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Right ventricular-pulmonary arterial uncoupling in mild-to-moderate asthma

Betul Banu Karasu, MD^a and Hatun Temel Aydıncak, MD^b

^aDepartment of Cardiology, Etimesgut Sehit Sait Erturk State Hospital, Ankara, Turkey; ^bDepartment of Chest Diseases, Etimesgut Sehit Sait Erturk State Hospital, Ankara, Turkey

ABSTRACT

Objective: Persistent pulmonary hypertension and resulting right ventricular (RV) failure are highly encountered phenomenon in severe pulmonary diseases. However, in this study, we aimed to examine the effects of mild-to-moderate asthma on RV functions, pulmonary arterial stiffness (PAS), and coupling of RV to the pulmonary artery (PA) in the absence of overt pulmonary hypertension.

Methods: We enrolled 53 patients with mild-to-moderate asthma, and 50 healthy control subjects. A comprehensive two dimensional transthoracic echocardiography was performed on each individual. The parameters measuring RV function were all examined. PAS was calculated by dividing maximal frequency shift of pulmonary flow by pulmonary acceleration time. RV-PA coupling was estimated by the tricuspid annular plane systolic excursion (TAPSE) to pulmonary artery systolic pressure (PASP) ratio (TAPSE/PASP).

Results: Baseline demographics, clinical and laboratory parameters of both groups were similar ($p > 0.05$). Most of conventional echocardiographic parameters measuring RV function were impaired in patients with asthma compared to control subjects. PAS values were significantly higher in the asthma group [24 (21–26) vs. 20 (18–22), $p < 0.001$], and TAPSE/PASP ratio was significantly lower in the asthma group versus the control group [0.81 ± 0.08 vs. 0.96 ± 0.11 , $p < 0.001$]. Multilinear regression analysis revealed PAS, TAPSE, and PASP as independent predictors of TAPSE/PASP ratio.

Conclusion: Mild-to-moderate asthma was shown to be associated with both subclinical RV dysfunction and increased PAS values. TAPSE/PASP ratio was also markedly decreased, suggesting RV-PA uncoupling even in the absence of overt pulmonary hypertension. PAS referring RV afterload was shown to be an independent predictor of TAPSE/PASP ratio.

Abbreviations: A: Late diastolic flow; A': Late myocardial diastolic velocity; DT: Deceleration Time; E: Early diastolic flow; E': Early myocardial diastolic velocity; EDD: End-diastolic diameter; ESA: End systolic area; ET: Ejection time; IVCT: Isovolumic contraction time; IVRT: Isovolumic relaxation time; IVS: Interventricular septum; LV: Left ventricle; LVEDD: LV end-diastolic dimension; LVEF: LV ejection fraction; LVEDS: LV end systolic dimension; LVpw: LV posterior wall thickness; MFS: Maximal frequency shift; MPI: Myocardial performance index; PA: Pulmonary artery; PAS: Pulmonary arterial stiffness; PASP: Pulmonary artery systolic pressure; PAT: Pulmonary acceleration time; RV: Right ventricle; RV EDA: RV end diastolic area; RV ESA: RV end systolic area; RV FAC: RV fractional area change; S': Systolic myocardial velocity; TAPSE: Tricuspid annular plane systolic excursion

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Introduction

The pulmonary vasculature is unique with its high-flow, low pressure and low resistance features. This circuit mainly differs from systemic circulation in terms of having much less vascular smooth muscle with the resultant decrease in the basal tone, the absence of autoregulation property and the type of response to hypoxia. Although systemic arteries dilate in hypoxic conditions, vasoconstriction occurs as a response to

hypoxia in the pulmonary vasculature. And in diseases where the hypoxia persists over a long time period, pulmonary vasoconstriction may initiate pulmonary vascular remodeling resulting in pulmonary hypertension (1,2).

Asthma is a commonly encountered chronic lung disease with a hypoxic nature. However, there are only a handful of studies revealing the effects of asthma on the cardiovascular system, and they are mainly

related to atherosclerosis or arrhythmia (3–5). Currently, the right ventricle (RV) is emerging as a particular area of focus, as this region forms a functional unit with lung circulation, and reflects the severity of diseases affecting this circulation. As a result, RV dysfunction, as well as pulmonary hypertension, are considered key hemodynamic abnormalities that determine the prognosis and treatment modalities of chronic lung diseases (6,7). Until recently, however, the importance of RV was largely unrecognized, so the number of studies exploring its function in patients with asthma remains quite limited (8,9).

