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Pulmonary Hypertension

Right Atrium Volume Index in Patients with Secondary Pulmonary Hypertension Due to Chronic Obstructive Pulmonary Disease

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Background: Right atrium volume index has recently been described as a quantitative and highly reproducible echocardiographic parameter associated with right ventricle systolic dysfunction in patients with chronic systolic heart failure. The aim of the current study was to assess right atrium remodeling and to establish correlations with echocardiographic parameters of right ventricle systolic and diastolic dysfunction in patients with pulmonary hypertension due to chronic obstructive pulmonary disease (COPD).

Methods: The study was conducted on 40 patients with secondary pulmonary hypertension due to COPD and 40 healthy volunteers (mean age 59 ± 6 years) who submitted to detailed echocardiographic examinations. Plasma levels of the soluble interleukin-1 receptor family member, N-terminal pro-B type natriuretic peptide and galectin-3 were measured in both groups.

Results: The right atrium volume index was significantly higher in the test group (45.7 ± 15.3 vs. 25.4 ± 4.0 mL/m^2) and showed strong correlations to tricuspid annular plane systolic excursion ($r = -0.733$, $p < 0.0001$), right ventricle fractional area change ($r = -0.662$, $p < 0.0001$), right ventricle ejection fraction ($r = -0.741$, $p < 0.0001$), and systolic pulmonary artery pressures ($r = 0.721$, $p < 0.0001$). Multivariate analysis facilitated the construction of a linear regression model which showed that right ventricle systolic dysfunction parameters (R^2-adjusted = 0.62, $p < 0.001$), elevated systolic pulmonary artery pressure (R^2-adjusted = 0.52, $p < 0.001$) and heart failure biomarkers (log-transformed sST2, galectin-3 and N-terminal pro-B type natriuretic peptide) (R^2-adjusted = 0.41, $p < 0.001$) were independently associated with right atrium volume index.

Conclusions: Right ventricle systolic dysfunction and elevated systolic pulmonary artery pressure are independently associated with right atrium volume index in patients with pulmonary hypertension due to COPD.

Key Words: Echocardiography • Right atrium volume index • Right ventricular diastolic function • Right ventricular systolic function

INTRODUCTION

Secondary pulmonary hypertension and chronic cor pulmonale are currently primarily determined by chronic obstructive pulmonary disease (COPD), which is an important cause of morbidity and mortality worldwide.[1,2] The development of pulmonary hypertension in such patients is mediated by complex mechanisms, which involve hypoxia, mechanical stress induced by hyperinflated lungs, as well as inflammation, the toxic effects of cigarette smoke and endothelial dysfunction.[3,4] Pulmo-

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nary hypertension has been shown to be associated with decreased exercise capacity and increased mortality.[5] The majority of patients with COPD have mild to moderate pulmonary hypertension, while severe pulmonary hypertension only occurs in a small number of cases, usually in connection with more severe pulmonary disease.[1] Patients with COPD and worsening pulmonary hypertension during exercise, sleep or acute severe exacerbations are more likely to suffer acute increases in afterload of the right ventricle (RV), which favors the development of right heart failure.[6] However, changes in pulmonary vasculature emerge in all stages of COPD, as demonstrated in a pathological study, which suggests that the early identification of such patients may improve prognosis through adequate management.[7] Although the crucial importance of early diagnosis and staging of pulmonary hypertension in patients with COPD is obvious, it has often proved to be quite challenging. Currently, right heart catheterization is still the gold standard for diagnosing and staging pulmonary hypertension, although it is hindered by some disadvantages, as it is invasive and seldom available in many institutions.[8] Novel imaging techniques, such as dynamic three-dimensional echocardiography and cardiac magnetic resonance imaging, show promising results in right heart assessment and overcome the inconveniences usually related to invasive procedures.[9,10] However, these techniques are fairly expensive, time consuming and not widely available. Under these circumstances, the cheap, non-invasive and widely available conventional two-dimensional echocardiography may remain a valuable alternative, despite its limitations. To this purpose, several echocardiographic parameters have been described and further studied. Cuttica et al. proved that pulmonary hypertension, as assessed by echocardiography, is associated with increased right atrium (RA) area, which is to be expected considering the fact that the RA is exposed to elevated pressures due to functional tricuspid regurgitation in such patients.[11] However, left atrium volume was previously shown to correlate better with emerging cardiovascular events than other left atrium dimensions, particularly if indexed to body surface area, an observation which may also apply to the RA.[12,13] Right atrium volume index (RAVI) has recently been described as a quantitative and highly reproducible echocardiographic parameter associated with RV systolic dysfunction in patients with chronic systolic heart failure.[14] Unfortunately, research involving this parameter is scarce at this point, leaving serious gaps in information. The aim of the current study is to assess whether there is a relationship between RAVI and RV dysfunction in patients with COPD-induced pulmonary hypertension, and if elevated levels of myocardial strain biomarkers are relevant for predicting increased RAVI and right heart failure.

MATERIALS AND METHODS

Patients and study protocol

This prospective study was conducted on 80 subjects – 40 patients with pulmonary hypertension due to COPD (test group) and 40 healthy volunteers (healthy group) with similar demographic characteristics. The study group included 40 consecutive patients with acutely decompensated heart failure due to acute respiratory exacerbation, which were admitted to the 2nd Department of Internal Medicine of Cluj-Napoca Emergency Clinical County Hospital from October 2011 until November 2012. The study was performed in accordance with the principles set out in the Declaration of Helsinki and was approved by the ethics committee on human research of the Iuliu Hatieganu University of Medicine and Pharmacy.

