Original Article

Right Ventricular Morphology and Function in Chronic Obstructive Pulmonary Disease Patients Living at High Altitude

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Introduction: **Pulmonary vasculature is affected in patients with chronic pulmonary obstructive disease (COPD). As a result of increased pulmonary resistance, right ventricular morphology and function are altered in COPD patients. High altitude and related hypoxia causes pulmonary vasoconstriction, thereby affecting the right ventricle. We aimed to investigate the combined effects of COPD and altitude-related chronic hypoxia on right ventricular morphology and function.**

Materials and Methods: **Forty COPD patients living at high altitude (1768 m) and 41 COPD patients living at sea level were enrolled in the study. All participants were diagnosed as COPD by a pulmonary diseases specialist depending on symptoms, radiologic findings and pulmonary function test results. Detailed two-dimensional echocardiography was performed by a cardiologist at both study locations.**

Results: **Oxygen saturation and mean pulmonary artery pressure were higher in the high altitude group. Right ventricular end diastolic diameter, end systolic diameter, height and end systolic area were significantly higher in the high altitude group compared to the sea level group. Parameters of systolic function, including tricuspid annular systolic excursion, systolic velocity of tricuspid annulus and right ventricular isovolumic acceleration were similar between groups, while fractional area change was significantly higher in the sea level groups compared to the high altitude group. Indices of diastolic function and myocardial performance index were similar between groups.**

Conclusion: **An increase in mean pulmonary artery pressure and right ventricular dimensions are observed in COPD patients living at high altitude. Despite this increase, systolic and diastolic functions of the right ventricle, as well as global right ventricular performance are similar in COPD patients living at high altitude and sea level. Altitude-related adaptation to chronic hypoxia could explain these findings.**

(Heart, Lung and Circulation 2013;22:31–37)

Keywords. Chronic obstructive pulmonary disease; Right ventricle; High altitude; Echocardiography

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide [1]. Hypoxic vasoconstriction and alterations in pulmonary microvasculature, which are both observed in COPD patients, leads to an increase in pulmonary vascular resistance [2]. As a result, this increase in right ventricular (RV) afterload causes right ventricular remodelling, including chamber dilatation and wall hypertrophy and ultimately to functional deterioration [3,4]. Right ventricular function is related to exercise capacity and prognosis in patients with COPD [5].

High altitude environments have decreased partial oxygen pressure in inhaled air. As a result of chronic hypoxia, pulmonary vasoconstriction ensues in inhabitants of high altitude environments [6]. Also, a secondary increase in blood haemoglobin content raises blood viscosity, therefore leading to an increase in both pulmonary and systemic vascular resistance [7]. Right ventricular

Received 1 July 2012; received in revised form 1 August 2012; accepted 5 August 2012; available online 2 September 2012

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1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2012.08.004

dilatation and hypertrophy is observed in highlanders, without an obvious loss of RV functions [8]. As adaptive responses are already recruited in residents of high altitude, it could be expected that additional hypoxic stressors such as COPD could lead to failure of right ventricle in these people.

In this study, we aimed to observe COPD related alterations in right ventricular morphology and function in high altitude residents. Also, as high altitude presents a natural environment of chronic hypoxia, additional effects of chronic hypoxia on right ventricle is studied on COPD patients and compared to patients living at sea level.

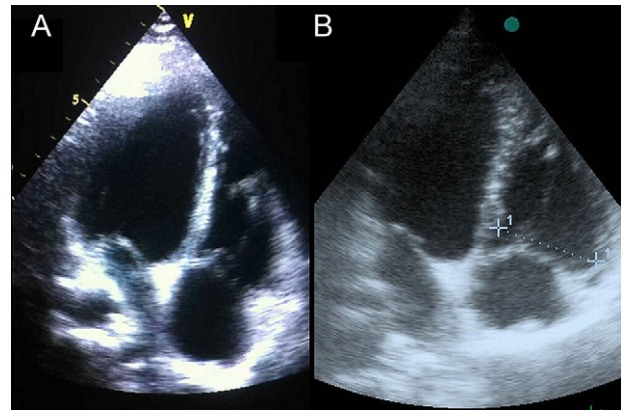

Figure 1. *2D echocardiographic measurement of right ventricular end diastolic diameter in COPD patients (A) residing at sea level and (B) residing at high altitude.*

