

Assessment of right ventricular geometry and mechanics in chronic obstructive pulmonary disease patients living at high altitude

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Abstract Degree of increase in pulmonary artery pressure (PAP) and adaptive responses in right ventricular morphology and mechanics play an important role in the prognosis of chronic obstructive pulmonary disease (COPD) patients. Three dimensional echocardiography and deformation imaging are recent advancements in echocardiography that allow more through assessment of right ventricle. We aimed to investigate right ventricular geometry and mechanics in a stable COPD population living at moderately high altitude. A total of 26 stable COPD patients with variable disease severity were included to this study. Pulmonary function tests, six minutes walking test (6MWT) and two- and three-dimensional echocardiography were performed for evaluation and data collection. Both systolic (43.06 ± 11.79 mmHg) and mean (33.38 ± 9.75 mmHg) PAPs were significantly higher in COPD patients compared to controls ($p < 0.05$, $p < 0.001$; respectively). Right ventricular volumes were similar

between groups, although right ventricular free wall thickness was significantly increased in COPD group. The number of subjects with a sub-normal ($<40\%$) right ventricular ejection fraction was significantly higher in COPD group (45.8 vs. 17.4% , $p < 0.05$), and the mean right ventricular strain was significantly lower (-21.05 ± 3.80 vs. -24.14 ± 5.37 ; $p < 0.05$). Only mean PAP and body surface area were found as independent predictors for 6MWT distance. Increased PAP and reduced right ventricular contractility were found in COPD patients living at moderately high altitude, although right ventricular volumes were normal. Similar findings can be expected in other COPD patients with high PAP, since these findings probably represents the effect of increased PAP on right ventricular mechanics.

Keywords Chronic obstructive pulmonary disease · Right ventricle · Echocardiography

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Introduction

Pulmonary hypertension (PH) is defined as an increase in resting mean pulmonary artery pressure (PAP) above 25 mmHg, and could be the consequence of a multitude of disorders [1]. Pulmonary parenchymal disorders, particularly chronic obstructive pulmonary disease (COPD), are a major cause of PH and constitutes group III according to Dana Point classification [1, 2]. Although the etiology of PH in association of COPD is multifactorial, hypoxia plays a pivotal role by both inducing vasoconstriction and promoting intimal proliferation and remodelling in pulmonary vasculature [3, 4]. Though the degree of PH observed in the setting of COPD is usually mild to moderate, i.e. mean PAP (mPAP) is between 25–35 mmHg; PH and/or cor

pulmonale are nevertheless associated with a worse prognosis in COPD patients [1, 5, 6].

A direct result of increased PAP is increased hemodynamic burden on right-sided cardiac chambers. Structural remodelling of right ventricle (RV), including RV hypertrophy and dilatation, is compensatory and ultimately leads to diastolic and systolic dysfunction and right-sided heart failure. Increased end-diastolic RV diameter is associated with poorer outcomes in patients with chronic pulmonary diseases [7]. Deterioration in RV contractility was observed in COPD patients, especially during the periods of acute exacerbations [8]. Also, structural changes in RV are associated with reduced functional status in COPD patients [9].

A special population of COPD patients is those living at high altitudes, since the reduced partial oxygen pressure at highlands leads to a natural increase in pulmonary vascular resistance and PAP [10]. Structural changes in RV, as a response to elevated PAP, are observed even in normal children born and raised at high altitudes [11, 12]. Alterations in RV mechanics, including abnormalities in diastolic properties of RV, were previously reported in healthy highlanders living at 4,000 m [13]. COPD patients living at moderately high altitude are also subject to higher PAP than their counterparts at sea level [14].

We hypothesized that a detailed evaluation of RV in COPD patients living at high altitudes can provide more information about the compensatory responses of RV to advanced and chronic increases in PAP and possible functional consequences of these alterations. In this study, we aimed to assess RV geometry and mechanics in COPD patients residing at a moderately high altitude using two dimensional speckle-tracking and three-dimensional echocardiography.

