

Evaluation of pulmonary artery stiffness in newly diagnosed adult patients with asthma

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Background: There are limited studies on the effects of asthma on cardiac function. Right ventricular dysfunction and pulmonary hypertension are cardiovascular complications that may be seen in advanced stages of the disease. Pulmonary artery stiffness (PAS), is a promising, relatively new echocardiographic index that has been reported to increase in right ventricular failure, providing information about pulmonary vascular bed.

Aim: In this study, we aimed to evaluate PAS, a marker of pulmonary artery elasticity, in adult-onset asthma.

Methods: Ninety-nine nonsmokers who had a new asthma diagnosis between the ages of 18 and 65 years and 97 healthy controls with similar age and sex distribution were included in the study. PAS was calculated by dividing the maximal frequency shift of pulmonary flow (MFS) in pulmonary acceleration time (PAT).

Results: Clinical and demographic characteristics of both groups were similar ($P > 0.05$). PAS values were higher in the asthma group than in the control group (25.2 ± 4.5 vs 22.4 ± 4.1 , $P < 0.001$). TAPSE was lower in the case group (24.9 ± 2.0 vs 25.5 ± 2.1 , $P = 0.043$), while RV MPI was higher (0.36 ± 0.07 vs 0.32 ± 0.06 , $P < 0.001$). In the multivariate linear regression analysis, RV MPI, RV Em, and TAPSE variables were independent predictors of PAS.

Conclusion: In our study, PAS values were higher in patients with newly diagnosed adult asthma and we found a significant weak correlation between PAS values and subclinical right ventricular dysfunction.

KEYWORDS

adult asthma, echocardiography, pulmonary artery stiffness, right ventricular function

1 | INTRODUCTION

Asthma is a disease characterized by chronic airway inflammation, which is accompanied by persistent structural changes in the airways in some cases that cause airflow restriction. In clinical episodes, shortness of breath, wheezing, and often accompanied cough are observed.¹ While affecting an estimated 300 million individuals worldwide, it is an important global health problem that is increasingly widespread in many developing countries, which can be seen in all age groups.^{2,3}

The incidence of cardiovascular disease and arrhythmia in asthma patients was higher than in the normal population.^{4,5} With repeated hypoxia attacks, inflammatory mediators that are released due to chronic inflammation cause structural changes in the pulmonary vascular vessels. This process leads to pulmonary hypertension (PHT), right ventricular systolic and diastolic dysfunction in later stages of the disease.^{6,7}

Pulmonary arterial stiffness (PAS) is a relatively new noninvasive echocardiographic index developed to assess the structural features

and functions of the pulmonary vascular bed. In primary bronchopulmonary diseases, hypoxia-induced changes may cause PAS to increase by triggering remodeling in the pulmonary vascular structure. Increased PAS values have been reported to contribute to right ventricular dysfunction by increasing right ventricular afterload. In various diseases affecting the right heart, this index was found to be higher than the normal healthy population.⁸⁻¹⁴

There is a limited number of studies on cardiovascular complications of asthma. These studies have shown that asthma affects cardiac functions from early stages.^{6,7,15} A study examining the elastic properties of the pulmonary artery and its association with ventricular function in patients with asthma has not been done before. In this study, we aimed to evaluate PAS (an indicator of pulmonary artery elasticity) and cardiac functions and the relationship between these in newly diagnosed asthma by a noninvasive method echocardiography in order to find out whether PAS could be a useful echocardiographic marker for early detection of cardiovascular complications due to asthma.

2 | MATERIALS AND METHOD

Between September 2016 and November 2017, 97 patients with a diagnosis of new asthma who were admitted to Mehmet Akif İnan Education and Research Hospital chest diseases outpatient clinic with complaints of shortness of breath were enrolled in our prospective observational study. The diagnosis of asthma was based on the criterias of Global initiative for Asthma guidelines (GINA), taking into account the results of the pulmonary function tests (PFT) and clinical findings of the patients by the pulmonologist.¹⁶ A total of 97 patients with similar age and sex without any disease were selected for the control group. PFT was applied to all patients according to the

European Respiratory Society consensus standards by the same technician. All patients were then referred to the cardiology outpatient clinic for further evaluation including electrocardiography and echocardiography. Routine biochemical blood analysis was performed on the same day as the outpatient evaluation. Patients with a history of cardiovascular or any systemic disease, history of drug use, smoking, and patients under 18 years of age and over 65 years of age were excluded from the study. All patients in the study group were diagnosed with mild intermittent asthma and applied had complaints of dyspnea for at least 6 months. Study received ethical approval by Harran University Ethics Committee, and all subjects voluntary signed the informed consent forms after study principles were explained to them.