Assessment and quantification of RV function is possible with various imaging techniques. In particular, two dimensional echocardiography is often the first line, as it is the simplest, and due to its widespread availability, safety, and noninvasive nature, it may become the only imaging tool in some situations. The echocardiographic assessment of RV functions is provided by commonly used parameters recommended in guidelines from the American Society of Echocardiography (10). However, each of these parameters has some disadvantages due to complex ventricular geometry, irregular heart beats, and angle or load dependency. Given these limitations, single use of each parameter avoids accurate quantification of RV function as a whole. As a result, Guazzi et al. proposed combining some parameters to provide an effective physiology-based approach. For example, the relationship of tricuspid annular plane systolic excursion (TAPSE) versus pulmonary arterial systolic pressure (PASP) has emerged as an index evaluating the RV and its coupling to the pulmonary artery (PA) (10–13).

This index has been validated as a reliable and important prognostic parameter in several clinical studies, and has even been identified as an echocardiographic surrogate of catheterization-based RV-PA coupling (11). Despite the well known pathophysiologic importance of RV-PA coupling, previous studies exploring the RV functions in asthma have focused on the RV and PA separately (8,9).

With this background, the need for a more integrated and physiology-based approach is noticed. Therefore, in addition to the assessment of RV functions with standard echocardiographic parameters, we aimed to investigate the TAPSE/PASP ratio as a key measure questioning the RV-PA coupling in patients with uncomplicated mild-moderate asthma.

Materials and methods

This single-center, prospective and observational study was conducted in our hospital between December 2019

and March 2020. Fifty-five patients who were being followed in our Chest Diseases outpatient clinic with the diagnosis of mild-moderate asthma were enrolled. For the control group, 50 healthy individuals with similar age, body mass index (BMI), and sex distribution were selected. Asthma was diagnosed by the pulmonologist according to the criteria of Global Initiative for Asthma Guidelines (GINA), which were based on the clinical findings and results of pulmonary function tests (14). The patients with asthma were grouped as follows: <5 years (Group 1), 5–10 years (Group 2), and ≥10 years (Group 3) according to their duration of asthma. All participants underwent a detailed cardiovascular and systemic examination, pulmonary function test, 12-lead electrocardiogram, and transthoracic echocardiography. Exclusion criteria included: being under 18 years of age, or over age 65; presence of pulmonary hypertension, heart failure, cerebrovascular disease, coronary artery disease, peripheral artery disease, moderate to severe valvular heart disease, diabetes mellitus, hypertension (confirmed by ambulatory blood pressure monitoring), obesity, chronic kidney disease, chronic liver disease, active infection, chronic lung disease rather than asthma, malignancy, collagen vascular disease, pregnancy, smoking, suboptimal echogenicity, or history of an acute asthma exacerbation within the preceding four weeks.

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. Written informed consent was obtained from each participant.

Pulmonary function tests

Each individual underwent a pulmonary function test, which was performed by the same technician applying the European Respiratory Society Consensus standards/American Thoracic Society guidelines (15). Measurements were obtained in a sitting position to ensure consistency of technique. The following parameters were acquired: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), forced expiratory volume in 1 s/forced vital capacity ratio (FEV1/FVC) and peak expiratory flow (PEF).

Transthoracic echocardiography

Transthoracic echocardiography was performed by an experienced cardiologist who was blinded to the patients' clinical status. Philips HD 11 XE (Andover, US) device was used for the echocardiographic assessment while the patient was lying in the left lateral decubitus position. Parasternal long axis, short axis, apical four-chamber and two-chamber views were

examined with the acquisition of M-mode, two dimensional, color doppler, pulsed-continuous wave doppler and tissue doppler images in accordance with American Society of Echocardiography and European Association of Echocardiography guidelines (16,17). Three consecutive cardiac cycles with simultaneous electrocardiographic monitoring were acquired for each echocardiographic parameter. The arithmetic mean of these three cycles was calculated to determine the value of each parameter. Both left ventricle (LV) and RV functions were taken into consideration with a comprehensive evaluation.

