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Original article

Assessment of left ventricular diastolic function in bronchial asthma: can we rely on transmitral inflow velocity patterns?

Background: *Left ventricular (LV) diastolic dysfunction has been reported in bronchial asthma (BA), based on the finding of abnormal transmitral inflow velocities on Doppler echocardiography, and attributed to the use of long-term β_2-adrenoceptor agonists. However, these indices of LV filling may be affected by other factors.* ***Objectives:*** *We aimed to assess the effect of acute severe asthma in children on Doppler-derived transmitral inflow velocities and determine the factors influencing them.* ***Methods:*** *23 asthmatic children [14 males, 9 females; age 8.4±4.2 years] and 15 age- and sex-matched, healthy children [10 males, 5 females; age 9.8±4.3 years] were studied clinically, by spirometry and by echocardiography both during and after resolution of acute severe asthma. Pulsed Doppler-derived right ventricular (RV) systolic time intervals [RV pre-ejection period corrected for heart rate (RVEPc), RV ejection time corrected for heart rate (RVETc), acceleration time (AT)], transmitral inflow velocities [peak E velocity, peak A velocity, E/A ratio], and isvolumic relaxation time (IVRT) were measured.* ***Results:*** *During acute exacerbations of BA, patients had significantly shorter RVETc ($p<0.05$) and AT ($p<0.05$), significantly higher peak A velocity ($p<0.01$), significantly lower E/A ratio ($p<0.01$), and significantly higher IVRT (<0.05). A highly significant inverse correlation existed between AT and peak A velocity [$r= -0.634$ ($p<0.01$)] during acute asthma exacerbation but disappeared after its resolution.* ***Conclusion:*** *Transmitral inflow velocity patterns during acute severe asthma in children are suggestive of altered LV preload due to an acute transient elevation in pulmonary artery pressure secondary to the altered lung mechanics, and are not reflective of intrinsic LV diastolic dysfunction.*

Key words: Bronchial asthma, right ventricular systolic time intervals, left ventricular diastolic function, transmitral inflow velocity; echocardiography, children

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ABBREVIATIONS

BA	*Bronchial Asthma*
β_2-AG	*β_2-adrenoceptor agonists*
LV	*left ventricle*
FEV1	*Forced expiratory volume in the first second*
FVC	*Forced vital capacity*
FEF_{25-75}	*forced expiratory flow rate during the middle half of the FVC*
RPEP	*right ventricular preejection period*
RVET	*right ventricular ejection time*
AT	*acceleration time*
IVRT	*isovolumic relaxation time*
LVEDD	*left ventricular end diastolic diameter*

INTRODUCTION

Bronchial asthma (BA) has a wide clinical spectrum ranging from a mild intermittent disease to one that is severe, persistent, difficult to treat, and in some cases, fatal[1,2,3]. Cardiovascular affection in BA can be related directly to the acute severe asthma, which profoundly alters cardiovascular status and function[4,5], or secondary to drug therapy, especially β_2- adrenoceptor agonists (β_2-AG). Several studies suggest an association between selective β_2-AG and increased mortality in patients with BA[6,7], as well as a relevance of oral β_2-AG to acute cardiac death[8,9,10] and heart failure[11,12]. Children with acute severe asthma may develop ECG changes compatible with myocardial ischemia on continuous inhalation of fenoterol[13], and the use of beclomethasone alone or in combination with salmeterol resulted in a significant increase in CK-MB not associated with

clinical or ECG changes[14]. These studies implicate β_2-AG as a cause of cardiac dysfunction in BA.