2.1 | Standard echocardiography and pulmonary artery stiffness index

Echocardiographic examination was performed by two cardiologists experienced in echocardiography unaware of the clinical data of all study patients with Philips iE33 (Andover, Md., USA) device using a 3.5 MHz adult probe in the left lateral decubitus position. The recordings consisted of three cardiac cycles, accompanied by a single derivation electrocardiogram. Parasternal long axis, short axis, apical four-chamber and two-chamber images were taken, and assessed by M-mode, 2-D, continuous wave Doppler and tissue Doppler (TDI) method in accordance with American Society of Echocardiography guidelines.¹⁷ Early (E) and late (A) mitral and tricuspid flow velocities, E/A ratio, and deceleration time were measured. In apical four-chamber imaging, systolic, early diastolic and late diastolic velocities were taken on septal, lateral, and tricuspid annulus using TDI. Isovolumic contraction time (ICT), acceleration time, isovolumic relaxation time (IRT), and ejection time (ET) were calculated. The TDI values of left ventricle (LV) were calculated using

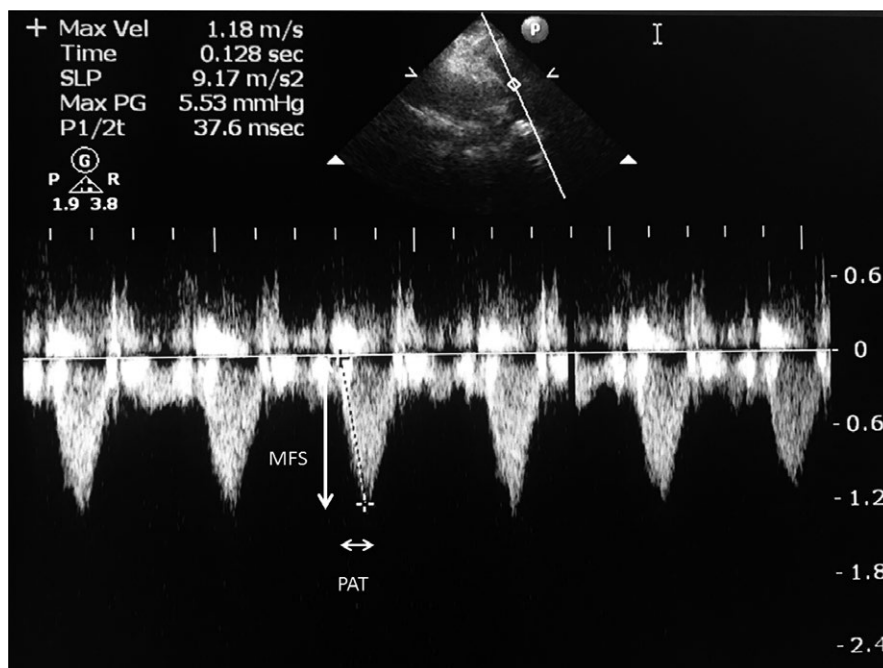


FIGURE 1 Pulmonary artery stiffness (PAS) was calculated from the ratio of maximal frequency shift of pulmonary flow (MFS) to pulmonary acceleration time (PAT)

TABLE 1 Clinical, laboratory, and pulmonary function test data of the study population

	Patients (n = 97)	Controls (n = 97)	P value
Age (years)	25.6 ± 4.0	25.2 ± 4.2	0.489
Male (n)	63	61	0.906
BMI (kg/m ²)	25.4 ± 1.9	25.0 ± 2.2	0.311
SBP (mmHg)	121.6 ± 6.9	120.5 ± 7.1	0.488
DBP (mmHg)	78.3 ± 6.4	76.9 ± 8.0	0.455
Heart rate (beats/minute)	78 ± 10	76 ± 9	0.256
HsCRP (mg/dL)	0.54 ± 0.38	0.41 ± 0.33	0.009
Leukocytes (G/l)	7.24 ± 0.44	6.92 ± 0.48	0.421
Hemoglobin (g/dL)	13.7 ± 1.9	14.1 ± 1.1	0.179
PEF	82.6 ± 11.4	85.3 ± 6.7	0.158
FEV ₁	91.7 ± 10.5	95.5 ± 9.3	0.024
FVC	87.5 ± 8.3	90.7 ± 7.8	0.015
FEV ₁ /FVC	98.1 ± 11.4	101.2 ± 9.1	0.175

BMI = body mass index, DBP = diastolic blood pressure, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, hsCRP = high sensitive C-reactive protein, PEF = peak expiratory flow, SBP = systolic blood pressure.