Materials and Methods

Patient Selection

A total of 40 COPD patients living at high altitude (Kars city centre, 1768 m above sea level) and 41 COPD patients living at sea level (İstanbul, Kadıköy district, at sea level) were enrolled for this study. Patients recruited at high altitude and sea level are natives to that altitude and did not reside

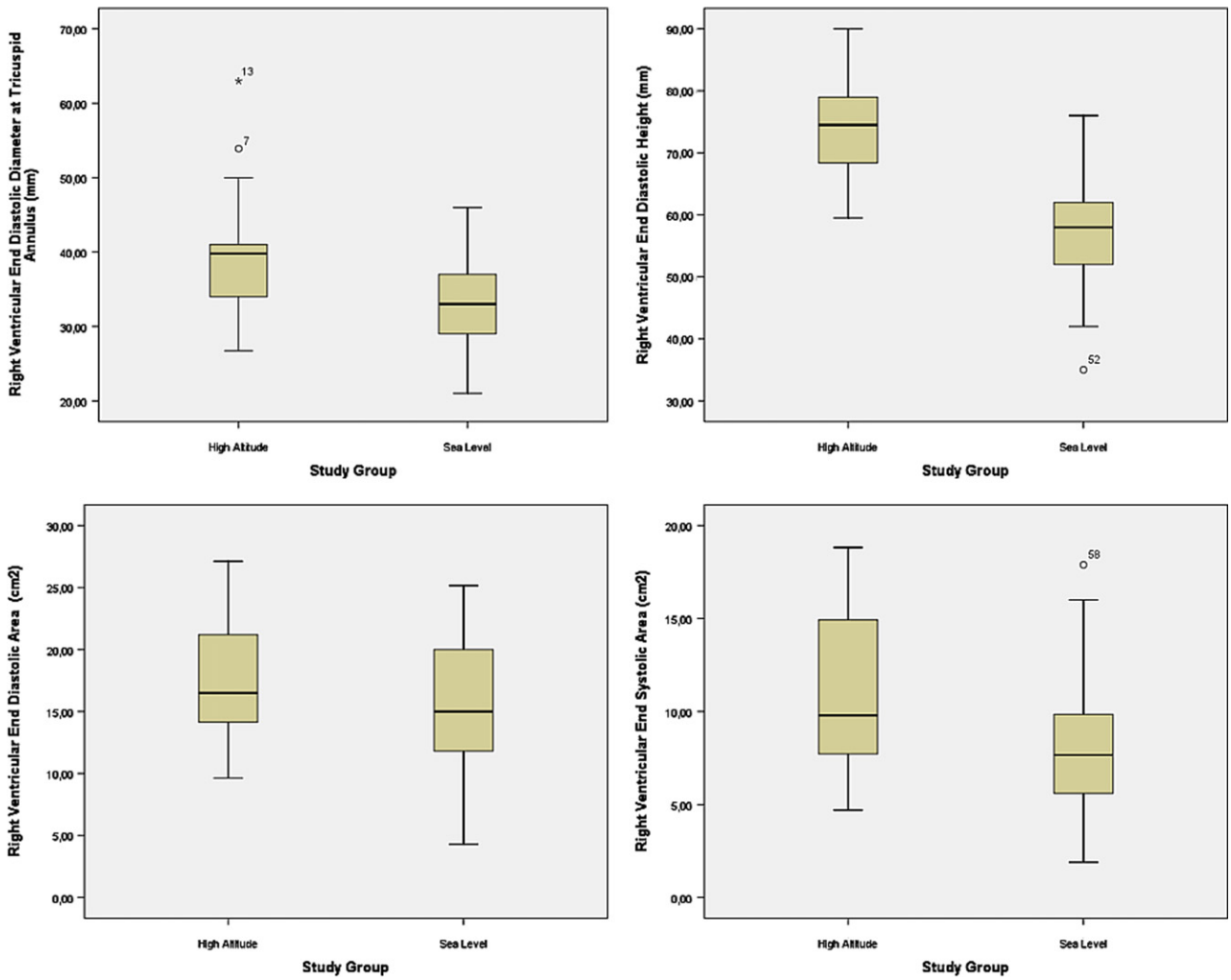

Figure 2. *Boxplot graphics for right ventricular morphologic variables for patients living at sea level and high altitude. (A) Right ventricular end diastolic diameter, (B) right ventricular end diastolic height, (C) right ventricular end diastolic area, (D) right ventricular end systolic area.*