Materials and methods

Patients with a previous diagnosis of COPD and under follow-up as an outpatient basis in Kafkas University pulmonary diseases clinic were prospectively enrolled for this study. All patients and healthy control subjects included to this study were enrolled at Kars (1,768 m above sea level) and all were natives to this altitude. Patients under 18 years old, with known disorders that can affect RV, such as idiopathic PH, obstructive sleep apnea and pulmonary embolism, those with an left-sided ejection fraction of <50 % or more than grade I diastolic dysfunction, more than mild valvular dysfunction in mitral, aortic or pulmonic valve, more than mild tricuspid stenosis or organic tricuspid insufficiency, known or newly diagnosed congenital heart disease, rhythm other than sinus (including those with frequent extrasystoles), or those who experienced COPD exacerbation (regardless of cause) within 3 months before

enrolment were excluded from study. For the rest of the patients, two-dimensional and three dimensional echocardiograms were obtained before enrolment to check the image quality; patients with poor echocardiographic views for image acquisition were excluded. Those in whom image acquisition could be adequate for either 2D strain analysis or three-dimensional imaging were included. Out of 48 patients that were initially screened, 26 subjects fulfilled these criteria (including image quality) and were therefore enrolled. Control subjects were selected from a population that had similar characteristics to study population (gender, age, etc.) with applying the same exclusion criteria previously stated. All subjects included in control group were evaluated with screening echocardiography and pulmonary function tests (PFTs) to rule out significant cardiac or pulmonary disease. Similar to COPD group, controls that lacked necessary image quality for 3D and deformation analyses were not included. Out of 35 controls screened initially, 26 were found adequate and enrolled.

All COPD patients were initially screened by a pulmonary disease specialist prior to enrolment to ascertain clinical stability and to rule out concurrent diseases such as respiratory tract infections or acute pulmonary embolism that can hinder interpretation of results. Relevant demographic and clinical data, including medications, were recorded from all participants. Blood pressure and heart rate measurements were performed according to standardized methods after 15 min of rest on a chair. Oxygen saturation was measured with a portable pulse oxymeter from tip of thumb before blood pressure measurement.

This study was performed in compliance to Helsinki Declaration. Informed consent was given by all COPD patients and controls, and ethical approval for the study was given by Kafkas University ethics committee.

Spirometry and six minutes walking test

Chronic obstructive pulmonary disease was diagnosed by demonstration of permanent restriction of expiratory air-flow following bronchodilator administration. All patients with an initial suspicion of COPD underwent spirometry after inhalation of 400 µg salbutamol or 1,000 µg terbutaline. Those with a FEV₁/FVC ratio of <70 % were accepted as COPD. Respiratory function tests were performed with MIR Spirolab III (Medical International Research s.r.l., Rome, Italy) platform. Severity of COPD was evaluated according to the ratio of FEV₁ to expected FEV₁ (perFEV₁) values. Patients with a perFEV₁ ratio of more than 50 % were accepted as mild to moderate COPD, while a perFEV₁ ratio of <50 % were accepted as severe COPD. All healthy controls without a suspicion of COPD also underwent spirometry, and those with a FEV₁/FVC ratio of <70 % were excluded from control group.

Six minutes walking test (6MWT) was conducted in a 30 m indoor hall. All subjects were instructed about the test before 6MWT and were allowed 10 min rest before beginning the test. None of the subjects required oxygen supplementation before test. All tests were supervised by a physician involved in this study and emergency equipment was prepared before test. The test was stopped after 6 min or when the subject notified the physician that he/she was unable to continue walking. Final walking distance was measured and noted after the test was terminated.

Blood withdrawal and analysis

Patients and healthy controls were recalled 1 day after echocardiographic examination with overnight fasting before collection of blood samples. Whole blood samples were obtained from subjects in the supine position from the antecubital vein with a 20-gauge needle by applying minimal tourniquet force and were collected in EDTA-containing tubes. Blood samples were studied within 1 h after collection. A complete blood count analysis was obtained from these samples with an automated analyzer (Gen-S, Coulter Corporation, Malvern, USA).

Echocardiographic analysis

Echocardiography was performed with an echocardiography platform (GE Vivid 7, GE Healthcare Systems, Piscataway, New Jersey, USA) with a 1.5–4.0 MHz matrix-array probe for two-dimensional image acquisition and a 1.5–3.6 MHz 4D sector array probe for three-dimensional image acquisition. All images recorded to echocardiography platform were transferred to a workstation with software (Echopac PC, GE Healthcare Systems, Piscataway, New Jersey, USA and TomTec, Tomtec Imaging Systems G.m.B.H., Unterschleissheim, Germany) suitable for analysis of echocardiograms. All recorded images were acquired and analyzed by an observer experienced in echocardiography (TSG).