Transmitral inflow velocity patterns[15] have been used to assess left ventricle (LV) diastolic function, and diastolic LV dysfunction has been reported in BA[16,17]. These velocity-derived indices are sensitive to filling impairment in many types of heart disease[18,19,20,21] but their interpretation can be difficult because they are influenced not only by changes in the intrinsic LV diastolic properties, but also by age, heart rate, valvular disease, loading conditions, and contractility of both ventricular and atrial myocardium[22,23,24]. Additionally, the relationship between right ventricular ejection profile and transmitral inflow velocity patterns in BA has not been studied. The purpose of this study was to assess the effect of acute severe asthma on transmitral inflow velocity patterns and determine the factors influencing these Doppler-derived indices in asthmatic children.

METHODS

This prospective study was carried out on 23 known asthmatic children [14 males; 9 females] following up at the Chest clinic, the Children's Hospital, Ain Shams University hospitals, and presenting in an attack of acute severe asthma. Their ages ranged from 3 years to 17 years [mean age: 8.4 ±4.2 years]. A group of 15 apparently healthy age and sex matched children [10 males; 5 females], with ages ranging from 3 years to 16 years [mean age: 9.8 ±4.3 years] were studied as a control group. Informed parental consent was obtained in all cases, as well as consent from the older children. The study protocol was ethically approved by the Departmental Meeting of the Paediatric Department, Ain Shams University. Patients presenting in severe, life-threatening attacks of bronchial asthma were excluded from the study, as were those with known history of cardiac disease, associating pulmonary disease, or signs of concurrent infection.

Patients were classified according to the asthma severity[25] as either moderate persistent asthma [n=11(48%)], or severe persistent asthma [n=12(52%)]. Sixteen (70%) patients were on both regular inhaled steroids and regular inhaled short-acting β_2-agonists. Five patients were on regular leukotriene inhibitors (22%), 4 of whom were also on regular inhaled steroids and regular inhaled short-acting β_2-agonists

Patients were assessed clinically and placed on the following scoring systems: Accessory muscle score; Wheeze score; and Dyspnea score[26]. Accordingly, the severity of the presenting attack of acute severe asthma was determined as mild in 8 [35%]; moderate in 6 [26%]; and severe in 9 [39%] patients[25]. The demographic data of the studied groups are illustrated in table (1).

Spirometric functions:

Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and forced expiratory flow rate over 25 to 75 of the FVC (FEF_{25-75}) were measured in 19 patients; Actual and predicted values for age, sex, weight, and height were obtained for each parameter, and percentages from predicted values were calculated. Four patients below 5 years of age were too young to be able to perform the test.

Echocardiographic examination:

Two dimensional (2D), M-mode, pulsed wave (PW), continuous wave (CW) and colour Flow (CF) Doppler echocardiographic examination was performed for all patients during the acute asthma exacerbation (Esaote S.P.A Model 7250, Italy). All measurements were calculated from an average of 3 consecutive cardiac cycles.

- M-mode parameters:

The following parameters were measured: left ventricular end diastolic diameter (LVEDD) and end systolic diameter (LVESD); interventricular septum thickness in diastole (IVSd) and systole (IVSs); left ventricular posterior wall thickness in diastole (LVWd) and systole (LVWs); Aortic root diameter (AO); Left atrial diameter (LAD); Percentage of fractional shortening (FS%) [=LVEDD –LVESD/LVEDD][27]; Ejection fraction (EF%) by the Tiechholtz method for assessment of LV volume [= (End diastolic volume –End systolic volume/ End diastolic volume) x 100][28] .

- Doppler derived measurements:

a. Right ventricular systolic time intervals:

Right ventricular pre-ejection period (RPEP), right ventricular ejection time (RVET), and acceleration time (AT) were measured from pulsed Doppler interrogation of the pulmonary flow by methods previously described, and both RPEP and RVET were corrected for heart rate (RPEPc, RVETc)[29]. The following ratios were then calculated: AT/RVET; RPEP/RVET[27].

b. Transmitral inflow velocities:

Peak E velocity, peak A velocity, E/A ratio, and E deceleration time were measured from pulsed Doppler of the transmitral flow in the four chamber apical view with the sample volume at the point of opening of the mitral leaflets. Isovolumic relaxation time (IVRT) was measured from continuous wave