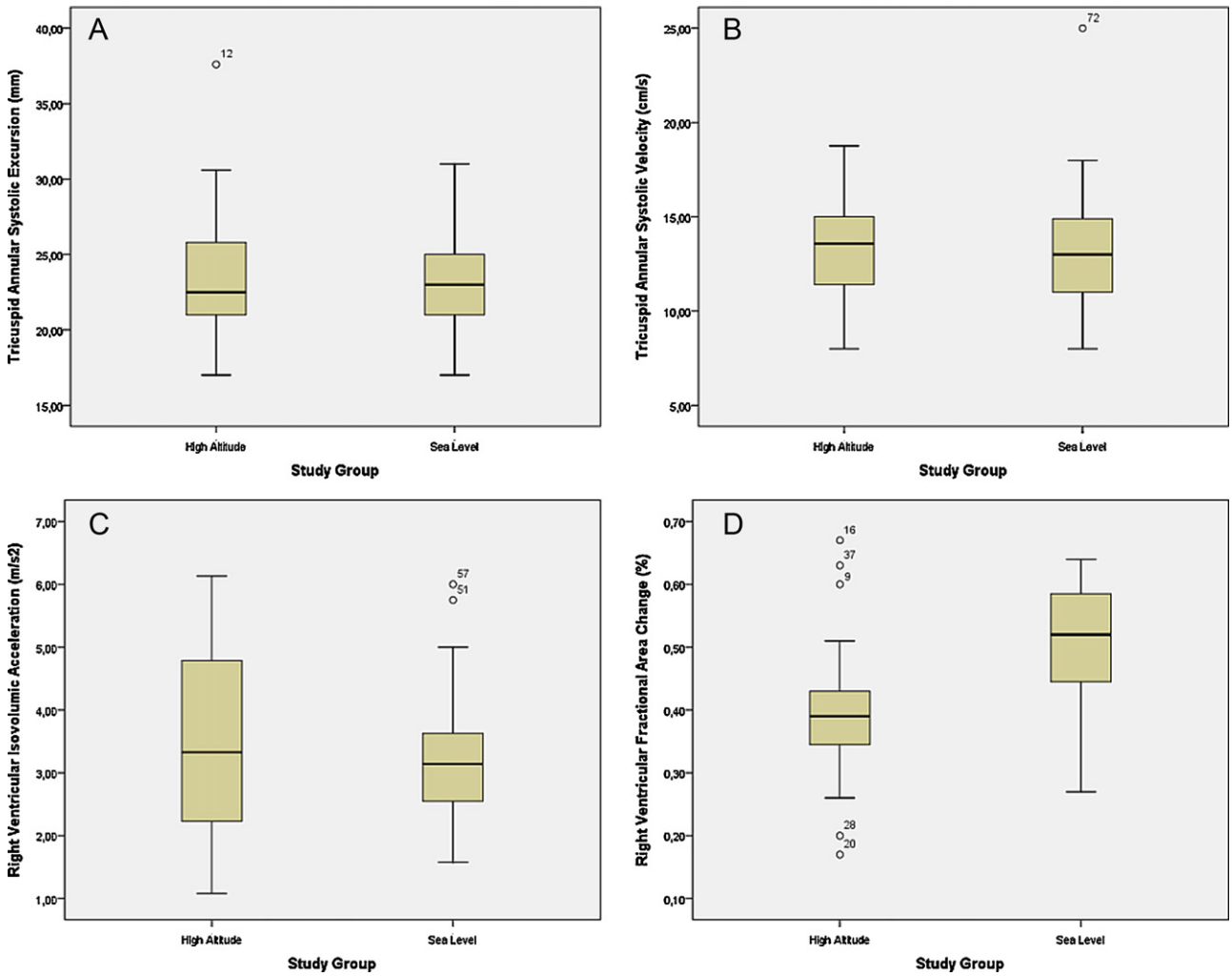

Figure 3. *Boxplot graphics for echocardiographic indices of right ventricular function for patients living at sea level and high altitude. (A) Systolic excursion of tricuspid annulus, (B) systolic velocity of lateral tricuspid annulus, (C) right ventricular isometric acceleration, (D) right ventricular fractional area change.*