Two-dimensional diameters of RV were measured from apical four chamber view, from immediately above tricuspid valve and at the level of tricuspid papillary muscles. Right atrial apicobasal and mediolateral dimensions were also measured from these images. Systolic PAP (sPAP) was measured from tricuspid regurgitation flow with continuous-wave (CW) Doppler using modified Bernoulli equation. Pulmonary artery flow velocity profile was recorded from apical short axis views taken from base of the heart with pulsed-wave (PW) Doppler, and pulmonary acceleration time was measured from these recordings. mPAP was calculated from pulmonary acceleration time using Mahan's formula. Tricuspid annular systolic excursion (TAPSE) was measured from M-mode recordings of

lateral tricuspid annulus. Right ventricular inflow velocities (E and A) were measured from the tips of tricuspid valve using PW-Doppler. From the tissue Doppler (TDI) recordings of the lateral tricuspid annulus, the following were measured: Tricuspid annular E and A waves (E' and A', respectively), systolic velocity of tricuspid valve (St), maximal velocity of RV isovolumic contraction, and time-to-peak velocity of RV isovolumic contraction. Right ventricular isovolumic acceleration (RVIVA) was calculated by dividing maximal velocity of RV isovolumic contraction to time to peak velocity of RV isovolumic contraction.

For RV strain analysis, measurement of longitudinal deformation was preferred, as the direction of shortening is mainly basal to apical in RV. Apical four chamber views were recorded with frame-per-second set at maximum (at least 50 fps) for each subject. A minimum of fifteen consecutive cycles were recorded for analysis, and three consecutive cycles that had highest image quality were analyzed offline using Echopac PC software. Endocardial border and myocardium of RV were drawn semi-automatically (Fig. 1). For each analysis, tracking was deemed adequate when at least five of six areas could be automatically tracked by software. As interventricular septal thickness of left ventricle (LV) is higher than RV, septal deformation is considered to reflect LV contractility and not included in analysis. Therefore, strain and strain rate were measured for three regions of RV free (lateral) wall.

For RV end-diastolic and end-systolic volume (RVEDv and RVESv, respectively) measurements, real-time three-dimensional images were taken from apical-lateral window for four consecutive cycles, and automatically reconstructed to obtain full-volume images of heart. Two full-volume images were obtained for each subject. These full-volume images were analyzed with TomTec software specifically designed for RV volume measurement. For each image, endocardial borders were marked in longitudinal, horizontal and oblique (inflow and outflow) views, and a RV cast was automatically generated by the software. Full-volume image that had the best quality for endocardial border tracing was used to produce RV cast. Right ventricular end-diastolic and end-systolic volumes, as well as stroke volume (SV) and RV ejection fraction (RVEF) were obtained from these datasets (Fig. 2). The cut-off for normal RVEF was accepted as 40 %. All volume measurements were also indexed to body surface area (BSA) to correct potential confounders related to body size. BSA of subjects was calculated according to Mosteller's formula.

Ten participants (control or COPD group) were recalled 1 week after initial echocardiographic examination to test inter- and intraobserver variability. Observer variability was calculated for two variables for two dimensional/ Doppler and three dimensional measurements [pulmonary

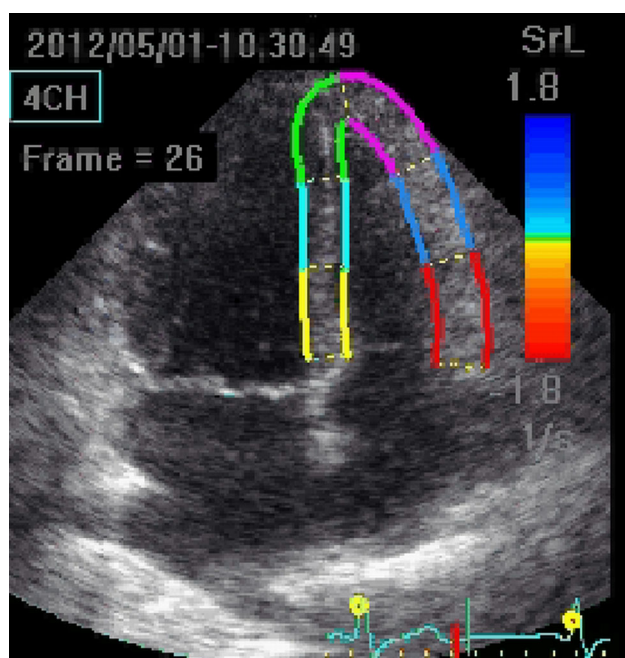


Fig. 1 An example for measurement of right ventricular longitudinal strain with speckle-tracking echocardiography. In this example; basal segment of right ventricular free wall is coded with *red*, mid segment of right ventricular free wall is coded with *blue*, and apical segment of right ventricular free wall is coded with *purple*

acceleration time, RV end diastolic diameter (basal), RV end diastolic and end systolic volumes]. These variables were measured by the same (TSG) and a different (YK) observer. Using this data, intraclass correlation coefficients were calculated to determine interobserver and intraobserver variability.