Interventricular septum (IVS), LV posterior wall thickness (LVpw), LV end-diastolic dimension (LVEDD) and LV end systolic dimensions (LVESD) were derived from M-mode measurements on parasternal long axis views. LV ejection fraction (LVEF) was measured by modified Simpson's method. LV and RV diastolic filling indices, including early (E) and late (A) mitral and tricuspid flow velocities, E/A ratio and deceleration time (DT), were obtained from apical four chamber view using the pulsed wave doppler. Myocardial wall motion properties including systolic (S'), early diastolic (E') and late diastolic (A') velocities were calculated through septal, lateral and tricuspid annulus via tissue doppler imaging. Isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), acceleration time, and ejection time (ET) were recorded to determine the myocardial performance index (MPI) of both ventricles. MPI was calculated by the formula of (IVRT+IVCT)/ET.

RV end diastolic area (RV EDA) and RV end systolic area (RV ESA) were assessed from the RV-focused apical four chamber view in order to calculate RV fractional area change (RV FAC). The following formula was used: $100 \times (\text{RV EDA} - \text{RV ESA}) / \text{RV EDA}$. Tricuspid annular plane systolic excursion (TAPSE) was examined by an apical four chamber view by placing the M-mode cursor on the lateral side of the tricuspid annulus to measure the excursion distance between end-diastole and end-systole. Pulmonary artery systolic pressure (PASP) was calculated by adding the estimated right atrial pressure to the transtricuspid gradient derived from tricuspid regurgitation velocity by using the Bernoulli formula: Transtricuspid pressure gradient: $4 \times \text{Tricuspid regurgitation velocity}^2$. RV-PA coupling was determined using a parameter of RV function against PA pressure. The formula of TAPSE/PASP was used as a measure to define the RV-PA coupling.

Pulmonary acceleration time (PAT) and maximal frequency shift (MFS) were obtained in the parasternal short axis view by measuring Doppler flow trace of pulsed

wave Doppler ultrasound placed at the PA just 1 cm distal to the pulmonary valve annulus. Pulmonary arterial stiffness (PAS) was calculated by the following formula: PAS (kHz/sec) = MFS of pulmonary flow/PAT (18).

Statistical analysis

Continuous variables that are normally distributed were expressed as mean $\pm$ standard deviation, while non-normally distributed continuous variables were presented as the median with interquartile range (IQR, range from the 25th percentile to the 75th percentile). Categorical variables were expressed as frequency and percentage, and were compared applying the χ^2 test. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Comparisons of the normally distributed continuous variables between groups were performed by independent samples t-test. The Mann-Whitney U test was used to compare non-normally distributed continuous variables. Differences among three groups were evaluated with one-way analysis of variance (ANOVA). *Post hoc* analysis was carried out by Tukey test. Spearman's correlation analysis was applied to demonstrate the correlations between non-normally distributed continuous variables. Multilinear regression analysis was performed to determine independent association of significantly correlated parameters with RV-PA coupling. Receiver operating characteristic (ROC) curve analysis was used to identify the sensitivity, specificity, and optimum cutoff levels of PAS and RV-PA coupling to distinguish between the patients with asthma and normal cases.

Two tailed $p < 0.05$ was considered statistically significant. SPSS statistical package (version 20.0, SPSS, Chicago, IL, USA) was used for the statistical analysis.

Results

Of the 55 patients with mild-moderate asthma, two cases were excluded due to suboptimal echogenicity. As a result, we enrolled 53 patients (56.6% female) with a mean age of 48.53 ± 8.68 years in the asthma group, and 50 individuals (56% female) with a mean age of 48.20 ± 7.98 years in the control group. Baseline demographic and clinical characteristics of the study groups are presented in Table 1. The groups did not differ significantly in terms of age, sex, BMI, systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin level and leukocyte count ($p > 0.05$). FEV1, FVC, FEV1/FVC, and PEF values were found to be significantly lower in the asthma group ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p = 0.002$ respectively).

Table 1. Baseline demographic, clinical, laboratory, and pulmonary function test data of the patients and control subjects.

	Patients (n=53)	Controls (n=50)	P value
Age (years)	49.53 ± 8.69	48.20 ± 7.98	0.422
Female (n, %)	30 (56.6)	28 (56)	0.951
BMI (kg/m ²)	27.12 ± 2.27	26.39 ± 1.88	0.830
SBP (mmHg)	122.64 ± 5.40	121.14 ± 6.06	0.187
DBP (mmHg)	80.41 ± 8.41	81.54 ± 6.41	0.449
HR (beats/minute)	79.36 ± 7.74	77.46 ± 7.80	0.218
FEV ₁	85.43 ± 5.75	93.24 ± 6.90	<0.001*
FVC	82.85 ± 5.71	89.42 ± 5.41	<0.001*
FEV ₁ /FVC	85.45 ± 7.51	96.38 ± 8.62	<0.001*
PEF	80.98 ± 5.15	84.56 ± 6.06	0.002*

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, FEV₁: forced expiratory volume in 1 s, FVC: forced vital capacity, PEF: peak expiratory flow. Values are presented as mean ± SD or number and percentage.