During the inclusion period, 60 consecutive patients previously diagnosed with COPD who presented with both cardiac and respiratory exacerbation were screened for admission to the study. Subjects were considered eligible provided that the following inclusion criteria were respected: presence of echocardiographic criteria of pulmonary hypertension (systolic pulmonary artery pressure > 36 mmHg, maximum velocity of the tricuspid regurgitation jet > 2.8 m/s), sinus rhythm, preserved left ventricle ejection fraction (LVEF) > 55%. Patients who had other causes for pulmonary hypertension, congenital heart disease, or associated pathology, such as neoplasia or inflammatory disorders likely to influence the levels of heart biomarkers, were not enrolled in the study. Subjects were only included after agreeing to the study protocol and signing the informed consent. Ultimately, 40 out of the 60 screened patients were finally included in research. For various reasons, 20 other pa-

tients were not considered eligible: 12 patients did not meet the echocardiographic criteria for pulmonary hypertension, 3 patients exhibited cardiac arrhythmia, 3 patients had poor echocardiographic views, and 2 others refused to take part in the research.

All participants to the study were interviewed about symptoms, personal and family medical history, exposure to active or passive smoking or other toxins, and submitted to detailed clinical examination upon admission. The New York Heart Association heart failure class was assessed and a rest 12-lead Electrocardiography (ECG) was performed. In addition to that, each patient performed the six-minute walk test. COPD was diagnosed and staged according to the Global Initiative for Chronic Obstructive Lung Disease, based on the forced expiratory volume in 1 sec (FEV1)/forced vital capacity (FVC) ratio < 70%.[15] Measurements were recorded using a water-sealed Collins Survey II volume displacement spirometer.

Biochemical testing

Two blood samples were drawn from each subject at the first visit in tubes containing ethylene-diamine tetra-acetic acid. One blood sample was immediately centrifuged and analysed for routine parameters, including fasting glycaemia, C-reactive protein and creatinine levels, according to the standard procedures of the biochemistry laboratory of the 2nd Medical Clinic. Glomerular filtration rate was estimated (eGFR by MDRD) using the Modified Diet Renal Disease equation and significantly impaired renal function was diagnosed when eGFR by MDRD was < 60 mL/min/1.73 m^2. Another blood sample was frozen and stored at -70 °C until the end of the study, then analysed for N-terminal pro-B type natriuretic peptide (NT-proBNP), soluble interleukin-1 receptor family member (sST2) and galectin-3 levels, using the same batches of specific reactives (Biomedica Gruppe, Vienna, Austria, Human IL-1 sRII – Quantikine ELISA Kit from R&D Systems, Minneapolis, MN, USA and Human Galectin-3 – Quantikine ELISA Kit from R&D Systems, respectively).

Echocardiography methods

Echocardiographic examinations were performed by two experienced independent examiners using an Aloka alpha-10 SSD-5500, Tokyo, Japan, ultrasound system with a 2.5 MHz phased array transducer and physiological ECG-lead recording function. Several acoustic views were captured in order to allow an accurate assessment of two-dimensional and Doppler parameters. All data was digitally stored and available for off-line analysis. A detailed echocardiography protocol was established and followed throughout the study. Standard examinations included left and right chamber dimensions, as well as different parameters of the left ventricle (LV) and RV systolic and diastolic function. Apical 4-chamber views were used to measure chamber volumes based on Simpson's modified rule, and LV and RV fractions were calculated accordingly. LVEF was considered preserved if > 55%.[16] RAVI was measured at end-systole from the same incidence based on Simpson's modified rule and was indexed to the body surface area. Normal acknowledged values for RAVI average 34 mL/m^2 in men and 27 mL/m^2 in women.[17] RV thickness was measured from the subcostal view at the tip of the anterior tricuspid leaflet in end-diastole, as previously described.[18]

The tricuspid regurgitation flow was analysed to determine RV-RA gradient values, which were added to RA estimated pressures, according to inferior vena cava diameter and inspiratory collapse, in order to calculate systolic pulmonary artery pressures. Pulmonary hypertension was considered at least possible, provided that systolic pulmonary artery pressure (sPAP) values were higher than 36 mmHg.[8] The severity of tricuspid regurgitation was assessed measuring the vena contracta of the regurgitation jet from the apical 4-chamber view; measurements were obtained from three cardiac cycles and an average value was finally taken into account; tricuspid regurgitation was considered severe if vena contracta was at least 7 mm and quantified as mild or moderate if values were lower than 6 mm.[19] Patients with severe tricuspid regurgitation were not included in the study.