at a different altitude during their lifetime except for short travels. Chronic obstructive pulmonary disease patients were selected by a pulmonary diseases specialist at both study locations (GP and Sİ) depending on clinical presentation, radiographic findings and pulmonary function test results. Patients with signs, symptoms and radiographic findings suggestive of COPD, with a postbronchdilator FEV1/FVC < 70% of predicted and FEV1 < 80% of predicted were diagnosed as COPD [1]. All patients included in the study had no history of chronic lung diseases before initial admission. Patients who were less than 18 years-old, had other previous pulmonary or cardiac disease, idiopathic or other type of pulmonary arterial hypertension, history of previous pulmonary embolism, and those having symptoms consistent with obstructive sleep apnea or prior documented nocturnal hypoxaemia were not included in this study. Additionally, patients who had an ejection fraction of less than 50% or constrictive/restrictive physiology, had more than mild valve stenosis or insufficiency, or congenital heart lesion found during echocardiographic evaluation were excluded. For the remaining patients, an informed consent regarding to study was obtained prior to inclusion in study. This study was approved by Kafkas University Medical Faculty Ethics Committee.

For all included patients, demographic variables and information regarding to past medical history were obtained before echocardiographic examination. Additionally, blood oxygen saturation was measured using a pulse oxymeter at both study locations.

Echocardiographic Examination

Echocardiographic examination was carried out with an echocardiography platform (GE Vivid 3, GE Healthcare Systems, Piscataway, New Jersey, USA) equipped with a 1,5–3,6 MHz phased array probe at both study locations by cardiology specialists experienced in echocardiography (TSG and HBE). Left ventricular end diastolic and end systolic measurements, as well as left ventricular septal and posterior wall thickness were obtained from

Table 1. *Demographic Variables, Past Medical Records and Pulse Oxymetry Findings of Groups.*

Parameter	Sea Level COPD Patients ($n = 41$)	High Altitude COPD Patients ($n = 40$)	p Value
Demographic variables and past medical history			
Age (years)	61.15 ± 13.06	59.65 ± 9.67	0.56
Gender (%Male)	32%	10%	0.09
Diabetes (%)	6.2%	6.0%	1
Hypertension (%)	37%	21%	0.18
Smoking (%)	79%	97%	0.06
Smoking (pack year)	17.64 ± 15.13	28.00 ± 17.78	0.25
Pulse oxymetry			
Oxygen Saturation (%)	95.11 ± 3.74	91.00 ± 5.4	<0.001

Continuous variables are presented as mean ± SD. COPD: Chronic Obstructive Pulmonary Disease.

parasternal long axis view in *M*-mode with ultrasound beam aligned to tips of mitral leaflets. From *M*-mode recordings, left ventricular ejection fraction was calculated using Teicholz formula [9]. Pulmonary ejection time and pulmonary acceleration time were obtained with pulse Doppler recordings of pulmonary valve from parasternal short axis view at aortic valve level. Mean pulmonary artery pressure was calculated from pulmonary acceleration time as defined by Mahan and co-workers [10]. Right heart dimensions, including right ventricular end diastolic diameter (RVEDd), right ventricular end diastolic height (RVEDH), right ventricular end systolic diameter (RVESd), right ventricular end diastolic area (RVEDA), right ventricular end systolic area (RVESA) and right atrial diastolic area were obtained from apical four chamber view (Fig. 1). Tricuspid annular systolic excursion was measured in *M*-mode from apical four chamber view with ultrasound beam aligned to lateral aspect of tricuspid annulus. Tricuspid E wave, A wave and duration from end of A wave to beginning of next E wave were measured from PW-Doppler recordings of tricuspid outflow obtained from apical four chamber view. Systolic velocity of right ventricular free wall (St), and diastolic velocities of right ventricle (Et and At) were recorded from lateral aspect of tricuspid annulus. Right ventricular free wall thickness was obtained from subcostal four chamber view. Right ventricular myocardial performance index (MPI) was calculated as defined by Tei et al. [11]. Right ventricular fractional area change was calculated by subtracting RVESA from RVEDA, and dividing the result by RVEDA. All measurements were made according to American Society of Echocardiography guidelines [12,13].