Doppler interrogation of the LV inflow and outflow with the transducer positioned at the cardiac apex [27]. Eighteen patients were available for follow up at least 4 weeks after resolution of the acute exacerbation of asthma. All were clinically free of symptoms and signs during the follow up assessment. Fourteen patients were able to perform the spirometric tests, whilst 4 patients were too young (<5 years). The same echocardiographic parameters listed previously were measured.
The control group (n=15) was studied using the same clinical, spirometric and echocardiographic parameters. Spirometric function tests were performed by 13 patients. Two patients were too young to be able to perform the manoeuvre properly.

Statistical analysis:
Standard computer program SPSS for Windows, release 10.0 (SPSS Inc, USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD). Comparison of different variables in various groups was done using student t test and Mann Whitney test for normal and nonparametric variables respectively. Comparisons of multiple subgroups were done using ANOVA and Kruskall Wallis tests for normal and nonparametric variables respectively. Paired t or Wilcoxon signed ranks tests were used to compare variables before and after therapy. Pearson's and Spearman's correlation tests were used for correlating normal and non-parametric variables respectively. For all tests a probability (p) less than 0.05 was considered significant[30]. Graphic presentation of the results was also done.

RESULTS

During the acute exacerbation of asthma there was no significant difference between patients and controls in heart rate (92.6±15.8 vs 92.3±9 [p>0.05]). Patients had significantly higher respiratory rates (RR) and significantly lower percentage of predicted values for FEV1, FVC and FEF_{25-75} than controls. Following resolution of the acute exacerbation, the patients continued to exhibit significantly lower values for all three spirometric variables when compared to controls (table 2).

Left ventricular systolic functions were normal in patients both during and after resolution of the acute asthma exacerbation and showed no significant difference when compared to the control group. LVEDD was significantly smaller in patients compared to controls, both during and after resolution of the acute asthma (table 2).

During the acute exacerbation of asthma, patients had significantly shorter AT ($p<0.05$) and lower AT/RVET ratio ($p<0.01$) than controls (table 2). These differences became statistically insignificant after resolution of the acute attack.

A significant positive correlation was found between FEF_{25-75} and AT/RVET ($r=0.553$; $p<0.05$) during acute severe asthma but disappeared after resolution of the acute attack.

As regards the transmitral velocity parameters, only peak E velocity was significantly lower ($p<0.05$) in patients compared to controls during acute asthma (0.86±0.12 vs 1.06±0.52 [$p<0.05$]).

Paired analysis of data of the 18 patients studied both during and after resolution of the acute asthma exacerbation (table 3) demonstrated that RVETc and AT were both significantly shorter during the acute attack ($p<0.05$; $p<0.05$). Peak E velocity was lower during the acute attack, but the difference was not statistically significant. Conversely, Peak A velocity was significantly higher during the acute exacerbation of bronchial asthma ($p<0.01$). Both resulted in a significant reduction in E/A ratio during the acute exacerbation compared to E/A ratio after resolution of the attack ($p<0.01$). Additionally, during the acute exacerbation patients had shorter E wave deceleration time ($p<0.05$), and longer IVRT ($p<0.05$) (table 3) (figure 1).

Correlation analysis demonstrated a highly significant negative correlation between AT and peak A velocity ($p<0.01$) and between RVETc and peak A velocity ($p<0.05$) and a highly significant positive correlation between RVETc and E/A ratio ($p<0.01$) during acute exacerbations of asthma. This correlation disappeared after resolution of the acute asthma exacerbation (figure 2).

Subgroup analysis showed no significant difference between patients on regular inhaled steroids and β_2-agonists and patients not on regular inhaler therapy in any of the studied parameters. Peak E and A velocities, E/A ratio, and IVRT were also unaffected by the grade of asthma (moderate vs. severe persistent asthma) or the severity of the presenting attack (mild, moderate or severe).