RV systolic function was assessed using either conventional bidimensional echocardiography or tissue Doppler. The apical 4-chamber view provided most measurements: tricuspid annular plane systolic excursion (TAPSE); Tissue Doppler S peak velocity; RV ejection fraction (RVEF); RV fractional area change (RVFAC); RV index of myocardial performance (RVIMP). RV volumes were measured from the apical 4-chamber view using Simpson's single plane modified rule and RVEF was derived accordingly as (end-diastolic volume – end-systolic

volume)/end-diastolic volume. RV areas were measured from the same view and used for determining RVFAC: (RV end-diastolic area – RV end-systolic area)/RV end-diastolic area. Tissue Doppler imaging allowed global RV function assessment based on the RVIMP. TAPSE was measured from the apical 4-chamber view. RVEF was only measured using 2D echocardiography, as 3D echocardiography was not available, and was considered impaired if lower than 50%. Systolic dysfunction was quantified as mild (RVEF 40-49%), moderate (RVEF 30-39%) or severe (RVEF < 30%). RV systolic dysfunction was diagnosed if TAPSE < 16 mm; Tissue Doppler S peak velocity < 10 cm/s; RVFAC < 35%; RVEF < 50%; RVIMP > 0.55.[18]

Tricuspid flow analysis from the apical 4-chamber view allowed the quantification of diastolic dysfunction. For this purpose, early (E wave) and late (A wave) diastolic flow velocities were measured and the E/A ratio was calculated; the E wave deceleration time was also measured. Tissue Doppler measurements of myocardial velocities at the level of the tricuspid annular plane (E' wave) provided additional data and allowed RV filling pressure assessment based on the E/E' ratio. RV diastolic dysfunction was considered mild (impaired relaxation pattern; E/A ratio < 0.8), moderate (pseudonormal pattern; E/A ratio between 0.8-2.1; E/E' ratio > 6), or severe (restrictive pattern; E/A ratio > 2.1 and E wave deceleration time < 120 ms).[18] All parameters were measured at end-expiration during normal breathing.[18]

Statistical analysis

All data were tested for normality using the Kolmogorov-Smirnov test. Continuous data with normal distribution were expressed as mean value ± standard deviation (SD) and further analysed using parametric tests (Student test, ANOVA test), while data with non-parametric distribution were expressed as median value ± interquartile range (IQR) and submitted to non-parametric tests (Chi square/Fisher-test, Mann-Whitney U test). The ANOVA test was used to follow the correlation between RAVI and the degrees of RV systolic and diastolic dysfunction severity. Pearson's correlation coefficient was used to evaluate significant relationships between other echocardiographic variables and RAVI. Multivariable analysis (multiple linear regression) was performed with RAVI as the dependent variable; log-transformed sST2, galectin-3 and NT-proBNP concentrations, RVEF, TAPSE, RVFAC, and the E/E' ratio were considered as independent variables. Results were considered statistically significant if $p < 0.05$. Receiver-operator characteristic (ROC) analysis was used to determine the sensitivity and specificity of sST2, galectin-3 and NT-proBNP for identifying patients with increased RAVI. For essential biomarkers, receiver type analysis was employed with cut-off value, significance levels and main reliability indices determination: sensitivity, specificity, positive predictive value, negative predictive value. RAVI intra-observer and inter-observer variability was assessed using the Bland and Altman method. The coefficient of variability was calculated as the SD of the differences between the sets of measurements divided by the mean value of the parameter under consideration. Statistical analysis was performed using MedCalc statistical software, version 12.7.0.0 for WindowsXP/Vista/7/8.

RESULTS

Patients in both groups had a mean age of 59 years and 53% were males. Systolic arterial blood pressure was significantly higher in the test group ($p = 0.001$), with a mean value of 140 mmHg, and active smokers were more frequent among COPD patients (67.5% vs. 22.5%, $p = 0.003$). Patients in the study group also showed a lower physical exercise capacity, as assessed by the 6-minute walk test distance (241 vs. 478 m, $p < 0.001$). Baseline clinical, echocardiography and laboratory characteristics are detailed in Table 1.

Pulmonary disease severity was classified according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease as follows: 13 patients had only moderate impairment, while 21 had severe and 6 had very severe COPD.

Regarding biological values, higher levels of C-reactive protein were recorded in the test group vs. the healthy group (2.2 mg/dL vs. 0.6 mg/dL, $p = 0.002$), while eGFR by MDRD was lower in the test group (64.8 ± 20.4 mL/min/1.73 m^2 vs. 83.1 ± 10.9 mL/min/1.73 m^2, $p < 0.001$). All biomarkers of myocardial remodelling (NT-proBNP, galectin-3 and sST2) were higher in the test group vs. the healthy group. The median values for

NT-proBNP were higher in COPD patients (1328 pg/mL vs. 220 pg/mL, p < 0.001), as were the levels of galectin-3 (15.2 ng/mL vs. 5.7 ng/mL, p < 0.001) and sST2 (1.2 ng/mL vs. 0.7 ng/mL, p < 0.001).

Subjects in the healthy group did not receive any medication. Patients in the test group were treated and the administered drugs are also mentioned in Table 1.

The echocardiographic characteristics of the two groups are detailed in Table 2. There was a significant difference between the two groups regarding both structural and functional parameters of the RV. The right cardiac chambers were more dilated in the test group vs. the healthy group, with mean RAVI values of 45.7 ± 15.3 mL/m^2 in the test group and only 25.7 ± 4.0 mL/m^2 in the healthy group. RAVI measurements had low intra-observer and inter-observer variability (intra-observer, coefficients of variability 1.4%, 95% CI, limits of agreement: -1.2 to 2.9 and coefficients of variability 1.6%, 95% CI, limits of agreement: -1.3 to 3.3; inter-observer, coefficients of variability 2.4%, 95% CI, limits of agreement: -2.3 to 3.1). RAVI was considered abnormally elevated if > 34 mL/m^2 in men and > 27 mL/m^2 in women, as previously described.[17] sPAP was also considerably higher in the study group, while RV systolic function parameters (TAPSE, Tissue Doppler S peak velocity, RVFAC, RVEF) were more depressed. RVIMP was higher in the test group (0.51 ± 0.1 vs. 0.36 ± 0.1, p < 0.001), also suggesting the presence of systolic dysfunction.