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 (International Business Machines Corp., New Orchard Road, Armonk, New York, USA). Quantitative data was given as mean ± SD and categorical data was given as percentages. Normal distribution and differences between variances were determined using Kolmogorov–Smirnov and Levene tests, respectively. For continuous variables, Student's *T* test and Mann Whitney *U* test were used as appropriate. For categorical variables, χ^2 test or Fisher's exact test was used. For all variable comparisons, exact p value was provided. A p value of less than 0.05 was accepted as significant.

Fifteen patients that were included in the study were called back two days after echocardiographic examination to test intraobserver consistency. Six patients at sea level and seven patients at high altitude came back for repeat echocardiographic examination. Cronbach's alpha was calculated for two parameters at each study institution.

Results

Demographic and clinical variables for high altitude and sea level groups were given in Table 1. There were no significant differences regarding to age, gender, history of diabetes, history of hypertension, or history of smoking. Oxygen saturation was significantly lower in high altitude group compared to sea level group (91.00 ± 5.4 vs. 95.11 ± 3.74; $p < 0.001$). Left ventricular parameters were not different between groups (Table 2). In contrast, right ventricular parameters, including RVEDd (38.95 ± 7.23 mm vs. 33.00 ± 5.69 mm; $p < 0.001$), RVEDH (74.48 ± 8.04 mm vs. 57.33 ± 9.35 mm; $p < 0.001$), RVESd (28.39 ± 7.16 mm vs. 22.07 ± 6.51 mm; $p < 0.001$), right ventricular free wall thickness (6.19 ± 1.10 mm vs. 4.38 ± 1.77 mm; $p < 0.001$) and end systolic area of right ventricle ($10.90 \pm 4.10\,mm^2$ vs. $7.79 \pm 3.43\,mm^2$; $p < 0.01$) were significantly higher in HA group compared to SL group. End diastolic area of right ventricle was also higher in HA group, while this finding had no statistical significance (17.85 ± 4.94 vs. 15.55 ± 5.12; $p = 0.053$) (Fig. 2). Mean pulmonary arterial pressure was higher in HA group compared to SL group (36.05 ± 10.19 mmHg vs. 26.78 ± 11.12 mmHg; $p < 0.001$). Parameters of right ventricular systolic function, including tricuspid annular systolic excursion (23.39 ± 4.32 mm vs. 22.97 ± 3.17 mm; $p = 0.63$), systolic velocity of tricuspid annulus (13.44 ± 2.59 cm/s vs. 13.10 ± 3.13 cm/s; $p = 0.61$) and acceleration of isovolumic contraction ($3.51 \pm 1.45\,cm/s^2$ vs. $3.20 \pm 1.01\,cm/s^2$; $p = 0.36$) were similar between groups, while right ventricular fractional area change was significantly higher in sea level group (0.50 ± 0.10 vs. 0.40 ± 0.11, $p < 0.001$) (Table 3). Parameters of right ventricular diastolic function,

Table 2. *Echocardiographic Variables for Left Ventricular Morphology and Function of Groups.*

Parameter	Sea Level COPD Patients ($n = 41$)	High Altitude COPD Patients ($n = 40$)	p Value
Left ventricular end diastolic diameter (mm)	45.77 ± 4.42	47.78 ± 5.49	0.1
Left ventricular end systolic diameter (mm)	27.27 ± 4.08	28.93 ± 5.77	0.18
Left ventricular ejection fraction (%)	67 ± 5.7	70 ± 8.3	0.10
Mitral E wave (m/s)	0.59 ± 0.18	0.66 ± 0.20	0.13
Mitral A wave (m/s)	0.81 ± 0.27	0.74 ± 0.20	0.19
Lateral mitral annulus E wave (cm/s)	9.40 ± 3.42	10.95 ± 3.56	
Lateral mitral annulus A wave (cm/s)	12.10 ± 3.05	12.53 ± 3.17	0.53
Lateral mitral annulus S wave (cm/s)	8.88 ± 3.63	10.24 ± 2.80	<0.01
Interventricular septum thickness (mm)	10.30 ± 1.27	10.15 ± 1.26	0.68
Posterior wall thickness (mm)	9.85 ± 2.13	9.03 ± 1.93	0.01
E/Em ratio	6.81 ± 2.33	6.62 ± 2.71	0.66