Table 1. Demographic Data of Patient and Control Groups.

Parameter		**Patients (n=23)**	**Controls (n=15)**	**Statistical test**
Age (yr)	Mean±SD (Range)	8.4 ± 4.2 (3 – 17)	9.8 ±4.3 (3 – 16)	t = 0.954 (p>0.05)
Males	n (%)	14 (61)	10 (67)	
Females	n (%)	9 (39)	5 (33)	
Male: Female ratio		1.6:1	2:1	$\chi^2 = 0.131$ (p>0.05)
Duration of asthma (yr)	Mean±SD (Range)	6.6 ± 3.9 (2 – 15)	----	----
Grade of asthma				
Moderate persistent	n (%)	11(48)	----	----
Severe persistent	n (%)	12 (52)	----	----
Severity of acute attack				
Mild	n (%)	8 (35)	----	----
Moderate	n (%)	6 (26)	----	----
Severe	n (%)	9 (39)	----	----
Medications				
Regular inhaled steroids and Inhaled β_2- AG	n (%)	12 (52.2)	----	----
Regular Steroids and inhaled β_2- AG and antileukotrienes	n (%)	4 (17.4)	----	----
Antileukotrienes alone	n (%)	1 (4.3)	----	----
No regular therapy	n (%)	6 (26.1)	----	----

β_2- AG: β_2- adrenoceptor agonists.

Table 2. Clinical, spirometric and echocardiographic data of patients in acute severe asthma and controls.

	Patients during Attack (n=23)	**Controls (n=15)**	**Statistical Test**	
			t	**p**
Heart rate (bpm)	92.6 (±15.8)	92.3 (±9.0)	0.06	>0.05 (NS)
SBP (mmHg)	103 (±12.2)	110.3 (±9.0)	2.07*	<0.05 (S)
DBP (mmHg)	69.1 (±7.3)	67.7 (±7.8)	0.654*	>0.05 (NS)
RR (brpm)	36.3 (7.0)	24.1 (±2.5)	4.518*	<0.001 (HS)
	(n=19)	**(n=13)**		
FEV 1 (%)	54.4 (±14.2)	94.1 (±2.25)	4.69*	<0.001 (HS)
FVC (%)	62.4 (±11.8)	83.2 (±2.62)	4.092*	<0.001 (HS)
FEF25-75 (%)	49.9 (±19.0)	105.8 (±6.22)	4.693*	<0.001 (HS)
	(n=23)	**(n=15)**		
LVEDD (cm)	3.6 (±0.57)	4.2 (±0.52)	3.24	<0.05 (S)
LVESD (cm)	2.1 (±0.46)	2.5 (±0.38)	2.69	<0.05 (S)
EF(%)	70.9 (±5.9)	70.1 (±6.9)	0.35	>0.05 (NS)
FS (%)	39.4 (±4.4)	39.5 (±5.35)	0.06	>0.05 (NS)
AO (cm)	1.9 (±0.31)	2.0 (±0.27)	1.29	>0.05 (NS)
LAD (cm)	2.4 (±0.40)	2.5 (±0.5)	1.164	>0.05 (NS)
RPEPc	97.8 (±19.5)	101.6 (±9.22)	0.68	>0.05 (NS)
RVETc	382.6 (±17.6)	390.9 (±14.4)	1.52	>0.05 (NS)
AT (msec)	92.8 (±22.7)	117 (±20.7)	3.32	<0.05 (S)
AT/RVET	0.30 (±0.05)	0.37 (±0.05)	2.986*	<0.01 (HS)
RPEP/RVET	0.21 (±0.06)	0.21 (±0.03)	0.14*	>0.05 (NS)
Peak E velocity (m/sec)	0.86 (±0.12)	1.06 (±0.52)	2.228*	<0.05 (S)
Peak A velocity (m/sec)	0.60 (±0.14)	0.53 (±0.1)	1.73	>0.05 (NS)
E/A ratio	1.5 (±0.5)	1.8 (±0.25)	1.78	>0.05 (NS)
E deceleration (msec)	122.1 (±77.8)	130.9 (±46.5)	1.18*	>0.05 (NS)
IVRT (msec)	52.4 (±13.5)	51.2 (±2.82)	0.33	>0.05 (NS)