Statistical analysis

Statistical analyses were carried out with SPSS 17.0 statistical package software (IBM Inc., USA). Continuous variables were expressed as mean $\pm$ SD, while categorical variables were expressed as percentages. For continuous variables, one-sample Kolmogorov–Smirnov test was conducted to test normal distribution. For parameters with normal distribution, student's T test was used to compare groups while Mann–Whitney U test was used in other instances. Chi square and Fisher's exact test were used as appropriate to compare categorical variables between groups. Correlations between parameters were analyzed with Spearman's Rho. A multiple regression model was build using variables that had significant correlation with 6MWT distance to predict independent clinical/spirometric/echocardiographic factors that affected 6MWT distance. A p value of <0.05 was accepted as significant for comparisons between groups. Additionally, a r value above 0.25 was accepted as significant correlation in correlation analysis.

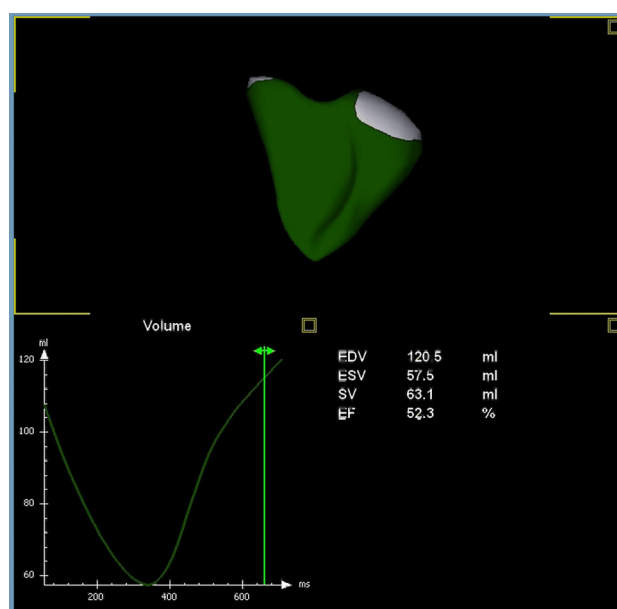


Fig. 2 An example for measurement of right ventricular volumes with three-dimensional echocardiography. *Still frame* of right ventricle was recorded in end-diastole

Results

There were no significant differences between groups regarding to age, gender, height, weight, BSA or accompanying disease, while percentage of smokers was significantly higher in COPD group (Table 1). In COPD group, 83.3 % were taking long-acting beta blockers, while 75 % were on inhaled corticosteroid therapy and a further 66.7 % were using thiotropium. Pulmonary function test findings including percentage of FEV1 to predicted FEV1 (preFEV1), percentage of FVC to predicted FVC (perFVC) and FEV1/FVC ratios were all significantly lower in COPD group (42.92 ± 12.54 % for perFEV1, 61.69 ± 14.28 % for perFVC and 54.42 ± 7.85 % for FEV1/FVC, all values were within normal ranges in control group, $p < 0.001$ for all values). Patients with COPD also had lower mean oxygen saturation (93.77 % $\pm$ 2.41 % vs. 96.35 % $\pm$ 0.59 %, $p < 0.001$) and 6MWT distance (429.69 ± 128.78 m vs. 585.58 ± 140.40 m, $p < 0.001$) compared to controls. Findings in two dimensional echocardiography and Doppler recordings were summarized in Table 2. Both systolic and mPAPs were higher in COPD patients (43.06 ± 11.79 mmHg vs. 35.91 ± 6.11 mmHg for sPAP and 33.39 ± 9.75 mmHg vs. 25.39 ± 8.27 mmHg for mPAP), while RV dimensions and indices of RV systolic function were comparable between groups with two exceptions: RV free wall was significantly thicker (6.19 ± 0.67 mm vs. 4.82 ± 1.16 mm, $p < 0.001$) and RV isovolumic acceleration was significantly lower (4.13 ± 1.04 cm/s² vs. 4.84 ± 1.09 cm/s², $p = 0.033$) in COPD patients. Patients

Table 1 Demographic, clinical and laboratory characteristics of COPD patients and health controls