*Indicates significance.

Table 2. Two-dimensional, Doppler and tissue Doppler echocardiographic data of the patients and control subjects.

	Patients (n=53)	Controls (n=50)	P value
LVEDD (mm)	4.69 ± 0.34	4.56 ± 0.40	0.074
LVESD (mm)	3.11 ± 0.30	3.06 ± 0.29	0.399
IVS (mm)	0.97 ± 0.10	1.00 ± 0.75	0.065
LVpw (mm)	0.94 ± 0.10	0.94 ± 0.09	0.918
LVEF (%)	62.16 ± 3.72	61.30 ± 3.26	0.217
Mitral E (cm/s)	90.01 ± 10.18	88.31 ± 8.87	0.368
Mitral E/A	1.06 ± 0.13	1.02 ± 0.11	0.121
DT (ms)	187.81 ± 10.80	190.06 ± 10.70	0.291
LV IVRT (ms)	88.66 ± 8.13	87.78 ± 7.80	0.577
LV E' (cm/s)	14.15 ± 1.39	13.98 ± 1.25	0.528
LV A' (cm/s)	10.96 ± 1.30	11.19 ± 1.24	0.370
LV S' (cm/s)	9.76 ± 1.30	9.96 ± 1.37	0.440
LV MPI	0.40 ± 0.02	0.39 ± 0.02	0.179
PAT (ms)	97.17 ± 10.03	104.00 ± 9.42	0.001*
PAS (kHz/s)	24.00 (21–26)	20.00 (18–22)	<0.001*
RV EDA (cm ²)	12.97 ± 2.02	14.20 ± 1.45	0.001*
RV ESA (cm ²)	7.94 ± 1.45	8.34 ± 1.18	0.131
RV FAC (%)	38.33 ± 4.73	41.68 ± 3.34	<0.001*
Tricuspid E (cm/s)	64.97 ± 5.42	65.39 ± 4.35	0.671
Tricuspid E/A	1.08 ± 0.11	1.07 ± 0.10	0.709
RV IVRT (ms)	53.26 ± 9.45	47.86 ± 10.33	0.007*
RV E' (cm/s)	12.54 ± 1.26	13.20 ± 1.01	0.004*
RV A' (cm/s)	11.35 ± 0.97	11.71 ± 1.24	0.098
RV S' (cm/s)	12.83 ± 1.15	13.01 ± 1.06	0.422
RV MPI	0.41 ± 0.02	0.36 ± 0.02	<0.001*
TAPSE (mm)	15.80 ± 1.03	18.40 ± 1.58	<0.001*
PASP (mmHg)	19.50 (19–20.30)	19.00 (18.5–20)	0.213
TAPSE/PASP (mm/mmHg)	0.81 ± 0.08	0.96 ± 0.11	<0.001*

LV: left ventricle, EDD: end-diastolic diameter, IVS: interventricular septum, LVpw: LV posterior wall, LVEF: LV ejection fraction, DT: deceleration time, IVRT: isovolumic relaxation time, E': early myocardial diastolic velocity, A': late myocardial diastolic velocity, S': systolic myocardial velocity, MPI: myocardial performance index, PAT: pulmonary acceleration time, PAS: pulmonary artery stiffness, RV: right ventricle, EDA: end diastolic area, FAC: fractional area change, TAPSE: tricuspid annular plane systolic excursion, PASP: pulmonary artery systolic pressure. Values are presented as mean ± SD and median (range from the 25th percentile to the 75th percentile).

*Indicates significance.

Echocardiographic findings of two groups are summarized in Table 2. There were no significant differences between groups for the various parameters regarding LV structure and functions. With respect to RV structure and functions, the following significant results were obtained: Tricuspid early diastolic

flow (E), late diastolic flow (A), E/A ratio, RV ESA, RV A', RV S' and PASP were similar between the two groups ($p > 0.05$). PAT, RV E', RV EDA, RV FAC, TAPSE, and TAPSE/PASP were significantly lower in the asthma group ($p = 0.001$, $p = 0.004$, $p = 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$ respectively). PAS, RV IVRT, and RV MPI were found to be significantly higher in the asthma group ($p < 0.001$, $p = 0.007$ and $p < 0.001$, respectively).