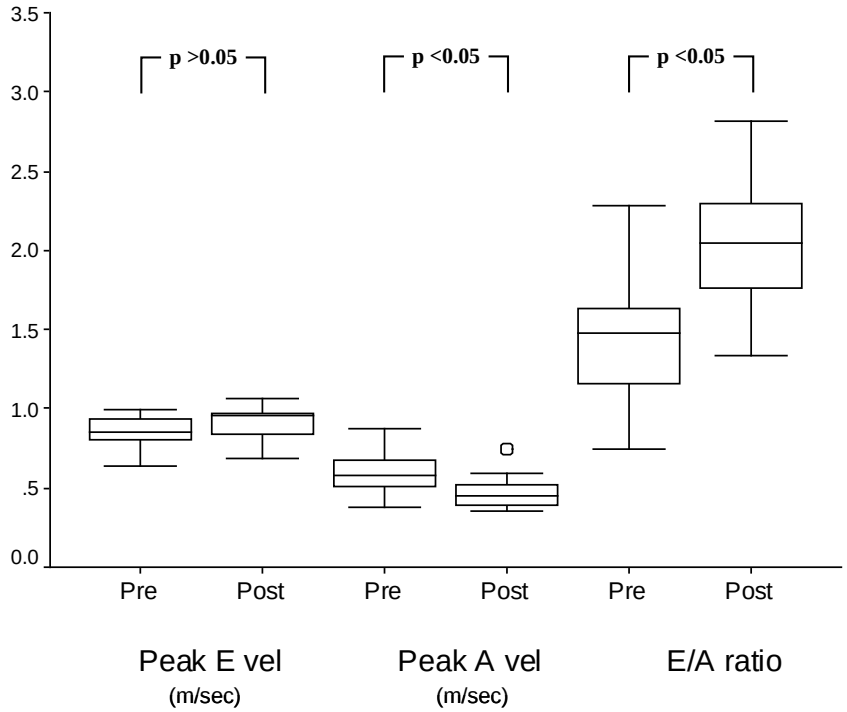
* z value: Mann Whitney test for non-parametric data
Ao: aortic diameter; AT: acceleration time; bpm: beats per minute; brpm: breaths per minute; DBP: diastolic blood pressure; EF: ejection fraction; FEF_{25-75}: percentage of predicted forced expiratory flow rate during the middle half of the FVC; FEV_1: percentage of predicted forced expiratory volume in the first second; FS: percentage of fractional shortening; FVC: percentage of predicted forced vital capacity; HR: heart rate; HS: highly significant; IVRT: isovolumic relaxation time; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; RPEPc: right ventricular preejection period corrected for heart rate; RR: respiratory rate; RVETc: right ventricular ejection time corrected for heart rate; S: significant; SBP: systolic blood pressure.

Table 3. Comparison between patients during acute asthmatic exacerbation and after its resolution