Parameter	COPD Patients (n = 26)	Control Group (n = 26)	p value
Gender (male %)	88 %	88 %	1
Age (years)	58.88 ± 9.23	56.31 ± 7.33	0.27
Height (cm)	170.1 ± 7.06	170.2 ± 6.7	0.98
Weight (kg)	75.1 ± 8.81	77.6 ± 13.6	0.49
Body surface area (m ²)	1.88 ± 0.13	1.91 ± 0.19	0.58
Smoking habits (%)	88	62	0.03
Exposure to biomass (%)	35	8	0.02
Accompanying disorders ^a (%)	19	23	0.73
Systolic blood pressure (mmHg)	128 ± 19.24	124.58 ± 11.96	0.66
Diastolic blood pressure (mmHg)	82 ± 8.33	78.75 ± 8.56	0.48
Heart rate (beats/min)	84.94 ± 13.55	72.25 ± 15.33	0.02
Oxygen saturation (%)	93.77 ± 2.40	96.35 ± 0.59	<0.001
Hematocrit (%)	49.76 ± 4.09	44.61 ± 5.35	<0.05

Significant differences were given in bold

^a Accompanying disorders were one or more of the following: Hypertension, diabetes, dislipidemia, nonobstructive coronary artery disease, thyroid disease

with COPD also demonstrated significantly increased E/E' ratio (6.04 ± 3.72 vs. 3.72 ± 0.99 , $p = 0.001$). Strain of RV free wall regions, including apical, mid and basal segments, were non-significantly decreased in COPD group, while mean strain of RV free wall was significantly reduced (-21.05 ± 3.80 vs. -24.14 ± 5.37 ; $p = 0.048$) (Table 2; Fig. 3). Among three dimensional echocardiography findings; RVEDv and RVESv, as well as RVEDv and RVESv indexed per BSA were slightly higher in COPD patients, while these findings did not reach statistical significance. Right ventricular ejection fraction was also similar between groups (44.25 ± 11.71 % vs. 45.82 ± 6.95 %, $p = 0.579$). However, number of patients with a RVEF% lower than normal (RVEF < 40 %) was significantly higher in COPD group compared to controls (45.8 % vs. 17.4 %, $p < 0.05$, OR: 4.01, CI 95 % 1.04–15.41) (Fig. 3).

On correlation analysis, the following parameters had significant correlation with 6MWT distance: Age ($p = 0.003$, $r = -0.409$), BSA ($p = 0.042$, $r = 0.327$), heart rate ($p = 0.001$, $r = -0.541$), SatO₂ ($p = 0.001$, $r = 0.502$), FEV₁/FVC ($p = 0.004$, $r = 0.395$), perFEV₁ ($p < 0.001$, $r = 0.552$), perFVC ($p < 0.001$, $r = 0.579$), hematocrit ($p = 0.042$, $r = -0.373$), strain of lateral basal RVFW ($p = 0.015$, $r = -0.381$), mPAP ($p < 0.001$, $r = -0.466$) and E to E' ratio ($p = 0.043$, $r = -0.314$). In multiple regression analysis model, only mPAP

Table 2 Echocardiographic characteristics of COPD patients and healthy controls

Parameter	COPD Group (n = 26)	Control Group (n = 26)	p value
Two dimensional and doppler echocardiography			
Systolic PAP (mmHg)	43.06 ± 11.79	35.91 ± 6.11	0.02
Mean PAP (mmHg)	33.38 ± 9.75	25.39 ± 8.28	<0.01
Basal RV end-diastolic diameter (cm)	38.76 ± 4.18	37.67 ± 4.25	0.38
Mid RV end-diastolic diameter (cm)	31.49 ± 4.01	30.98 ± 4.32	0.68
RV end-diastolic height (cm)	73.55 ± 7.61	69.89 ± 6.37	0.08
RVFW thickness (mm)	6.19 ± 0.67	4.82 ± 1.16	<0.001
TAPSE (mm)	21.71 ± 3.70	22.96 ± 2.93	0.21
Velocity of tricuspid S wave (cm/s)	16.02 ± 3.41	16.51 ± 2.89	0.61
RV isovolumic acceleration (cm/s ²)	4.13 ± 1.04	4.84 ± 1.09	0.03
Tricuspid E/A ratio	1.63 ± 2.45	1.22 ± 0.39	0.26
Tricuspid E/E' ratio	6.04 ± 2.42	3.72 ± 0.99	0.001
Two dimensional deformation imaging and three dimensional echocardiography			
Strain of basal RVFW	-24.45 ± 5.75	-27.91 ± 7.08	0.1
Strain of mid RVFW	-23.05 ± 5.31	-25.85 ± 5.74	0.12
Strain of apical RVFW	-17.12 ± 7.05	-18.67 ± 7.00	0.49
Strain rate of basal RVFW (1/s ⁻¹)	-1.80 ± 1.04	-1.96 ± 0.50	0.55
Strain rate of mid RVFW (1/s ⁻¹)	-1.55 ± 0.37	-1.65 ± 0.27	0.34
Strain rate of apical RVFW (1/s ⁻¹)	-1.50 ± 0.69	-1.36 ± 0.31	0.41
RV end-diastolic volume (ml)	88.41 ± 20.34	81.93 ± 17.87	0.25
RV end-diastolic volume per BSA (ml/m ²)	47.57 ± 10.06	42.57 ± 7.39	0.09