Bolded data indicate significance.

the arithmetic mean of the measurements taken from the lateral and septal, mitral annulus. The values were determined by taking the average of three consecutive beats. The right ventricular (RV) myocardial performance index (MPI) was then calculated using the formula $ICT+IRT/ET$. Tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode by placing the cursor on tricuspid lateral to the annulus and the motion of lateral side of the tricuspid valve annulus from apical four-chamber to apex was measured in mm during right ventricular systole.

In the parasternal short axis view, PAS was calculated using the measurements from the pulse Doppler trace obtained from the pulmonary flow at one cm distal to the pulmonary valve annulus.

PAS was calculated according to the formula mentioned below:

$PAS \text{ (kHz/sec)} = \text{maximal frequency shift of pulmonary flow (MFS)/pulmonary acceleration time (PAT)}$ (Figure 1).

PAT was corrected by RR interval.

2.2 | Statistical analysis

For statistical evaluation, SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA) was used. The results were expressed as mean ± standard deviation or frequency and percentages. Shapiro-Wilks test was applied to examine the normal distribution of continuous variables. Univariate comparison of continuous variables with normal distribution was performed using independent *t* test. Pearson correlation analysis was applied to analyze the correlation between PAS and other parameters. Multilinear regression analysis was performed to determine the

TABLE 2 Two-dimensional, Doppler, and tissue Doppler echocardiography data of the study population

	Patients (n = 97)	Controls (n = 97)	P value
LV EDD (mm)	45.5 ± 3.7	44.9 ± 3.6	0.339
IVS thickness (mm)	9.7 ± 0.4	9.4 ± 0.7	0.548
LV EF (%)	65.6 ± 3.5	66.2 ± 3.4	0.179
RA diameter (mm)	31.9 ± 2.5	31.5 ± 2.3	0.521
Mitral E (cm/s)	85.8 ± 8.3	83.7 ± 8.8	0.412
Mitral A (cm/s)	67.9 ± 8.8	65.1 ± 8.0	0.392
Mitral E/A	1.26 ± 0.23	1.28 ± 0.21	0.442
Tr. E (cm/s)	68.3 ± 9.5	68.7 ± 7.2	0.745
Tr. A (cm/s)	53.0 ± 8.8	52.1 ± 7.1	0.411
Tr. E/A	1.31 ± 0.20	1.34 ± 0.20	0.431
RV Sm (cm/s)	13.1 ± 3.1	13.5 ± 2.2	0.427
RV Em (cm/s)	11.9 ± 2.0	13.0 ± 2.3	0.003
RV Am (cm/s)	11.4 ± 1.9	12.2 ± 1.9	0.007
RV IVRT (ms)	47.1 ± 8.6	43.3 ± 5.9	0.004
RV MPI	0.36 ± 0.07	0.32 ± 0.06	<0.001
TAPSE (mm)	24.9 ± 2.0	25.5 ± 2.1	0.043
sPAP (mmHg)	23.9 ± 4.1	23.1 ± 3.6	0.238
MFS (kHz)	2.36 ± 0.32	2.22 ± 0.34	0.007
PAT (msec)	95 ± 16	101 ± 18	0.025
PAS (kHz/s)	25.2 ± 4.5	22.4 ± 4.1	<0.001

Am = late myocardial diastolic velocity, EF = ejection fraction, Em = early myocardial diastolic velocity, IVRT = isovolumetric relaxation time, IVS = interventricular septum, LV: left ventricle, LV EDD = LV end-diastolic dimension, MFS = maximal frequency shift, MPI = myocardial performance index, PAS = pulmonary artery stiffness, PAT = pulmonary acceleration time, RA = right atrium, RV = right ventricle, TAPSE = tricuspid annular plane systolic excursion, Tr. = Tricuspid, Sm = systolic myocardial velocity, sPAP = systolic pulmonary artery pressure. Bolded data indicate significance.

independent relationship between the parameters showing significant correlation and PAS. Receiver operating characteristic (ROC) analysis was performed to determine the sensitivity and specificity of PAS, and to determine the cutoff values to discriminate subjects with asthma. A value of $P < 0.05$ was considered significant.