	Patients during Attack (n=18)	Patients in-between attacks (n=18)	Statistical test	
			t	p
Heart rate (bpm)	90±16.5	83±9.4	1.61	0.05 (NS)
SBP (mmHg)	102.7±11.8	102.7±12.3	0*	0.05 (NS)
DBP (mmHg)	68.9±6.76	67.2±8.26	1.134*	0.05 (NS)
RR (brpm)	37±6.9	23.3±1.1	3.682*	<0.001 (HS)
FEV 1 (%)	54.8±12.7	80±10.1	3.299*	<0.01 (HS)
FVC (%)	63.6±11.6	76.6±9.8	2.512*	<0.05 (S)
FEF25-75 (%)	51.9±18.5	75.7±19.9	3.211*	<0.01 (HS)
LVEDD (cm)	3.6±0.63	3.7±0.55	1.177	0.05 (NS)
LVESD (cm)	2.2±0.43	2.3±0.35	1.95	0.05 (NS)
EF (%)	71.3±5.9	67.4±5.7	1.85	0.05 (NS)
FS (%)	39.7±4.3	36.7±4.8	1.85	0.05 (NS)
AO (cm)	1.9±0.3	1.9±0.3	0.59	0.05 (NS)
LAD (cm)	2.35±0.43	2.4±0.4	0.0924	0.05 (NS)
RPEPc	95.7±21.1	98.3±8.6	0.573	0.05 (NS)
RVETc	381.2±19.3	394.9±19.7	2.669	<0.05 (S)
AT (msec)	94.2±23.74	109.8±28.3	2.293	<0.05 (S)
AT/RVET	0.31±0.06	0.33±0.07	1.613*	0.05 (NS)
RPEP/RVET	0.21±0.07	0.21±0.03	0.259*	0.05 (NS)
Peak E velocity (m/sec)	0.85±0.1	0.92±0.1	1.722*	0.05 (NS)
Peak A velocity (m/sec)	0.6±0.14	0.47±0.1	3.36	<0.01 (HS)
E/A ratio	1.5±0.4	2.05±0.4	3.733	<0.01 (HS)
E deceleration (msec)	118.5±68.1	157.1±65.3	2.047*	<0.05 (S)
IVRT (msec)	51.9±9.5	45.2±7.8	2.137	<0.05 (S)

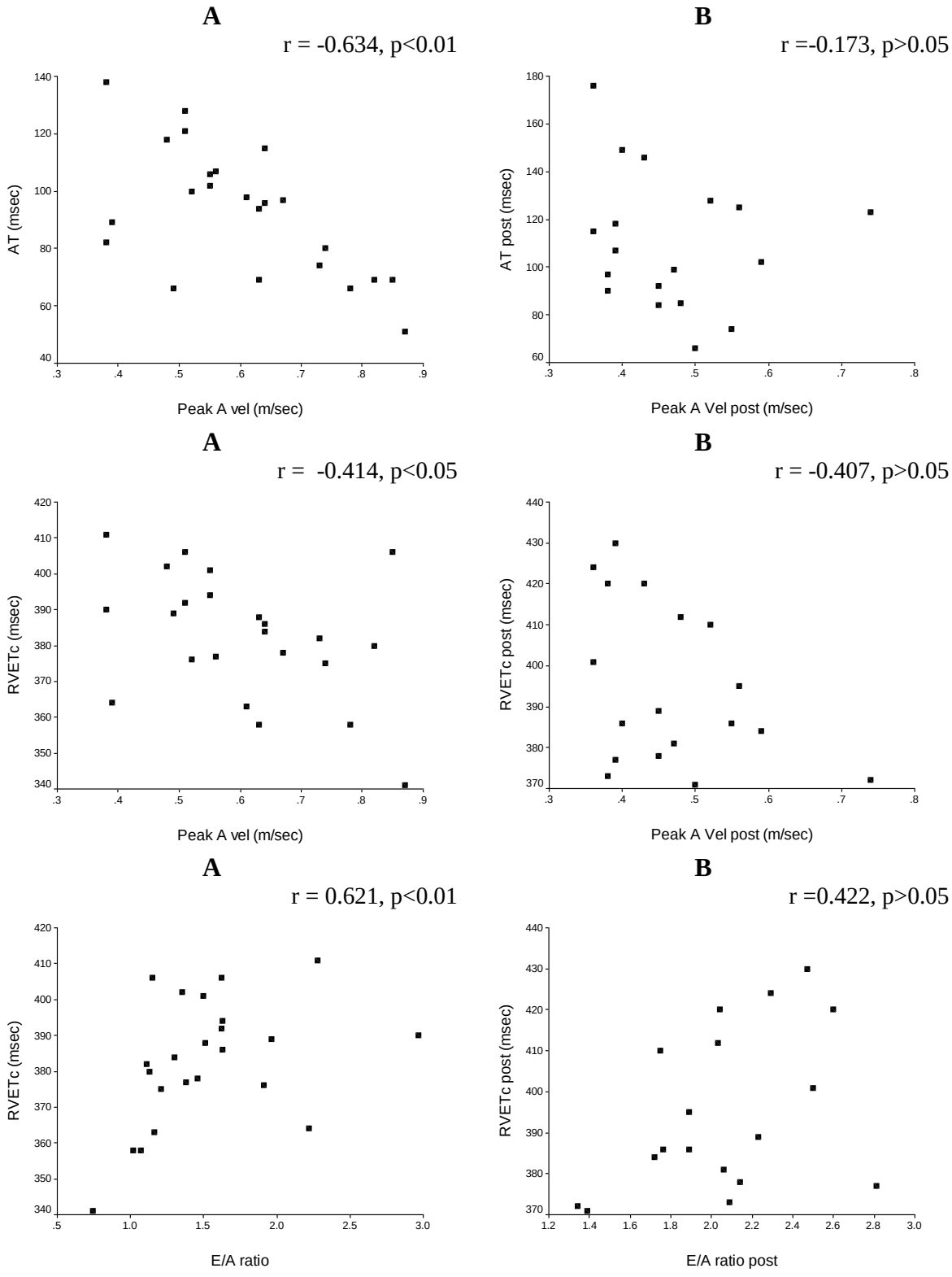
*z value: Wilcoxon signed ranks test for paired non-parametric data