Table 2 continued

Parameter	COPD Group (n = 26)	Control Group (n = 26)	<i>p</i> value
RV end-systolic volume (ml)	48.76 ± 13.08	44.31 ± 10.88	0.21
RV end-systolic volume per BSA (ml/m ²)	25.07 ± 6.84	22.75 ± 4.42	0.24
Right ventricular stroke volume (ml)	39.65 ± 15.14	37.50 ± 9.69	0.56
Right ventricular ejection fraction (%)	44.25 ± 11.71	45.82 ± 6.95	0.58

Significant differences were given in bold

PAP pulmonary artery pressure, RV right ventricle, RVFW right ventricular free wall, TAPSE tricuspid annular plane systolic excursion, BSA body surface area

($\beta = -0.793$, $p < 0.001$) and BSA ($\beta = 0.30$, $p = 0.041$) were independent predictors of 6MWT distance.

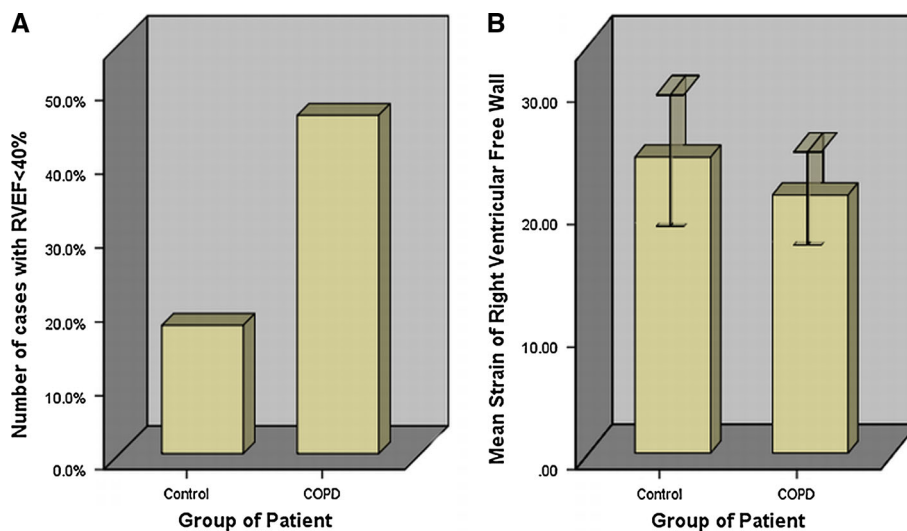
For all tested measurements, intraclass correlation coefficients for intra- and interobserver variability were above 95 %.

Discussion

Main findings in this study can be summarized as follows: (1) COPD patients living at moderately high altitude demonstrate higher PAP than healthy volunteers living at same altitude, (2) Both two-dimensional linear measurements and three-dimensional volume measurements of RV were comparable between groups, and all measurements were within previously defined reference ranges (RR), (3) Although mean ejection fraction of RV was comparable between groups, a higher fraction of subjects in COPD group demonstrated a sub-normal RVEF% and (4) Both RV isovolumic acceleration and mean RV free wall strain were significantly reduced in COPD group. These last two findings reflect underlying RV systolic dysfunction in COPD patients.

Increased PAP is a well-known complication of COPD. Although the reported frequency of COPD-associated PH widely varies between studies, at least 35 % of patients with COPD have a mPAP of more than 20 mmHg, and more than half of patients with advanced disease have PH [15, 16]. PH is usually mild to moderate (i.e. mPAP 20–35 mmHg) and PAP slowly over years in the majority of COPD patients, with an estimated increase of 0.5–1.5 mmHg annually [15, 17]. Approximately 5 % of COPD patients demonstrate high mPAP (above 35 mmHg, with catheter based measurement), which is frequently considered as out-of-proportion [3, 17]. In one series which included patients undergoing lung reduction surgery due to severe COPD, the frequency was found as high as 13.5 % [18]. While not detailed in results section, our results indicate that 57 % of subjects in COPD group had a sPAP of >35 mmHg, and a further 10 % of patients had a sPAP of >50 mmHg, who should be classified as possible and likely echocardiographic PH, respectively [1]. Since the measurements in this present study were made with echocardiography, it is not possible to conclude that COPD patients living at high altitude have increased PH frequency (compared to previous literature) based on these results.