3 | RESULTS

In our study, the data of a total of 194 patients were analyzed, including 97 asthmatic patients (63 males, 64.9%) and 97 control groups (61 males, 62.8%). Demographic, clinical, laboratory, and pulmonary function testing data of the groups are presented in Table 1. All asthmatic patients are at a mild stage of disease. The hsCRP level in the asthma group was found to be higher than the control group (0.54 ± 0.38 vs 0.41 ± 0.33 , $P = 0.009$). In addition, demographic and clinical characteristics of the groups are similar ($P = 0.05$).

	Bivariate correlation		Multivariate analysis	
	<i>r</i>	<i>P</i>	B (% 95CI)	<i>P</i>
Tr. E/A	−0.019	0.797		
RV Sm (cm/s)	−0.135	0.071		
RV Em (cm/s)	−0.211	0.004	−0.163 (−0.602; −0.061)	0.017
RV Am (cm/s)	−0.087	0.245		
RV IVRT (ms)	0.109	0.144		
RV MPI	0.286	<0.001	0.131 (0.054;0.207)	0.039
TAPSE (mm)	−0.432	<0.001	−0.445 (−1.238; −0.667)	<0.001
sPAP (mmHg)	0.329	<0.001		
PEF	0.092	0.222		
FEV ₁	0.021	0.785		
FVC	0.034	0.651		
FEV ₁ /FVC	−0.010	0.897		

Am = late myocardial diastolic velocity, Em = early myocardial diastolic velocity, FEV₁ = forced expiratory volume in 1 second, FVC = forced vital capacity, IVRT = isovolumetric relaxation time, MPI = myocardial performance index, PEF = peak expiratory flow, RV = right ventricle, TAPSE = tricuspid annular plane systolic excursion, Tr. E, Tr. A, Tr. E/A, RV Sm, and systolic pulmonary artery pressure (sPAP) values were similar in both groups ($P > 0.05$).

Bolded data indicate significance.

TABLE 3 Evaluation of variables associated with pulmonary artery stiffness

Echocardiographic measurements of the study population are summarized in Table 2. RV Em, RV Am, and RV IVRT values were significantly lower in the asthma group compared to control group. TAPSE measurements were also lower in the patient population (24.9 ± 2.0 vs 25.5 ± 2.1 , $P = 0.043$). RV MPI and PAS parameters were statistically significantly higher in the case group (0.36 ± 0.07 vs 0.32 ± 0.06 , $P < 0.001$, 25.2 ± 4.5 vs 22.4 ± 4.1 , $P < 0.001$ respectively). Mitral E, mitral A, mitral E/A, Tr. E, Tr. A, Tr. E/A, RV Sm, and systolic pulmonary artery pressure (sPAP) values were similar in both groups ($P > 0.05$).

Correlation analysis showed significant, weak positive correlation between PAS and RV Em ($r = -0.211$, $P = 0.004$) and TAPSE ($r = -0.432$, $P < 0.001$) significant, weak negative correlation between PAS and RV MPI ($r = 0.286$, $P < 0.001$) and sPAP ($r = 0.329$, $P < 0.001$) (Table 3, Figure 2). These parameters were included in the multivariate linear regression analysis using the backward method and their role in determining PAS was evaluated. As a result of this analysis RV MPI, RV Em and TAPSE variables were independently associated with PAS (Table 3). We did not detect any correlation with PAS in the analysis with PFT parameters.

When we performed ROC analysis of PAS to detect the presence of asthma, the area under the curve (AUC) value for PAS was 0.679 (95% CI: 0.601–0.756; $P < 0.001$). Above the cutoff value of 23.31, the sensitivity and specificity values were 68.9% and 64.4%, respectively.

4 | DISCUSSION

To the best of our knowledge, PAS was evaluated for the first time in literature using echocardiographic method in asthmatic patients in this study. It was observed that in patients with nondrug user,

nonsmoker, and newly diagnosed asthma, PAS values were increased in comparison to healthy populations. RV MPI, RV Em, and TAPSE were determined as independent indicators of PAS in multiple linear regression analysis.