Table 1. Baseline characteristics in the test group vs. healthy group

	Test group	Healthy group	p-value
Clinical data			
Age, years, mean (SD)	59 (6)	59 (6)	NS
Male gender, n (%)	21 (53)	21 (53)	NS
Body surface area, m^2, mean (SD)	1.99 (0.3)	1.96 (0.3)	NS
Body-mass index, kg/m^2, mean (SD)	29 (7)	27 (4)	NS
Systolic blood pressure, mmHg, mean (SD)	140 (25)	124 (13)	0.001
Diastolic blood pressure, mmHg, mean (SD)	83 (13)	80 (8)	NS
Current smoking status, n (%)	27 (67.5)	9 (22.5)	0.003
Six-minute walk distance, m, median (IQR)	241 (126-588)	478 (310-772)	< 0.001
Respiratory function			
PaO_2, mmHg, mean (SD)	78 (11)	95 (3)	< 0.001
$PaCO_2$, mmHg, mean (SD)	55 (8)	42 (3)	< 0.001
FEV1, L, mean (SD)	1.56 (0.1)	2.7 (0.2)	< 0.001
FVC, L, mean (SD)	2.6 (0.3)	3.4 (0.3)	< 0.001
FEV1/FVC ratio, mean (SD)	0.59 (0.05)	0.80 (0.04)	< 0.001
Laboratory characteristics			
Fasting glucose, mg/dL, median (IQR)	106.7 (75-186)	101.2 (77-113)	NS
C-reactive protein; mg/dL, median (IQR)	2.2 (0.6-4.8)	0.6 (0.1-1.2)	0.002
eGFR by MDRD, mL/min/1.73 m^2, median (IQR)	64.8 (23-103)	83.1 (64-105)	< 0.001
Plasma NT-proBNP, pg/mL, median (IQR)	1328 (270-5700)	220 (30-420)	< 0.001
Plasma Galectin-3, ng/mL, median (IQR)	15.2 (2.2-24.4)	5.7 (0.8-8.8)	< 0.001
Plasma sST2, ng/mL, median (IQR)	1.2 (0.5-2.5)	0.7 (0.2-1.3)	< 0.001
Discharge medication			
Inhaled β2-agonists, n (%)	40 (100)		
Inhaled corticoids, n (%)	34 (85)		
Diuretics, n (%)	27 (67.5)		
Angiotensin-converting-enzyme inhibitors, n (%)	31 (77.5)		
β-blockers, n (%)	9 (22.5)		

eGFR by MDRD, Estimated Glomerular Filtration Rate by Modified Diet in Renal Disease; FCV, forced vital capacity; FEV1, forced expiratory volume in 1 second; IQR, interquartile range; NT-proBNP, N-terminal pro-B type natriuretic peptide; PaCO2, partial pressure of carbon dioxide of arterial blood; PaO2, partial pressure of oxygen in arterial blood; SD, standard deviation; sST2, soluble interleukin receptor family member.

Table 2. Echocardiographic characteristics in the test group vs. healthy group

Variables	Test group (n = 40)	Healthy group (n = 40)	p-value
RV morphology and function			
RV-basal diameter, mm, mean (SD)	47.5 (3.9)	36.9 (4.9)	0.001
RV-medial diameter, mm, mean (SD)	27.6 (5.4)	21.2 (3.0)	0.001
RV-base-to-apex length, mm, mean (SD)	74.5 (5.3)	69.4 (6.5)	0.001
RV wall thickening, mm, mean (SD)	6.4 (0.8)	3.5 (0.5)	< 0.001
RV end-diastolic volume index, mL/m^2, mean (SD)	76.2 (16.0)	45.1 (9.7)	< 0.001
RV end-systolic volume index, mL/m^2, mean (SD)	47.7 (14.4)	15.0 (4.1)	< 0.001
RAVI, mL/m^2, mean (SD)	45.7 (15.3)	25.4 (4.0)	< 0.001
TAPSE, mm, mean (SD)	15.0 (1.8)	22.4 (2.7)	< 0.001
RVIMP, mean (SD)	0.51 (0.1)	0.36 (0.1)	< 0.001
RVFAC, %, mean (SD)	34.1 (4.0)	42.9 (3.8)	< 0.001
RVEF, %, mean (SD)	40.3 (8.4)	64.4 (5.8)	< 0.001
Tissue Doppler S peak velocity, cm/s, mean (SD)	9.3 (2.5)	12.3 (2.4)	< 0.001
E peak velocity tricuspid flow, cm/s, mean (SD)	50 (17.0)	49.3 (12.3)	NS
A peak velocity tricuspid flow, cm/s, mean (SD)	42 (8.2)	39.4 (9.2)	NS
E deceleration time, ms, mean (SD)	191 (24)	203 (29)	NS
Tissue Doppler E' peak velocity, cm/s, mean (SD)	8.9 (2.2)	12.5 (2.4)	< 0.001
E/A ratio, mean (SD)	1.25 (0.4)	1.25 (0.3)	NS
E/E' ratio, mean (SD)	6.4 (2.6)	3.9 (1.5)	< 0.001
sPAP, mmHg, mean (SD)	57.2 (9.7)	20.3 (4.7)	< 0.001
LVEF, %, mean (SD)	58.6 (3.3)	69.6 (5.7)	0.001
LV end-diastolic volume index, mL/m^2	58.3 (24.3)	47.2 (13.2)	0.001
LV end-systolic volume index, mL/m^2	26.3 (11.3)	18.1 (8.3)	0.001
E peak velocity mitral flow, cm/s	61 (9.2)	71 (10.1)	0.001
A peak velocity mitral flow, cm/s	69 (7.3)	50.3 (9.2)	0.002
E/A mitral ratio	0.9 (0.3)	1.4 (0.4)	0.001
Tissue Doppler E' mitral velocity, cm/s	7.9 (1.2)	13.4 (2.3)	0.001
E/E' mitral ratio	7.7 (1.1)	5.2 (1.1)	0.008