Fig. 3 Fraction of subjects with a sub-normal (< 40 %) right ventricular ejection fraction **a** and mean longitudinal strain of right ventricular free wall **b** within COPD and control groups. For panel **b**, bars represent $\pm$ 1SD and the strain values were changed to positive numbers for illustrative purposes. p value is <0.05 for both measurements



However, present results nonetheless show that PAP is significantly elevated in these patients, leaving RV under a high afterload burden.

In both healthy highlanders and in patients with COPD, hypoxia plays a major role in induction of pulmonary vasoconstriction, increased PAP and adaptive structural changes in right heart [19]. Presence of these two conditions in one subject may lead to a greater degree of hypoxemia, with subsequent derangements in pulmonary circulation. Normal subjects living at high altitude have increased PAP which is attributed to hypoxia-induced pulmonary arteriolar vasoconstriction and increased blood viscosity [20, 21]. In healthy highlanders, PAP increases as the altitude increases, paralleling the reduction of partial oxygen pressure in atmosphere [8, 22, 23]. Although scarce data is available, a few studies showed that COPD patients living above sea level demonstrate higher than expected PAP values. A study conducted at Kathmandu, Nepal (1,400 m above sea level) reported that in patients with acute COPD exacerbation, mild PH (sPAP >40 mmHg) was present in about half of COPD patients (49.1 %), while 17.6 % of the patients had a calculated sPAP of more than 60 mmHg [24]. Our previous work had showed that COPD patients living at >1,500 m above sea level had higher PAP compared to COPD patients living at sea level [14]. Present study also demonstrates that COPD patients also have higher PAP compared to healthy counterparts living at same altitude, and shows that PAP is an independent predictor of 6MWT test distance [25, 26]. Since increased PAP is a predictor of poor prognosis, those COPD patients living at high altitudes could have higher risk for adverse events, but clinical outcome studies are needed to verify this hypothesis.

Right ventricular dilatation and hypertrophy are observed in COPD-related PH to compensate additional pressure load. This adaptation is beneficial as it allows maintenance of a normal cardiac output despite an increase in pulmonary vascular resistance [27, 28]. Although these responses are adaptive in nature, increased RV end-diastolic dimension (indexed to BSA) indicates reduced survival in patients with chronic pulmonary disorders [7]. Since the RV has a complex shape, two-dimensional echocardiographic measurements are inadequate to fully assess these adaptive changes [29]. In addition, correlation of RV dimensions with RV volumes becomes poorer as PAP increases [30]. Three dimensional echocardiographic measurements of RV volumes are free of geometric assumptions. As a result, 3D-TTE is more reproducible than linear measurements and has a higher correlation with MRI measurements [29]. Our findings indicate that end-diastolic and end-systolic values (indexed to BSA) did not differ between COPD and control groups, and both values were within acknowledged RR [29]. In contrast, RV free

wall thickness was significantly higher in COPD group (Table 2). Therefore, it can be assumed that RV hypertrophy, rather than dilatation, is still the primary response of RV to chronically-increased afterload, since these patients have higher PAP values compared to COPD patients living at sea level [14]. In contrast to dilatation, the prognostic implications of RV hypertrophy with clinical outcomes are less clear, although some studies have associated that with worse functional status [9, 29].

Although compensatory RV remodelling allows preservation of SV in the presence of increased afterload, these mechanisms are ultimately detrimental and lead to wall fibrosis, decreased compliance, reduced contractility and finally, RV failure. Both increased PAP and reduced RV contractility are factors that are associated with poor outcomes and mortality in chronic pulmonary disorders, including COPD [7, 15, 31]. As COPD is usually associated with mild or moderate PH, the incidence of RV failure is low in the majority of COPD patients [17]. However, subclinical deterioration in RV contractility is reported in COPD patients, as well as reduced contractility in patients with acute COPD exacerbations [8, 32]. Our findings indicate that neither TAPSE nor annular velocity of lateral tricuspid annulus show a reduction in RV contractility in COPD group. In contrast, mean strain of RV free wall is significantly lower in COPD patients, along with a small but significant reduction in RV isovolumic acceleration. Although both TAPSE and St are robust measures of RV function with a good repeatability, they can be less sensitive to rather small changes in contractility and are affected by overall cardiac motion and loading conditions [29, 33]. RVIVA is a novel parameter that is less load dependent, and is found as an early indicator of RV systolic function [33, 34]. Experimentally, strain and strain rate are closely related to myocardial contractility; and reduced RV strain and strain rate was observed in a number of diseases, such as pulmonary embolism and PH, where RV function is known to be decreased [29]. In a recent study, reduced strain was also demonstrated in diseases such as pulmonary sarcoidosis (without apparent cardiac involvement) where conventional parameters such as TAPSE remained normal [35]. In addition, although mean RVEF% values did not differ between groups, a significant fraction (45.8 %) of subjects within COPD group has a RVEF% value of less than <40 %. Taken together with reduced RVIVA and mean RVFW strain, we consider that these results indicate a reduction in RV contractility, at least in a fraction of COPD patients. Notably, conventional measures of TAPSE and St were not able to show this reduction. It can be assumed that compensatory mechanisms of RV to cope with increased afterload begin to fail after a certain point, similar to other causes of PH, which leaves these patients vulnerable to right-sided heart failure.

