previously that inhaled corticosteroid/long acting beta agonist likely reduces arterial stiffness, and this reduction is greatest in those with the highest stiffness in adults.19 Beta agonists may also reduce arterial stiffness via nitric oxide synthesis and vasodilatation.20 In the current study, asthmatic children were using prophylactic inhaled corticosteroid; increased arterial elastance may be due to using inhaled corticosteroid. Otsuki et al. reported that carotid atherosclerosis was reduced in asthmatic adult patients treated with inhaled corticosteroids compared with matched controls, and they found that inhaled corticosteroids had protective effects against atherosclerosis as our suggestion.21 Bhatt et al. found no significant associations between markers of systemic inflammation and arterial stiffness in elderly COPD patients.22 Since inhaled corticosteroids exert a strong anti-inflammatory effect on airways, they represent the most effective agents for long-term disease control. On the other hand, corticosteroids also have some potential pro-atherogenic and metabolic effects such as the induction or worsening of hypertension, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia. Due to such effects, it has been proposed that the use of corticosteroids may associate with the development of atherosclerosis, although until now this connection has not been clearly established.23 Since there is an increased risk of atherosclerosis in inflammatory conditions, it may be that corticosteroids may somehow alleviate the atherosclerotic vascular diseases through
their anti-inflammatory properties. A cohort study from UK indicated that treatment with oral corticosteroids were associated with the risk of myocardial infarction, whereas inhaled corticosteroids were not increased risk of myocardial infarction in general population. On the other hand, another study showed inhaled corticosteroids were associated with decreased risk of acute myocardial infarction in asthmatic patients. These findings indicate inhaled corticosteroids might have properties that are protective against atherosclerosis whereas oral corticosteroids might have a role in atherosclerosis. Further investigations are recommended before and after using inhaled corticosteroid/beta-agonist by using this more sensitive and simple method to measure arterial and ventricular elastance in asthmatic children. Also considering the severity and the duration of the disease, it may be beneficial when it is comparing with the healthy individuals, because measuring arterial elastance and VAC are associated with increased cardiovascular risk and potential novel markers of adverse cardiovascular events in patients with asthma.

CONCLUSION

Although ventricular elastance did not change, arterial elastance and ventriculo-arterial coupling was increased in asthmatic children. This may be due to using prophylactic inhaled corticosteroid. Using inhaled corticosteroid could have protective effects against atherosclerosis.

REFERENCES