LV, left ventricle; RAVI, right atrium volume index; RV, right ventricle; RVEF, RV ejection fraction; RVFAC, RV fractional area change; RVIMP, RV index of myocardial performance; SD, standard deviation; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

However, between-group differences in most RV diastolic function parameters of tricuspid flow failed to reach statistical significance. Significant differences were recorded regarding myocardial velocities (E' wave) measured by tissue Doppler at the level of the tricuspid annular plane. The E/E' ratio was higher in the test group, suggesting elevated RA pressure.

Statistically significant differences occurred in the LV systolic and diastolic function parameters. Although only patients with preserved LVEF were included in the study, in the COPD group LVEF was significantly lower, while both LV end-diastolic volume index and LV end-systolic volume index were higher. Diastolic function parameters were also impaired in the test group patients, who exhibited lower mitral E/A ratio and higher E/E' ratio.

Correlation between right atrium volume index and other echocardiographic parameters

Univariate analysis was performed in order to assess the relationship between echocardiographic covariates, functional capacity, biomarkers and RAVI. Results are shown in Table 3. RAVI was proven to be positively correlated with RV dimensions, the strongest correlations being observed with the RV wall thickness ($r = 0.745$, $p < 0.0001$) and RV basal diameter ($r = 0.618$, $p < 0.0001$). When considering systolic function, strong negative correlations were established between RAVI and TAPSE ($r = -0.733$, $p < 0.0001$), RVFAC ($r = -0.662$, $p < 0.0001$) and RVEF ($r = -0.741$, $p < 0.0001$). However, results were less consistent for diastolic function parameters (E/E' ratio, $r = 0.478$, $p < 0.0001$). There were no correlations be-

Table 3. Univariate correlation analysis of RAVI

Variables	Pearson's r	p-value
RV-basal diameter, mm	0.618	< 0.0001
RV-medial diameter, mm	0.437	< 0.0001
RV-base-to-apex length, mm	0.345	0.0017
RV wall thickening, mm	0.745	< 0.0001
RV end-diastolic volume index, mL/m²	0.504	< 0.0001
RV end-systolic volume index, mL/m²	0.569	< 0.0001
TAPSE, mm	-0.733	< 0.0001
Tissue Doppler S peak velocity, cm/s	-0.417	0.0001
RVIMP	0.412	0.0001
RVFAC, %	-0.662	< 0.0001
RVEF, %	-0.741	< 0.0001
E peak velocity tricuspid flow, cm/s	0.135	NS
A peak velocity tricuspid flow, cm/s	0.087	NS
E/A ratio	0.162	NS
E deceleration time, ms	-0.256	0.022
Tissue Doppler E' peak velocity, cm/s	-0.480	< 0.0001
E/E' ratio	0.478	< 0.0001
sPAP, mmHg	0.721	< 0.0001
LVEF, %	-0.580	< 0.0001
LV end-diastolic volume index, mL/m^2	0.372	0.001
LV end-systolic volume index, mL/m^2	0.540	< 0.001
E/A mitral ratio	0.166	NS
E/E' mitral ratio	0.435	< 0.001
Six-minute walk test distance, m	-0.527	< 0.0001
FEV1/FVC ratio	-0.661	< 0.0001
NT-proBNP, pg/mL	0.516	< 0.0001
Galectin-3, ng/mL	0.453	< 0.0001
sST2, ng/mL	0.461	< 0.0001

FCV, forced vital capacity; FEV1, forced expiratory volume in 1 second; LV, left ventricle; LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide; RAVI, right atrium volume index; RV, right ventricle; RVEF, RV ejection fraction; RVFAC, RV fractional area change; RVIMP, RV index of myocardial performance; sPAP, systolic pulmonary artery pressure; sST2, soluble interleukin receptor family member; TAPSE, tricuspid annular plane systolic excursion.

tween RAVI and tricuspid flow parameters, while correlations with tissue Doppler parameters were only moderate or weak. Correlations to left chamber function parameters were also only moderate or weak, if present. The strongest correlation was noted with LVEF (r = -0.580, p < 0.001), while differences in the E/A ratio failed to reach statistical significance.

Significant correlations were noted between the six-minute walk test distance and RAVI (r = -0.527; p < 0.0001), and between RAVI and sPAP (r = 0.721; p < 0.0001). Significant correlations were found between RAVI and log-transformed NT-proBNP, galectin-3, sST2 (p < 0.0001).