Ao: aortic diameter; AT: acceleration time; bpm: beats per minute; brpm: breaths per minute; DBP: diastolic blood pressure; EF: ejection fraction; FEF_{25-75}: percentage of predicted forced expiratory flow rate during the middle half of the FVC; FEV_1: percentage of predicted forced expiratory volume in the first second; FS: percentage of fractional shortening; FVC: percentage of predicted forced vital capacity; HR: heart rate; HS: highly significant; IVRT: isovolumic relaxation time; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; RPEPc: right ventricular preejection period corrected for heart rate; RR: respiratory rate; RVETc: right ventricular ejection time corrected for heart rate; S: significant; SBP: systolic blood pressure.



Peak E vel: peak E velocity; Peak A vel: peak A velocity

Figure 1. Comparison between patients during (A) and after resolution of (B) acute severe asthma as regards peak E velocity, peak A velocity and E/A ratio.



AT: Acceleration time; RVETc: right ventricular ejection time corrected for heart rate

Figure 2. Correlations between AT and peak A velocity, RVETc and peak A velocity, and RVETc and E/A ratio during the acute attack (A) and after its resolution (B).

DISCUSSION

Acute severe asthma resulted in characteristic alterations in the transmitral inflow velocity patterns in children, which were reversible with resolution of the acute attack. Of particular note was the statistically significant increase in the atrial contribution to left ventricular filling as evidenced by the significantly higher peak A velocity during the attack, with a resultant significant drop in E/A ratio. However, these findings were not statistically significant when compared to healthy controls, and therefore could not be considered abnormal.

Our study demonstrated that, during an attack of acute severe asthma in children, peak E velocity was lower, E deceleration time shorter, Peak A velocity higher, E/A ratio lower, and IVRT longer than after its resolution. This pattern of diastolic filling is consistent with slower LV isovolumic pressure fall, decreased early diastolic filling and increased filling with atrial contraction[31], and a shift in the proportion of blood entering the LV away from early diastole to late diastole. Although this pattern is usually taken as indicative of impaired LV relaxation[27], it can also be consistent with decreased LV preload [32]. Prompt reversibility of impaired LV compliance confirms the assumption of a functional rather than a structural change of the LV myocardium[33]. Our study demonstrates that the changes in transmitral inflow velocity patterns were transient, reversible and directly related to the acute exacerbation of bronchial asthma. Therefore we believe that they are not due to intrinsic myocardial LV diastolic dysfunction but a reflection of changes in LV preload.