TAPSE/PASP differed significantly among asthmatic patients and was inversely proportional to duration of asthma [0.87 ± 0.08 (Group 1) vs. 0.80 ± 0.05 (Group 2), $p = 0.003$; 0.87 ± 0.08 (Group 1) vs. 0.75 ± 0.05 (Group 3), $p < 0.001$; 0.80 ± 0.05 (Group 2) vs. 0.75 ± 0.05 (Group 3), $p = 0.025$]. It was the lowest for patients who had asthma more than 10 years (Figure 1). Although, all patients had either mild or moderate asthma, the duration of asthma may reflect some aspect of asthma severity related with the underlying chronic and systemic inflammatory process.

Correlation analysis showed significant positive correlations between TAPSE/PASP and FEV₁ ($r = 0.394$, $p < 0.001$); FVC ($r = 0.309$, $p = 0.002$); FEV₁/FVC ($r = 0.461$, $p < 0.001$); PEF ($r = 0.250$, $p = 0.011$); RVEDA ($r = 0.257$, $p = 0.009$) and TAPSE ($r = 0.852$, $p < 0.001$). Also, there were significant negative correlations between TAPSE/PASP and RVIVRT ($r = -0.285$, $p = 0.003$), RVMPI ($r = -0.653$, $p < 0.001$); PASP ($r = -0.553$, $p < 0.001$) and PAS ($r = -0.787$, $p < 0.001$) (Figure 2). After subjecting the variables correlating with TAPSE/PASP to multilinear regression analysis, we detected that PAS ($\beta = -0.097$, $p = 0.013$), TAPSE ($\beta = 0.788$, $p < 0.001$), and PASP ($\beta = -0.411$, $p < 0.001$) were independently associated with TAPSE/PASP.

The ROC analysis was performed to detect the diagnostic ability of PAS and TAPSE/PASP to predict asthma. We found the following results: Area under curve (AUC) for PAS was 0.805 (95% CI: 0.723–0.888, $p < 0.001$) with a cut off value of >22.5 , sensitivity of 0.679, and specificity of 0.780. The AUC for TAPSE/PASP was 0.876 (95% CI: 0.812–0.940, $p < 0.001$) with a cut off value <0.875 , sensitivity of 0.792, and specificity of 0.780 (Figure 3).

Discussion

This study demonstrates that the parameters including RV E', RV IVRT, RVMPI, RVFAC and TAPSE are impaired, which confirms the presence of subclinical right ventricular dysfunction in patients with mild-moderate asthma compared to healthy individuals. PAS is worsened in patients with asthma,

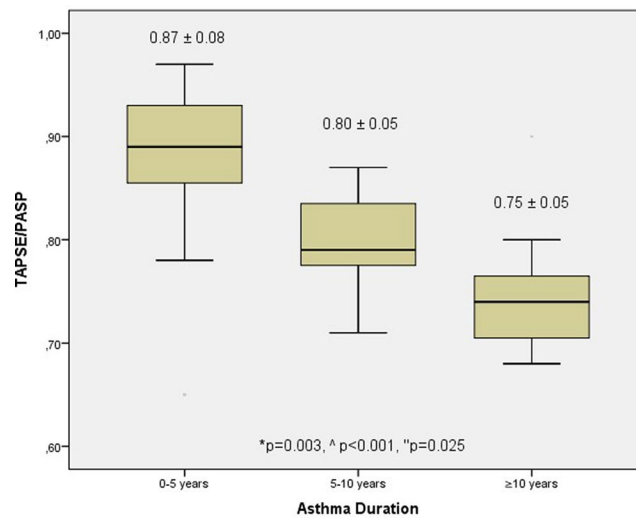


Figure 1. Box plot graph showing the TAPSE/PASP ratio in Group 1 (Asthma duration <5 years), Group 2 (Asthma duration 5–10 years) and Group 3 (Asthma duration >10 years), respectively (p values for *groups 1 and 2, ^groups 1 and 3, "groups 2 and 3).