Multiple linear regression analysis was used to test the relationship between RAVI and RV variables that emerged after univariate analysis – such as RVEF, RVFAC, TAPSE (for RV systolic function), the E/E' ratio (for RV diastolic function), sPAP, and sST2, galectin-3 and NT-proBNP levels (Table 4). Accord-

Table 4. Multiple regression analysis testing the independent relation between RAVI and variables emerging from univariate analysis

	β coefficients (SD)	Overall R²-adjusted
Model 1		
Age	0.093 (0.199)	
sST2 levels	6.394 (2.817)†	0.41
Galectin-3 levels	0.481 (0.214)$^{\#}$	p < 0.001
NT-proBNP levels	0.004 (0.001)*	
Model 2		
Age	-0.112 (0.160)	
RVEF	-0.435 (0.109)*	0.62
RVFAC	-0.413 (0.148)$^{\#}$	p < 0.001
TAPSE	-1.240 (0.358)$^{\#}$	
Model 3		
Age	-0.065 (0.223)	0.32
E/E' ratio	2.712 (0.567)$^{\#}$	p < 0.001
Model 4		
Age	-0.003 (0.176)	0.52
sPAP	0.495 (0.054)*	p < 0.001
Model 5		
Age	-0.087 (0.207)	0.33
LVEF	-1.097 (0.175)	p < 0.001

Model 1: model including – age and heart failure biomarkers (sST2, galectin-3, NT-proBNP); Model 2: model including – age and RV systolic function parameters (RVEF, RVFAC, TAPSE); Model 3: model including – age and RV diastolic function parameters (E/E' ratio); Model 4: model including – age and sPAP; Model 5: model including – age and LVEF.
R²-adjusted, overall model significance; β coefficients (SD), beta coefficients expressed as calculated value (standard deviation). LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal pro-B type natriuretic peptide; RV, right ventricle; RVEF, RV ejection fraction; RVFAC, RV fractional area change; RAVI, right atrium volume index; SD, standard deviation; sPAP, systolic pulmonary artery pressure; sST2, soluble interleukin receptor family member; TAPSE, tricuspid annular plane systolic excursion. Significance level: * p < 0.0001; $^{\#}$ p < 0.001; † p < 0.01.

ingly, log-transformed sST2, galectin-3 and NT-proBNP (Model 1) levels were shown to be independently associated to RAVI (R^2-adjusted = 0.41; $p < 0.001$), with NT-proBNP reaching the highest statistical significance level ($p < 0.0001$). Correlations were the strongest between RVEF, RVFAC and TAPSE (Model 2) and RAVI (R^2-adjusted = 0.62, $p < 0.001$), while correlations to RV diastolic dysfunction as assessed by the E/E' ratio (Model 3) were only modest (R^2-adjusted = 0.32, $p < 0.001$). A moderate correlation between sPAP and RAVI (Model 4) was also revealed (R^2-adjusted = 0.52, $p < 0.001$). Despite reaching statistical significance, the correlation to LVEF was only weak (R^2-adjusted = 0.33, $p < 0.001$). Age was included in all five models and was not independently associated to RAVI.

Correlation between right atrium volume index and the degree of right ventricular dysfunction

Most patients in the current study had mild to moderate RV diastolic dysfunction. More precisely, 14 had mild, 16 had moderate and 7 had severe RV diastolic dysfunction, while 3 patients had normal RV diastolic function (Figure 1A). For most subgroups, the median value was at the lower end of the box, suggesting an asymmetric distribution towards lower RAVI values. The IQR varied with the severity of RV diastolic dysfunction, but there was no tendency of continuous increase or decrease. Still, a higher variability was obvious in the group with severe diastolic dysfunction. For all degrees of RV diastolic dysfunction, RAVI values remained mainly within the IQR, and median values increased proportionally to the severity of diastolic dysfunction. In our study, 5 patients had normal RV systolic function and 5 had severe RV systolic dysfunction (Figure 1B). Obviously, the majority of patients had mild (18 patients) or moderate (12 patients) RV systolic dysfunction. For most subgroups, the median value was at the lower end of the box, which allowed us to estimate an asymmetric distribution towards lower RAVI values. The IQR varies with the severity of the RV systolic dysfunction, but there is no tendency of continuous increase or decrease. A higher variability is obvious in the group with severe systolic dysfunction.

Right atrium volume index according to NT-proBNP, galectin-3, and sST2 levels

The ability of NT-proBNP, galectin-3 and sST2 to detect the presence of an increased RAVI was evaluated by ROC curve analysis (Figure 2). This showed an AUC of 0.878 for NT-proBNP (95% confidence interval 0.786 to 0.941; $p < 0.0001$; cut-off value of 420 pg/mL), of 0.801 for galectin-3 (95% confidence interval 0.697 to 0.882; $p < 0.0001$; cut-off value of 12.6 ng/mL) and of 0.788 for sST2 (95% confidence interval 0.683 to 0.872; $p < 0.0001$; cut-off value of 0.92 ng/mL). The sensitivity and specificity for predicting increased RAVI were lower for galectin-3 and sST2 when compared to NT-proBNP.