An important point that should be emphasized that morphological/functional alterations of right heart and pulmonary circulation of COPD patients were compared with healthy highlanders living at the same altitude. Although this work does not present a direct comparison between healthy highlanders and those residing at sea level, both PAP (mean and systolic) and RV dimensions (including minor and major RV axis, as well as RV free wall thickness) were higher than expected (Table 2). Mean diameters for RV minor axis (as measured from basal and mid levels) were 37.67 ± 4.25 mm and 30.98 ± 4.32 mm, respectively. These values were close to upper limit of normal RR (40 mm and 33 mm), as defined by American Society of Echocardiography [29]. In addition, right ventricular free wall thickness was 4.82 ± 1.16 mm, indicating possible adaptive hypertrophy of RV since the upper limit of RVFW is 5 mm [29]. Although conventional measures of RV longitudinal function and RV-IVA were within RR, mean RVEF% of control group was $45.82 \% \pm 6.95 \%$, which was distinctly lower than normal 3D-TTE measured RVEF% ($67 \% \pm 8 \%$) derived from a large population study [36]. Mild PH, as well as RV dilatation, wall hypertrophy and reduced RV systolic and diastolic function in healthy highlanders was previously described in literature, but it should be emphasized that the majority of these studies were conducted in altitudes above 3,500–4,000 m [11, 13, 20, 37]. In a comprehensive echocardiographic study, Huez and associated had demonstrated increased RV/LV ratio, as well as a reduction in RV systolic and diastolic performance in healthy highlanders (living at 4,000 m) compared to controls from sea level [13]. In the aforementioned study, the authors also noted a decrease in TAPSE (exact values not provided) and St (10.9 ± 1.6 m/s) values in highlanders [13]. Although no studies so far has specifically evaluated echocardiographic features in healthy highlanders living at moderately high altitudes; when previous findings in literature and our current findings are taken together, it is highly possible that similar changes also occur at moderately high altitudes. Therefore, it can be assumed that these findings represent additive effects of COPD-related PH on top of altitude-led adaptation, presuming that “control” group also demonstrate adaptive changes.

Study limitations

Chief limitation of this study is the low number of enrolled subjects, due to the technical difficulties in obtaining good-quality images from COPD patients. While three-dimensional echocardiography is a more robust way to evaluate RV geometry and mechanics, it is nonetheless inferior to gold-standard cardiac magnetic resonance evaluation. Only

longitudinal strain from free wall is measured in this study, since longitudinal axis is the major axis of RV contraction. Adaptive responses to increased PAP develop soon after birth in highlanders and therefore also present in COPD patients native to high altitude [11]. Therefore, these results could not fully represent adaptive RV responses to advanced PH related with COPD in a more general population.

Conclusions

Patients with COPD native to high altitude have higher PAP compared to healthy highlanders, and a significant fraction of these patients have possible or likely PH based on echocardiographic measurements. Hypertrophy, rather than chamber enlargement, is the chief adaptive mechanism of RV to cope with additional pressure load caused by COPD-induced PH. Although not clinically evident, RV systolic dysfunction, as well as abnormal RV diastolic filling, is present in this population, which probably reflects high afterload burden. Discriminative power of conventional parameters (TAPSE and St) to reflect increase in PAP and reduction in RV contractility in COPD patients seems low in this setting. This slight reduction in RV contractility, however, can be demonstrated with newer techniques such as RV-IVA and mean RVFW strain. Also, an important subset of these patients demonstrate a reduction of RVEF% below $<40 \%$. Further studies are needed to assess clinical implications of this RV dysfunction in COPD patients with advanced PH.

Conflict of interest None.

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