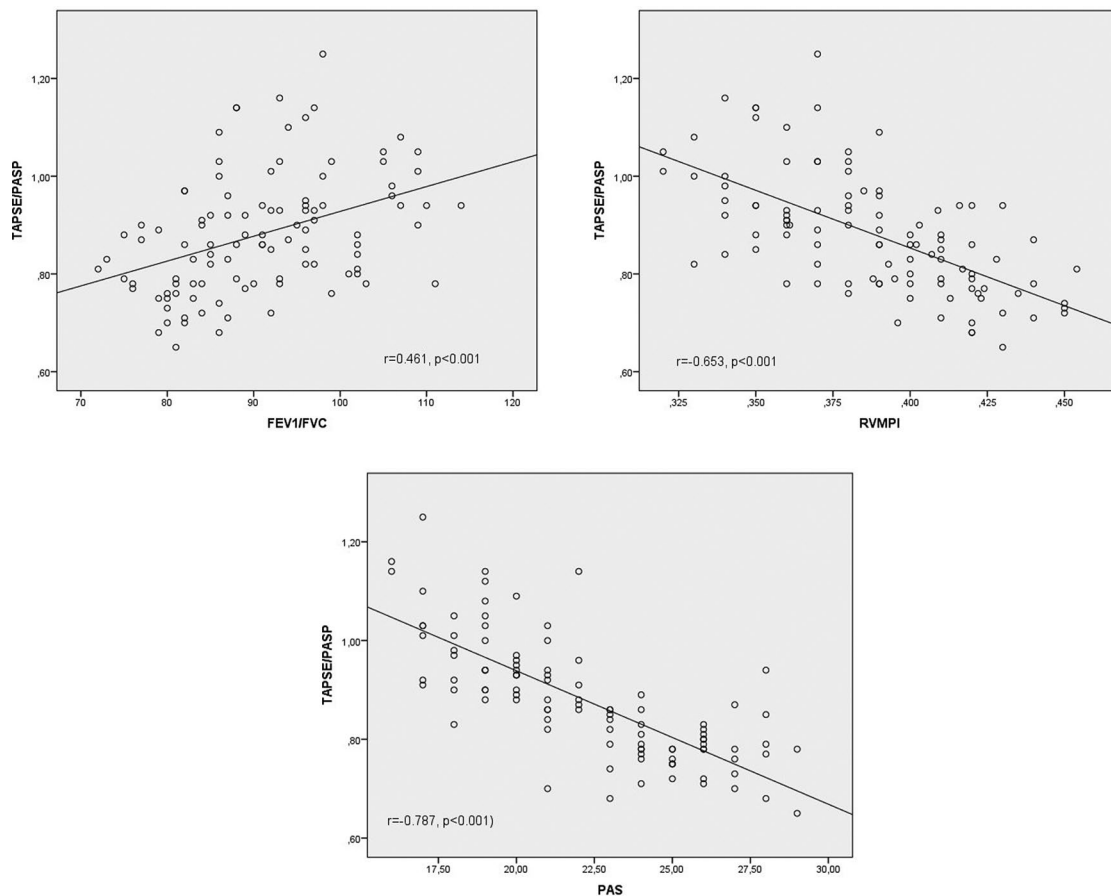


Figure 2. Scatter dot plot graphs revealing correlation analysis between (A) TAPSE/PASP and FEV1/FVC, (B) TAPSE/PASP and RV MPI, (C) TAPSE/PASP and PAS. TAPSE: tricuspid annular plane systolic excursion, PASP: pulmonary arterial systolic pressure, FEV1/FVC: forced expiratory volume in 1 s/forced vital capacity ratio, PAS: pulmonary arterial stiffness, RV MPI: right ventricle myocardial performance index.

indicating increased RV afterload in the absence of overt pulmonary hypertension. TAPSE/PASP ratio is decreased, suggesting altered coupling of RV to PA in patients with mild-moderate asthma. TAPSE/PASP

ratio also significantly differs among patients with asthma in accordance with the duration of asthma. FEV1, FVC, FEV1/FVC, PEF, RVEDA and TAPSE are positively correlated with TAPSE/PASP, while RVIVRT,