Data is given as mean ± SD. COPD: Chronic Obstructive Pulmonary Disease; Em: Lateral Mitral Annulus E Wave.

Table 3. *Echocardiographic Parameters for Right Ventricular Morphology and Function of Study Groups. Data is Given as Mean ± SD. COPD: Chronic Obstructive Pulmonary Disease; E: Early Tricuspid Flow; Et: Lateral Tricuspid Annular E Velocity.*

Parameter	Sea Level COPD Patients ($n = 41$)	High Altitude COPD Patients ($n = 40$)	p Value
Right ventricular end diastolic diameter (mm)	33.00 ± 5.69	38.95 ± 7.23	<0.001
Right ventricular end systolic diameter (mm)	22.07 ± 6.51	28.39 ± 7.16	<0.001
Right ventricular height at end diastole (mm)	57.33 ± 9.35	74.48 ± 8.04	<0.001
Right ventricular free wall thickness (mm)	4.38 ± 1.77	6.19 ± 1.10	<0.001
Right ventricular end diastolic area (cm^2)	15.55 ± 5.12	17.85 ± 4.94	0.053
Right ventricular end systolic area (cm^2)	7.79 ± 3.43	10.90 ± 4.10	<0.01
Right ventricular fractional area change (%)	50 ± 9.98	40 ± 10.61	<0.001
Right atrial end diastolic area (cm^2)	14.70 ± 4.63	13.97 ± 6.19	0.572
Lateral tricuspid annulus S wave (cm/s)	13.10 ± 3.13	13.44 ± 2.59	0.61
Tricuspid annular excursion at systole (mm)	22.97 ± 3.17	23.39 ± 4.32	0.63
Right ventricular isovolumic acceleration (cm/s^2)	3.20 ± 1.01	3.51 ± 1.45	0.36
Maximal velocity of tricuspid regurgitation (m/s)	2.22 ± 0.50	2.61 ± 0.40	<0.01
Mean pulmonary artery pressure (mmHg)	26.78 ± 11.12	36.06 ± 10.19	<0.001
E/A ratio	1.00 ± 0.40	1.20 ± 0.48	0.09
E/Et ratio	4.64 ± 1.88	5.28 ± 1.60	0.12
Right ventricular myocardial performance index	0.46 ± 0.22	0.53 ± 0.28	0.29

including tricuspid E/A ratio, E/Et ratio and right atrial area were not different between groups. Right ventricular myocardial performance index (MPI) was higher in HA group (0.53 ± 0.28) compared to SL group (0.46 ± 0.22), but this finding had no significance ($p = 0.238$) (Fig. 3).

Cronbach's alpha values were 0.98 and 0.95 for observer at sea level; 0.94 and 0.89 for observer at high altitude.

Discussion

This study shows that pulmonary artery pressure and right ventricular dimensions are increased in COPD patients living at high altitude, probably related to chronic hypoxic environment of high altitude. Although right ventricular afterload is higher in COPD patients living at high altitude, systolic and diastolic functions are similar to COPD patients living at sea level. Global right ventricular MPI is similar between groups, while mean MPI is higher than reference limits in all COPD patients.

Pulmonary vasculature is affected early in the course of COPD [14]. Vasoconstrictor stimuli of arterial hypoxaemia lead to trophic changes in small pulmonary arteries and arterioles [15]. During the course of disease, further loss of parenchymal tissue along with associated pulmonary vascular bed and a change of balance towards vasoconstrictor substances causes further increases in pulmonary vascular resistance [3,16]. As a result of increased pulmonary resistance, morphologic remodelling and functional alterations occur in right ventricle. Alterations in right

ventricle are reported even in the absence of pulmonary hypertension [17].