PAS is a relatively new Doppler echocardiographic parameter and is a method developed to assess pulmonary artery stiffness and distensibility noninvasively.⁸ The gold standard method in PAS evaluation is invasive measurements performed by right heart catheterization. Noninvasive methods with echocardiography, CT and MRI have been developed due to the difficulty of clinical application of invasive methods. Among these methods, echocardiography seems to be more advantageous in clinical use because of the ease of use, low cost, and no need for radiation and contrast agent exposure.^{10,18} How primary pulmonary diseases (OSAS, COPD, asthma, etc.) affect heart functions is a complex mechanism. But in all these diseases, including asthma, the main mechanism is hypoxia-induced changes.^{7,19} Recurrent hypoxia attacks in asthma lead to structural changes by triggering remodeling in the airways with chronic inflammation. These structural changes in the pulmonary vascular bed increase right ventricular afterload which contributes to impaired RV performance and remodeling.²⁰

Although the relationship between them has not been fully explained, it was reported that the increase in PAS is an important factor contributing to RV afterload and eventual RV failure.²¹ Echocardiographically measured PAS was increased in studies performed with patients with diseases affecting right heart function.^{8–14} In this population, pulmonary diseases affecting the right heart, especially OSAS and COPD, may cause right heart dysfunction without PHT.^{10,18,22} We found that TAPSE, RV Em, RV Am were lower, RV MPI and RV IVRT were higher in our study. In our study population,

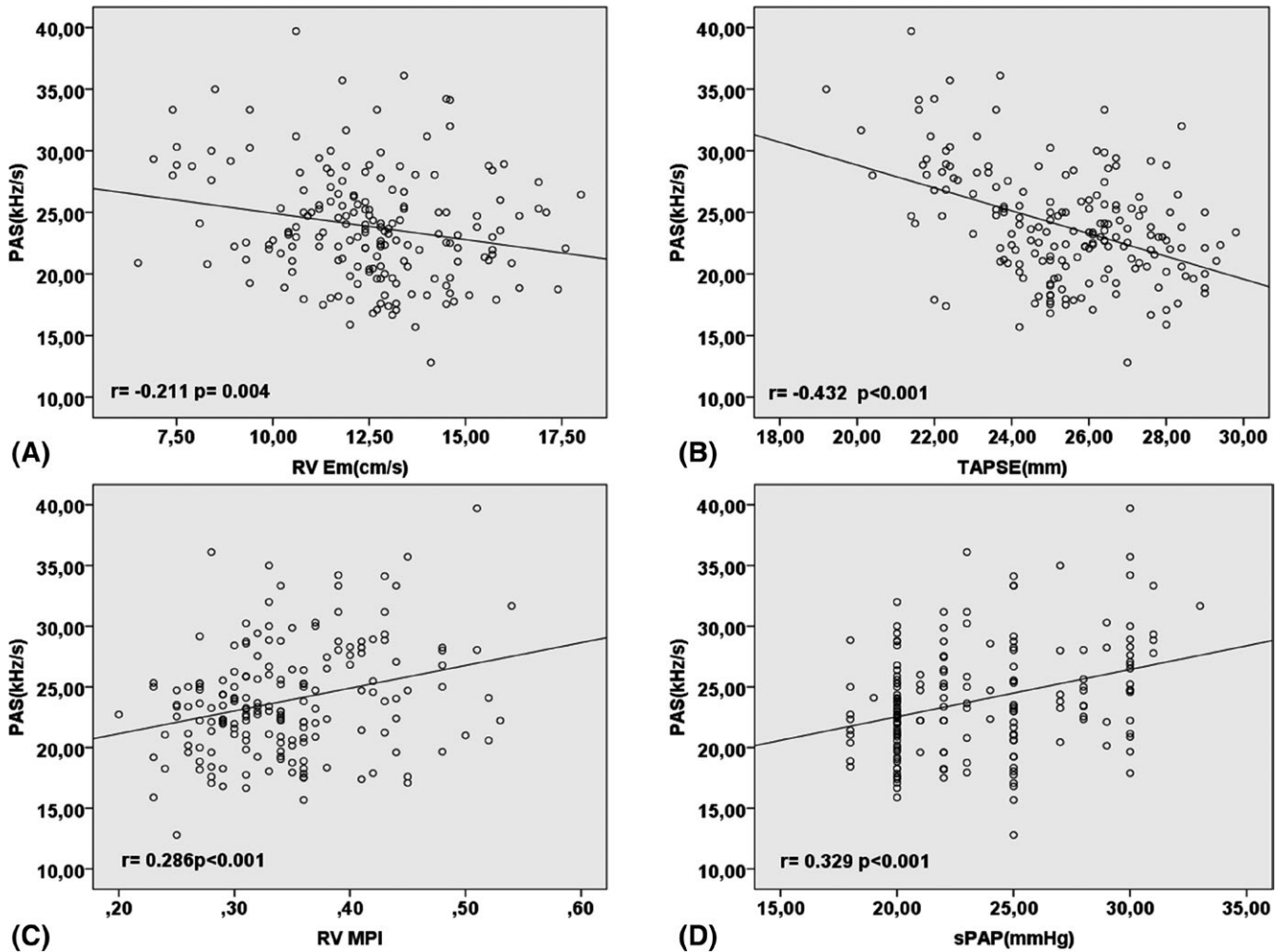


FIGURE 2 Scatter dot plots for correlation analysis between (A) PAS and RV Em (B) PAS and TAPSE (C) PAS and RV MPI (D) PAS and sPAP. Em = early myocardial diastolic velocity, MPI = myocardial performance index, PAS = pulmonary artery stiffness, RV = right ventricle, sPAP = systolic pulmonary artery pressure