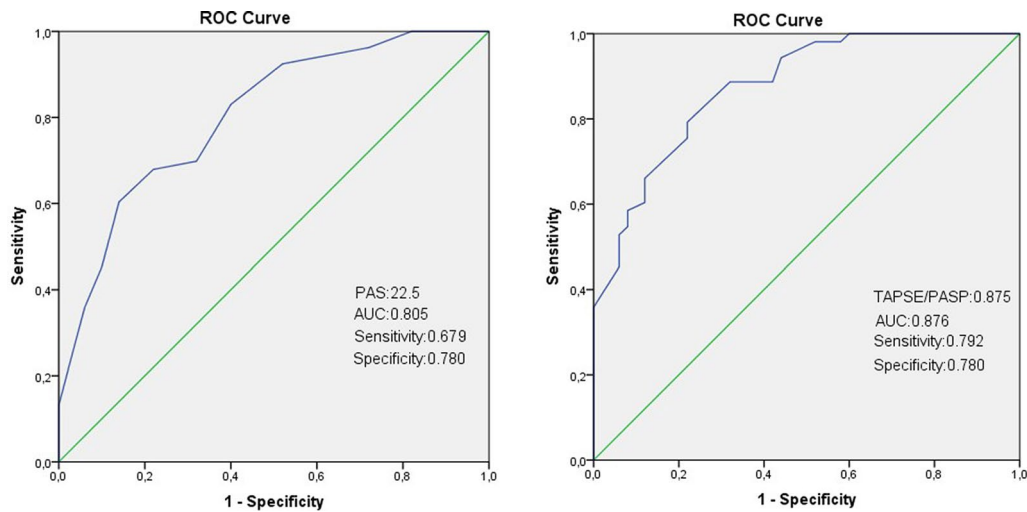


Figure 3. Receiver Operating Characteristics (ROC) curve analysis of (A) PAS and (B) TAPSE/PASP ratio to predict asthma. PAS: pulmonary arterial stiffness, AUC: area under curve, TAPSE/PASP: tricuspid annular plane systolic excursion/pulmonary arterial systolic pressure.

RVMPI, PAS and PASP are negatively correlated with this ratio. Of these, PAS, TAPSE and PASP are observed as independent indicators of TAPSE/PASP. Moreover, PAS and the TAPSE/PASP ratio have high sensitivity, specificity, and AUC values, revealing their diagnostic potential in the assessment of patients with asthma.

As mentioned above, TAPSE/PASP ratio is positively correlated with pulmonary function test results including FEV1, FVC, FEV1/FVC and PEF. However, this doesn't necessarily mean that TAPSE/PASP correlates with the severity of asthma as patients with asthma weren't furtherly graded into mild and moderate groups just based on a single measurement of FEV1, FVC, FEV1/FVC and PEF. Additionally, the significantly inverse relation between TAPSE/PASP ratio and duration of asthma may not indicate a similar relation between TAPSE/PASP ratio and severity of asthma because asthma severity is a dynamic feature and may change over time. With regard to the high sensitivity, specificity and AUC values of PAS and TAPSE/PASP ratio, these measures may be potentially useful markers to prevent over- and underdiagnosis of asthma especially in cases where the patient has normal LV and RV functions and his/her symptoms or pulmonary function test results remain inconclusive to make an exact differential diagnosis as pulmonary function tests may not strongly correlate with asthma symptoms.

Asthma is a commonly seen chronic lung disease with a potentially systemic impact. The inflammatory component of asthma has provoked some studies searching for a link between asthma and atherosclerosis, which resulted in reporting a causal relationship

between asthma and coronary artery disease, carotid artery disease, stroke, or atrial fibrillation (5,19–21). However, asthma is a complex and multifaceted disease characterized by chronic airway inflammation, and RV is a potentially important site which is in continuity with pulmonary circulation, and forms a functional unit with the lungs (22). Despite this, little attention has been paid to the investigation of RV function in patients with asthma, until now (8,9). To the best of our knowledge, there are no studies in the literature evaluating the relationship between asthma and the TAPSE/PASP ratio referring to RV-PA coupling.

The chronic airway inflammation in asthma may lead to obstruction of the small airways, which can cause hypoxemia. In severe cases, the chronic nature of the disease and repeated asthma attacks may result in a long term and global hypoxia state, which induces intimal thickening, endothelial dysfunction, fibrosis and constriction of pulmonary arterioles. This reconstruction of pulmonary circulatory tissue structure may lead to increased pulmonary vascular resistance, sustained pulmonary hypertension and eventually right heart failure (14,23–25). However, in addition to severe cases, there are also milder cases of asthma presenting with good control, and fewer asthma attacks. Yet, it is not clear as to whether there are detrimental effects of mild-moderate asthma on PA, RV function, and RV-PA coupling in the absence of overt pulmonary hypertension.