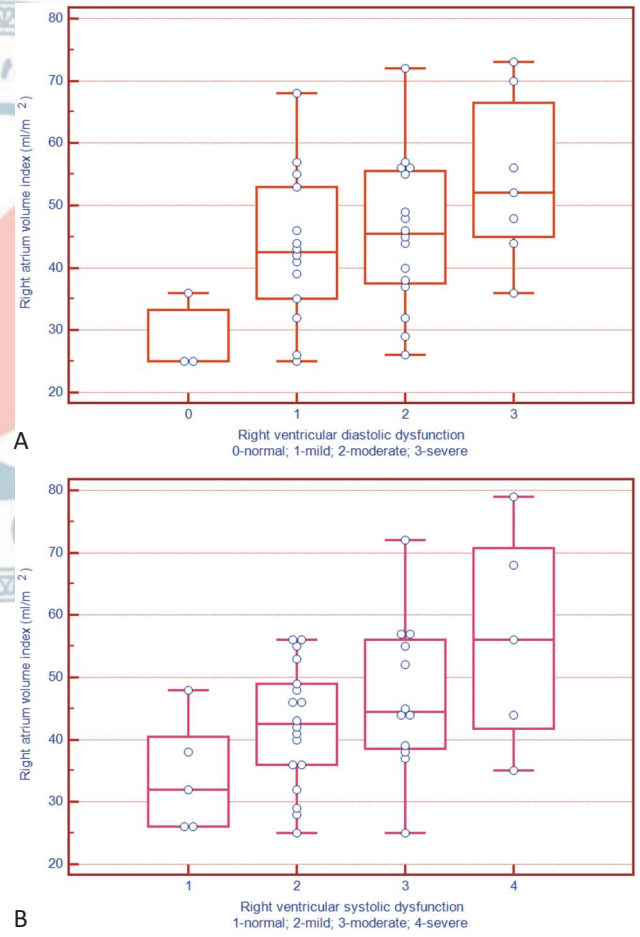

Figure 1. *Correlation between right atrium volume index and the degrees of right ventricle diastolic dysfunction (A) and the degrees of right ventricle systolic dysfunction (B). The box lines report the median and interquartile range, and the whiskers extend to the 10th and 90th percentiles.*

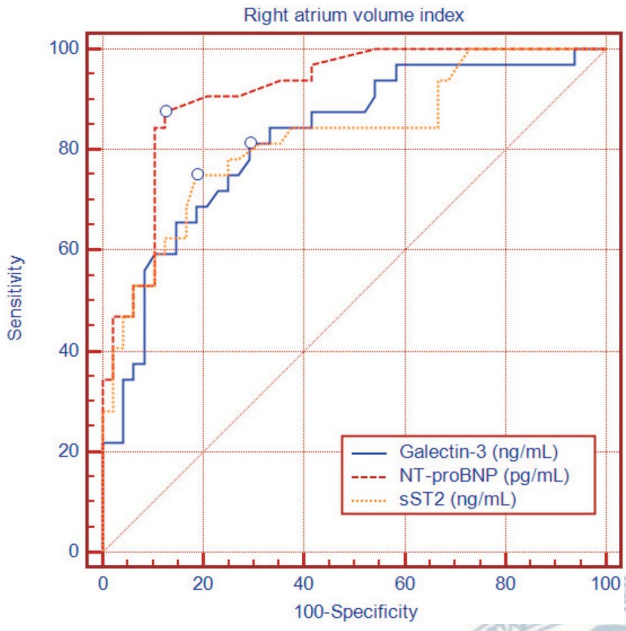

Figure 2. *Receiver-operator characteristic curve analysis of heart failure biomarkers for predicting right atrium volume index. NT-prpBNP, N-terminal pro-B type natriuretic peptide; sST2, soluble interleukin receptor family member.*

DISCUSSION

The results of this study confirmed the initial hypothesis that RAVI is associated with RV systolic and diastolic dysfunction in patients with secondary pulmonary artery hypertension due to COPD. In univariate analysis, elevated RAVI showed strong correlations with RV systolic function parameters, such as RVEF, RVFAC and TAPSE, as well as sPAP. These correlations persisted in multivariate analysis. Usually, most COPD patients have mild or moderate pulmonary hypertension,[1] while only a small percentage have severe pulmonary hypertension; the same tendency was noted in our study. However, patients with severe pulmonary hypertension should be identified as early as possible, as they carry a worse prognosis[20] and may require special management. A previous study focused on RA size, and functions in patients with pulmonary hypertension demonstrated that the adaptive changes of the RA such as dilatation and increased systolic performance emerge before the onset of RV systolic dysfunction, as a consequence of exposure to chronic pressure overload, triggering the Frank Starling mechanism.[21] Similar findings were reported in an animal model, in which RV diastolic dysfunction triggered an increase in RA contractility and distensibility in order to maintain an adequate RV filling, despite normal RV systolic function.[22] Also, the RA was shown to adapt its conduit and reservoir functions to compensate for increased RV filling pressures.[23] These data seem to suggest that there may be a correlation between RV diastolic dysfunction and RA function and dimensions. Therefore, accurate measurements of the RA may provide essential data regarding the progression of heart failure in COPD patients. Due to anatomical particularities of the right chambers, a satisfactory assessment of cardiac remodeling by conventional echocardiography may be challenging. Many examiners prefer using more advanced techniques, such as 3D echocardiography or cardiac magnetic resonance imaging. Voeller et al. suggested the assessment of myocardial strain by cardiac magnetic resonance imaging, showing that circumferential strain was diminished in dogs with severe RV overload, although it was preserved when RV load was mild.[24]