there was not any patient with PHT. De-Paula et al.¹⁵ reported similar results in mild-moderate asthma patients. In this study, we found that PAS was higher in early stage asthmatic patients with subclinical right ventricular dysfunction than in controls. We did not find any study that evaluated PAS in asthmatic patients before. Similarly, Özkeçeci et al.¹¹ also found higher PAS values in OSAS patients without PHT. We also found that there was a significant but weak association between PAS and echocardiographic parameters that inform us about right ventricular functions such as RV Em, RV MPI, and TAPSE in the correlation analysis we performed. This suggests that pulmonary artery stiffness is increased due to vascular involvement in the pulmonary artery early in asthmatic patients and this increase may play a role in the development of subclinical right ventricular dysfunction without PHT.

We obtained low specificity, sensitivity, and AUC values in our ROC analysis which was performed to determine the diagnostic potential of PAS in the assessment of patients with asthma. These results make us to conclude that PAS has a poor diagnostic value in the diagnostic evaluation of asthma patients.

PHT is a serious complication of asthma and may develop in later stages of the disease. Asthma-induced chronic inflammation and recurrent hypoxia cause structural changes and remodeling of the pulmonary vascular bed. In the early stages of the disease, endothelial dysfunction develops and in the following stages, the proliferation of smooth muscle cells and the accumulation of matrix proteins in the vascular wall trigger to deteriorate the elastic structure of the pulmonary artery.^{6,7,19,20,23,24} Pulmonary artery stiffness increases and distensibility decreases. The resistance in the pulmonary vascular bed increases and then pulmonary artery pressure increases. All of these could lead to the development of PHT in later stages.^{25,26} In previous studies, the relationship between sPAP and PAS was determined.^{8,27} In our study, we found a significant weak relationship between sPAP and PAS. In addition, we found that PAS was an independent variable in predicting SPAP in linear regression analysis. All these findings suggest clinicians that PAS may be a parameter to guide clinicians in predicting PHT development in asthma.

We did not determine any association between PAS and PFT parameters in our correlation analysis. Also, correlations between

PAS and RV Em, RV MPI, TAPSE, sPAP were weak and specificity, sensitivity, and AUC values obtained from ROC analysis were low. The reason for these may be that we only enrolled mild stage, newly diagnosed asthmatic patients in our study. Again, because of this, we could not evaluate whether there would be an increase in PAS values with progression to advanced stages of the disease. However, the results of our study make us to think that echocardiographic assessment of PAS may give clinicians an idea about right ventricular function in asthmatic patients from the early phase.

4.1 | Limitations

There are a few limitations in our study. First of all, our patient group includes only mild asthma patients. Therefore, we can not comment on the PAS values in the advanced stages of the disease. In addition, right heart catheterization, which is a gold standard method for assessing pulmonary artery stiffness, pulmonary artery pressure, and right ventricular functions, was not performed and the use of echocardiography in evaluating these parameters is another limitation of our study. Our study did not benefit from some echocardiographic validation with right pulmonary artery M-mode dmax/dmin or relative area. Also, the reproducibility of the echocardiographic technique was not evaluated and there is not a certain consensus about the normal range of PAS measured by this echocardiographic method.

5 | CONCLUSION

In our study, we found higher PAS values in patients with mild asthma who were newly diagnosed, who did not receive any medication, and who did not smoke than control group and detected a significant but weak correlation between PAS and subclinical right ventricular dysfunction in our study population. Based on these findings, we suggest that echocardiographic estimates of PAS may be applied to provide additional information to clinicians in detecting subclinical right ventricular dysfunction in the early stage of asthma. In order to prove the feasibility of this in clinical use, prospective controlled studies with more advanced stage patients, large populations and long-term clinical follow-up are needed.

CONFLICT OF INTEREST

None of the authors has a conflict of interest to declare. All support for this study came from institutional and departmental resources.

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