PAS, a relatively new echocardiographic parameter, is used to define the elastic properties of the pulmonary artery (18). It was reported that pulmonary arteries subjected to chronic hypoxia respond by

pulmonary vasoconstriction and marked increase in collagen synthesis, which then decreases the elastin-to-collagen ratio and distensibility, while elevating the tensile strength per unit collagen, viscous energy loss, and arterial stiffness. The stiffness itself results in additional damage on pulmonary vasculature over time, ultimately leading to pulmonary hypertension. And any rise in PAS contributes to increased right ventricular afterload, which eventually causes RV dysfunction (26–29). In our study, PAS is shown to be significantly higher in the asthma group compared to healthy individuals, revealing a higher right ventricular afterload. So, it can be proposed that the long term hypoxia present even in mild-moderate asthma may lead to increased PAS, which predicts developing pulmonary hypertension.

RV is a structure designed to adapt to its afterload with compensatory mechanisms overwhelming the pressure changes in pulmonary circulation. This relationship between RV contractility and RV afterload is defined as RV-PA coupling. Preserved RV-PA coupling refers to increased RV contractility to maintain the normal right heart function in response to increased pulmonary vascular load (RV afterload). However, if the compensatory mechanisms fail to withstand the pressure changes in the pulmonary circulation, RV-PA uncoupling develops, which in turn leads to RV dysfunction and clinical right heart failure (30–32). The most accurate method for RV-PA coupling evaluation is right heart catheterization, however it is invasive and technically demanding. Therefore, simpler and completely non invasive ratios have been developed as an echocardiographic surrogate for RV-PA coupling

For echocardiography, these ratios have presented a more quantified and physiology based approach rather than qualitative assumptions. Of these, the TAPSE/PASP ratio has emerged as the independent predictor of catheterization-based RV-PA coupling (11,30,33,34). Some studies examined TAPSE/PASP ratio with concomitant right heart catheterization, revealing its contribution to the evaluation of RV function and PA structure (11,35). The relationship of TAPSE versus PASP provides a precise index of in vivo changes in RV length (TAPSE) versus developed force (PASP), which describes the RV contractile state beyond the information provided by each separate variable. In addition, this ratio has been validated in several clinical studies, revealing a pathophysiological importance and prognostic significance. Research indicates that prognostic significance has been linked to mortality outcomes (30,36–40).

In our study, the TAPSE/PASP ratio is markedly decreased in mild-moderate asthma, suggesting an early RV-PA uncoupling, which could be of functional and prognostic relevance in these patients. PAS, TAPSE, and PASP are observed as independent predictors of TAPSE/PASP. Because PASP is within normal range, it can be proposed that the lower TAPSE/PASP ratio in patients with asthma is mainly driven by lower TAPSE, which is the first component of systolic function to be impaired. We also presume that the observed decrease in TAPSE is mainly related to the increased RV afterload, which manifests as increased PAS in patients with mild-moderate asthma. One may expect a corresponding increase in RV contractility to ensure RV-PA coupling as a function of compensatory mechanisms, however, it has been shown that even mild increases in the pulmonary vascular load may result in uncoupling of RV from PA due to multiple interactions of additional factors. These factors may include altered gene expression, neurohormonal activation, and cytokine release in the clinical setting of the primary disease (41–45).

This study has several limitations. First, the observational nature of the study limits causal inference. Second, the sample size was relatively small and lacked long-term follow up data to evaluate clinical impact of subclinical RV dysfunction. Third, PAS, PASP, and TAPSE/PASP ratio were not confirmed by simultaneous right heart catheterization that would strengthen the results of the study.

Conclusion

We found that RV function is impaired and may not couple adequately to increased afterload in patients with mild-moderate asthma compared to healthy individuals. TAPSE/PASP ratio may be helpful for identifying subclinical RV dysfunction in these patients even before the development of pulmonary hypertension. PAS may provide additional information about RV afterload, and together with TAPSE/PASP ratio, they may provide more insight into causes and consequences of RV dysfunction compared to other measures of RV function alone.

These findings help to identify patients with asthma who are at higher risk for developing pulmonary hypertension or RV failure, and signify the importance of 2D echocardiography in early detection and monitoring of impaired parameters. Moreover, we suggest that echocardiographic interpretation may help to determine new therapeutic goals in asthma treatment. Future studies are needed

to confirm these findings and to elucidate their clinical implications.

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Declaration of interest

There is no conflict of interest.

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