Oxygen content and partial oxygen pressure drops at high altitude environments. This drop of oxygen fraction in inhaled air causes hypoxaemic vasoconstriction in small pulmonary arteries and arterioles [7], and stimulates secondary polycythemia [18]. Both conditions lead to an increase in pulmonary arterial resistance. In residents living at high altitude, right ventricular hypertrophy is observed as a response to pressure load [19], which is similar to patients with pulmonary hypertension. Our results showed an increase in tricuspid regurgitant velocity, shortened pulmonary ejection time and increased mean pulmonary artery pressure in COPD patients residing at high altitude. Also, right ventricular dimensions and right ventricular free wall thickness were significantly higher in high altitude COPD patients compared with sea level group.

Despite an obvious increase in afterload and morphological alterations in RV, our results indicate that indices of RV systolic function, including TAPSE, tissue velocity of systolic annular motion, and right ventricular isovolumic acceleration were not different between groups. Only right ventricular fractional area change was significantly higher in SL group, which was a result of decreased RV end diastolic and end systolic dimensions observed at sea level. Similar to systolic function, echocardiographic parameters of RV diastolic function such as E/A ratio, E/Et ratio or right atrial area were similar between groups. When considered globally, these findings demonstrate that right ventricular systolic and diastolic functions in COPD patients residing at high altitude are no further compromised than COPD patients living at sea level.

Right ventricular function is an important determinant of prognosis in patients with COPD and pulmonary hypertension. A recent study highlighted the importance of RV function in exercise tolerance of COPD patients [5]. Acute hypoxia was shown to increase pulmonary vascular resistance and pulmonary arterial pressure, without affecting right ventricular systolic performance [20]. Treatment of acute COPD exacerbations was shown to reduce pulmonary artery pressure and improve right ventricular function [21]. However, the effect of chronic hypoxia on RV function in COPD patients was not studied before. Our results show that haemodynamic effects induced by COPD do not further deteriorate RV function in a chronic hypoxic environment.

In residents living at high altitudes, the right ventricular free wall is thicker than populations living at sea level. In children born at high altitudes, the right ventricular wall fails to regress after first year of life, and remains thicker throughout their life [8,19]. This adaptation of the right ventricle is possibly related to preservation of right ventricular systolic function in COPD patients living at high altitude observed in our study.

Right ventricular myocardial performance index reflects overall systolic and diastolic performance of the right ventricle. Normal value for RV-MPI is identified as 0.28 ± 0.04, while this value was found 0.93 ± 0.34 in patients with primary pulmonary hypertension [22]. A previous study demonstrated that COPD patients with or without pulmonary hypertension had increased RV-MPI values compared to normal controls [23]. Our results also confirm this observation, while increased pulmonary pressure observed at high altitude (mPAP > 30 mmHg in COPD patients living at HA) did not translate into significantly higher RV-MPI values compared to COPD patients living at sea level. Again, this "preservation" of overall RV performance could be a result of adaptation to chronic hypoxia in COPD patients living at high altitudes.

Conclusions

Right ventricular morphology in COPD patients living at high altitude is different from COPD patients living at sea level. Right ventricular systolic and diastolic performances are similar in high altitude COPD patients and sea level COPD patients despite the former having elevated mean pulmonary artery pressure. This preservation of right ventricular function is probably related to right ventricular adaptation induced by altitude-related chronic hypoxia.

Study Limitations

This study was designed to observe the additional effects of chronic hypoxia on right ventricular functions in patients with COPD, and the control group was formed from individuals with COPD living at sea altitude. Therefore, our study showed that altitude and associated hypoxia has negligible negative effects on right ventricular function in COPD patients native to high altitude. Although we did not make comparisons with normal individuals, mean values for echocardiographic indices of right ventricular systolic function, such as tricuspid annular systolic excursion, systolic velocity of lateral tricuspid annulus or fractional area change of right ventricle were within normal limits. As there were no standardised indices for right ventricular diastolic function, no comparisons could be made for parameters of RV diastolic function.