Unfortunately, such methods of assessment are seldom available in most centers. Sallach et al., proposed the measurement of RAVI as a quantitative echocardiographic marker for RV dysfunction severity, demonstrating strong correlations with RV systolic function parameters.[14] These findings are consistent with the results of our study, which showed significant individual correlations to indices of RV systolic dysfunction, such as TAPSE, RVFAC or RVEF. Additionally, we have shown that progressively elevated RAVI levels correlate with advancing RV systolic and diastolic dysfunction. However, in both studies, correlations between RAVI and diastolic function parameters were only modest, although some authors suggest that increased RAVI is often encountered in patients with RV diastolic dysfunction.[25] Interestingly, in the study by Sallach et al., RAVI was associated with the E/A ratio and E wave deceleration time, but not with the E/E' ratio.[14] The authors attributed this finding to the fact that chronic diastolic dysfunction is more likely to influence RAVI than elevated filling pressures, as estimated by the E/E' ratio, which is a measure of instantaneous diastolic function. In our study, however, the mean E/A ratio was not significantly different between the test group and the healthy group. By contrast, the E/E' ratio was positively associated to RAVI, although the correlation was only weak. This measure-

ment was previously shown to be well-correlated to mean systolic pulmonary artery pressures in patients with and without RV diastolic dysfunction.[26] Consequently, data regarding possible correlations between RAVI and diastolic function are conflicting. It is debatable, however, whether this lack of correlation does not have its origin in some possible drawbacks of the current methods to assess RV diastolic dysfunction by echocardiography. As previously discussed, data from animal models suggests that there is a correlation between RA dimensions and functions and RV diastolic dysfunction.[22,23] Moreover, tricuspid flow parameters are highly dependent on intrathoracic pressure variations associated with normal breathing, thus the recommendation of taking these measurements either in post-expiratory apnoea or to determine average values of five different beats.[27,28] A more easily achievable and reproducible measurement such as RAVI may bring incremental value to RV diastolic function assessment, provided that further studies are conducted to support its use. Although our test group patients were selected provided they had preserved LVEF, a statistically significant difference was observed by comparison with controls. However, it is likely that decreased LVEF may be a consequence of pulmonary artery hypertension in a series of patients with pulmonary disease, as previously shown, and is not necessarily a causal factor for RV dysfunction and increased RAVI.[29] In multivariate analysis, LVEF was only weakly correlated to RAVI.

Concerning clinical outcomes, elevated RAVI was also shown to be associated with higher long-term mortality rates, as well as with low functional capacity as assessed by the Duke Activity Status Index.[30] In our study, we assessed functional capacity by the six-minute walk test, and managed to show that walking distances were considerably lower in the test group.

Moreover, significant correlations were established between RAVI values and levels of biomarkers for cardiac remodeling and heart failure, such as NT-proBNP, sST2 and galectin-3, although the latter markers showed lower sensitivity and specificity than NT-proBNP. The value of NT-proBNP in identifying RV dysfunction has already been confirmed in previous studies and our results support that statement.[31] Interestingly, sST2 showed the lowest sensitivity and specificity for an increased RAVI. A possible explanation for this finding may be the fact that sST2, which is involved in the inflammatory response leading to cardiac remodeling, but was also shown to be elevated in other inflammatory states such as sepsis, autoimmune disease or acute asthma, may also be elevated due to COPD itself.[32-36] In fact, previous research provided evidence regarding the involvement of the IL-33/ST2 axis in COPD patients.[37] However, previously confirmed associations to RV dysfunction parameters suggest that this biomarker might have some value in right heart failure diagnosis and management, and should be supported by more extensive research.[38] Despite insufficient evidence regarding correlations to RV function, galectin-3 has been acknowledged as a valuable parameter for predicting mortality at 4 years in patients with acute heart failure, and it is possible that its use in clinical practice may be expanded provided that more extensive research is conducted.[39] Currently, data regarding the use of RAVI determined by echocardiography is scarce, but, considering the fact that this parameter is easily measured and highly reproducible, it has the potential to become a routine measurement if sufficient data is gathered to support its use.

Limitations

The main limitations of the study are the small number of recruited patients and the short follow-up period. Also, echocardiography measurements were particularly focused on right chamber function parameters, and therefore some left chamber parameters, such as left atrium volume index, were not included in the examination protocol. Moreover, systolic pulmonary artery pressures were only indirectly assessed by echocardiography, as right heart catheterization was not available. Although measurements were performed by experienced examiners, the results may have been hindered as myocardial border tracing is challenging when measuring right chambers. As 3D echocardiography was not available, RVEF was only calculated by using 2D echocardiography, which is less accurate. For that reason, RV systolic function assessment was based on more parameters, such as TAPSE, tissue Doppler systolic S' wave velocity, RVIMP and RVFAC. We aimed to reduce all the impediments by a rigorous selection of patients and by following a standard, accurate evaluation protocol.

CONCLUSIONS

Right ventricle systolic dysfunction, as assessed by RVFAC, RVEF and TAPSE, and elevated systolic pulmonary artery pressure are independently associated with RAVI in patients with pulmonary hypertension due to COPD. Correlations to diastolic parameters are, however, weaker, as only the E/E' ratio was shown to have any correlation at all to RAVI, while the E/A ratio showed no significant correlations.

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The research collective included five members, each with specific research tasks:

Lucia Agoston-Coldea – project coordinator and corresponding author; research tasks included conception and study design, acquisition and interpretation of data, final approval of the submitted manuscript.

Dana Petrovai and Isabella Mihalcea – critical revising for intellectual content.

Radu Revnic – revision of statistical analysis and critical revising for intellectual content.

Teodora Mocan – statistical analysis and interpretation of data and critical revising for intellectual content.

Silvia Lupu – interpretation of data, drafting of the manuscript, critical revising for intellectual content.

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