With increasing heart rates, the proportion of blood entering the ventricle during atrial contraction is increased[34]. However, there was no significant difference in the patients' heart rate during, and after resolution of, the acute attack in our study, and it therefore appears unlikely that changes in heart rate were responsible for our findings.

In our study we demonstrated that children in acute severe asthma had significantly shorter AT and lower AT/RVET ratios than healthy controls. On resolution of the acute attack, these parameters were no longer significantly different from controls. Both AT and AT/RVET ratio are decreased when the pulmonary artery pressure is elevated[35,36]. In BA pulmonary artery pressure may be increased due to lung hyperinflation[37] or exaggerated respiratory effort[38], impeding pulmonary blood flow. We found a significant positive correlation between FEF_{25-75} and AT/RVET during the acute attack, further supporting the premise that the altered pulmonary functions secondary to acute severe asthma result in elevated pulmonary artery pressure. Our findings indicate an acute, transient elevation in pulmonary artery pressure during acute asthma.

The significant negative correlation between pulmonary artery AT and RVETc and peak A velocity during acute severe asthma demonstrated in our study suggests that altered pulmonary blood flow pattern secondary to acute severe asthma contributes to the transmitral inflow velocity pattern recorded in our patients. To our knowledge, this is the first time this relationship has been demonstrated in asthmatic children.

It is important to note that in our study the LV inflow pattern abnormalities were related to an increase in pulmonary artery pressure, which in turn is directly related to the severity of airway obstruction as confirmed by the significant correlation between peak A velocity and AT and AT/RVET ratio, and AT/RVET and FEF_{25-75}, respectively.

Impairment of diastolic filling may also be related to impediment to rapid filling as a result of leftward interventricular septal shift and distortion of early diastolic geometry, similar to what is reported in chronic obstructive lung disease (COPD) patients[39] due to the phenomenon of ventricular interdependency[40,41,42]. This can explain the lowered LV end-diastolic diameters found in our patients. Further studies which would include RV function and area change would be of value in further clarifying this.

A previous study[16] reported LV diastolic dysfunction in patients with BA after long-term intake of oral β_2-AG, based solely on transmitral inflow velocity patterns. Incidentally, we could find no difference in transmitral inflow velocity patterns between patients on regular inhaled β_2-AG and those not receiving inhaled β_2-AG. In view of our findings, which suggest that factors other than intrinsic LV diastolic dysfunction can cause the altered transmitral inflow velocity patterns in BA, and in addition to the important role of β_2-AG therapy in BA[43], it seems prudent to search for alternative, non-preload dependent measurements to either confirm, or refute, the effect of long-term oral β_2-AG use on LV diastolic function. Tissue Doppler imaging (TDI) provides a superior method for the identification of patients with impaired LV relaxation[44], and investigators now suggest that that it is relatively independent of loading and superior to conventional mitral Doppler indices in the assessment of LV relaxation[45,46,47]. Future TDI studies might yield important information on myocardial relaxation patterns in BA.

In conclusion, we describe a transient reversible change in the transmitral inflow velocity patterns in children in acute severe asthma, which appears related to elevation of pulmonary artery pressure and deterioration of spirometric functions. We believe that this is a reflection of altered LV preload secondary to the effect of altered lung mechanics on the right sided structures and altered right ventricular function, rather than a reflection of altered intrinsic LV diastolic functions. Interpretation of transmitral inflow velocity patterns and their use as a reflection of LV diastolic function in bronchial asthma should therefore be done with extreme caution, taking into account all the variables that might influence them.

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