Patients included in HA group were all natives and therefore lived under high altitude conditions after birth. Therefore, this study does not provide information about right ventricular function in COPD patients native to sea levels who travel to high altitudes. Although acute, short term hypoxia was not shown to have any effect on the right ventricle, functional impairment in RV could happen after exposure to long term hypoxia. Further studies are required to ascertain effects of long term hypoxia on the right ventricular function in COPD patients who reside at sea level.

References

[1] Global strategy for diagnosis, management and prevention of chronic obstructive pulmonary disease (Revision 2011). Global Initiative for Chronic Obstructive Lung Disease (GOLD), www.goldcopd.com.

[2] Peinado VI, Pizarro S, Barberà JA. Pulmonary vascular involvement in COPD. Chest 2008;134:808–14.

[3] Gupta NK, Agrawal RK, Srivastav AB, Ved ML. Echocardiographic evaluation of heart in chronic obstructive pulmonary disease patient and its co-relation with the severity of disease. Lung India 2011;28:105–9.
[4] Gao Y, Du X, Qin W, Li K. Assessment of the right ventricular function in patients with chronic obstructive pulmonary disease using MRI. Acta Radiol 2011;52:711–5.
[5] Cuttica MJ, Shah SJ, Rosenberg SR, Orr R, Beussink L, Dematte JE, et al. Right heart structural changes are independently associated with exercise capacity in non-severe COPD. Plos One 2011;6:e29069.
[6] Berger MM, Dehnert C, Bailey DM, Luks AM, Menold E, Castell C, et al. Transpulmonary plasma ET-1 and nitrate differences in high altitude pulmonary hypertension. High Alt Med Biol 2009;10:17–24.
[7] Naeije R. Physiological adaptation of the cardiovascular system to high altitude. Prog Cardiovasc Dis 2010;52: 456–66.
[8] Penazola D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation 2007;115:1132–46.
[9] Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic–angiographic correlations in the presence of absence of asynergy. Am J Cardiol 1976;37:7–11.
[10] Dabestani A, Mahan G, Gardin JM, Takenaka K, Burn C, Allfie A, et al. Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography. Am J Cardiol 1987;59:662–8.
[11] Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function–a study in normals and dilated cardiomyopathy. J Cardiol 1995;26:357–66.
[12] Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al. ACC; AHA; ASE, ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr 2003;16: 1091–110.
[13] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.
[14] Wright JL, Churg A. A model of tobacco smoke-induced airflow obstruction in the guinea pig. Chest 2002;121:188S–91S.
[15] Stenmark KR, Fagan KA, Frid MG. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. Circ Res 2006;99:675–91.
[16] Wrobel JP, Thompson BR, Williams TJ. Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. J Heart Lung Transplant 2012;31:557–64.
[17] Vonk-Noordegraaf A, Marcus JT, Holverda S, Roseboom B, Postmus PE. Early changes of cardiac structure and function in COPD patients with mild hypoxemia. Chest 2005;127:1898–903.
[18] Pugh LGCE. Blood volume and hemoglobin concentration at altitudes above 18,000 ft (5500 m). J Physiol 1964;170:344–54.
[19] Aparicio Otero O, Romero Gutierrez F, Haris P, Anand I. Echocardiography shown persistent thickness of the wall of the right ventricle in infancts at high altitude. Cardioscience 1991;2:63–9.
[20] Akgül F, Batyraliev T, Karben Z, Pershukov I. Effects of acute hypoxia on left and right ventricular contractility in chronic obstructive pulmonary disease. Int J Chronic Obstruct Pulm Dis 2007;2:77–80.
[21] Akcay M, Yeter E, Durmaz T, Akar Bayram N, Uyar M, Davutoglu M, et al. Treatment of acute chronic obstructive disease exacerbation improves right ventricle function. Eur J Echocardiogr 2010;11:530–6.
[22] LaCorte JC, Cabreriza SE, Rabkin DG, Printz BF, Coku L, Weinberg A, et al. Correlation of the tei index with invasive measurements of ventricular function in a porcine model. J Am Soc Echocardiogr 2003;16:442–7.
[23] Yılmaz R, Gencer M, Ceylan E, Demirbag R. Impact of chronic obstructive pulmonary disease with pulmonary hypertension on both left ventricular systolic and diastolic performance. J Am Soc Echocardiogr 2005;18:873–81.