

Assessment of the Ventricular Function of Patients with Advanced Chronic Obstructive Pulmonary Disease by Using Magnetic Resonance Imaging

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Objective

To assess the mechanisms that may be involved in the evolution of right and left ventricular dysfunction in patients with chronic obstructive pulmonary disease (COPD).

Methods

Magnetic resonance imaging was used in 11 control patients (group C) and 27 patients with COPD, who were divided into 2 groups, COPD_c and COPD_s, according to the presence or absence of right ventricular dysfunction, respectively. Doppler echocardiography was used for assessing the degree of pulmonary hypertension.

Results

The right ventricular diameter was similar in the 3 groups, COPD_s, COPD_c and C (29 ± 8 mm; 31 ± 7 mm; and 30 ± 6 mm; respectively, $P = \text{NS}$). Right ventricular hypertrophy was observed only in the COPD groups (8 ± 2 mm and 9 ± 3 mm vs 5 ± 1 mm; $P < 0.01$). The percentage of systolic right ventricular lateral wall thickening (%RVLWT) in the 3 groups were as follows: $86 \pm 82\%$ vs $41 \pm 35\%$ vs $86 \pm 89\%$; $P = \text{NS}$). Different left ventricular ejection fractions were observed in the groups as follows: $69 \pm 9\%$ vs $55 \pm 16\%$ vs $76 \pm 6\%$; $P < 0.01$. A positive and significant linear correlation was observed between the left ventricular (LV) diastolic diameter and the LV systolic volume ($r = 0.72$; $P < 0.01$). No correlation was observed between the pulmonary volumes, arterial blood gas analysis, and ventricular function.

Conclusion

No correlation was observed between the severity of pulmonary function and the degree of ventricular function impairment. Whether a preserved %RVLWT means the possibility of reversibility of right ventricular function remains to be elucidated. However, the presence of the phenomenon of ventricular interdependence was confirmed.

Keywords

chronic obstructive pulmonary disease, ventricular function, magnetic resonance imaging.

Despite optimized medical therapy, patients with chronic obstructive pulmonary disease (COPD) tend towards progressive dyspnea, low tolerance to exercise, and an increase in morbidity and mortality when compared with those in cohorts of similar ages. When the forced expiratory volume in the first second (FEV_1) is lower than 0.75 L or 30% of that predicted, the mortality rate is 40% to 50% in 3 years. Age > 65 years also contributes to increased mortality^{1,2}, and pulmonary hypertension, the major complication of the disease, predisposes to the development of cor pulmonale, which, by itself, is associated with a poor prognosis³. The study of the ventricular function through conventional methods, such as echocardiography and computed tomography, is difficult^{4,5}. Therefore, magnetic resonance imaging has been used as a more reliable method for analyzing the right ventricle (RV). In recent years, due to the difficulty in performing lung or heart-lung transplantation, lung volume reduction surgery (LVRS) has become an option to patients in an advanced stage of chronic obstructive pulmonary disease^{6,7}. From the cardiovascular point of view, LVRS has been contraindicated to those with right and/or left ventricular dysfunction and to those with severe pulmonary hypertension⁸. Recently, some authors⁹ have reported the possibility of reverting right ventricular function with LVRS. If better ventricular function can be observed in some cases after pulmonary resection, why not expand its indication? What can truly suggest that the ventricular function is irreversible? Other questions regarding the left ventricle (LV) still persist. Is left ventricular dysfunction consequent to hypoxia? Is coronary artery disease associated with or secondary to right ventricle dysfunction itself?¹⁰⁻¹³

In the present study, the right and left ventricular functions of a group of patients with moderate to severe chronic obstructive pulmonary disease were carefully analyzed, aiming at, through the precise knowledge of biventricular function, understanding the mechanisms involved in the deterioration of the functions of 1 or both ventricles.

Methods

Twenty-seven patients with chronic obstructive pulmonary disease and 11 healthy individuals (control) were studied. The diagnosis was based on the definition of the American Thoracic Society (ATS)¹⁴. The inclusion criteria of the control group were the presence of a normal physical examination, chest radiography, electrocardiography, and exercise testing, in addition to the absence



of a history of smoking. All participants signed a written informed consent after approval of the protocol by the local committee on ethics.

The patients with chronic obstructive pulmonary disease underwent pulmonary function tests and assessment of the ventricular function and the degree of pulmonary hypertension in a period of 10 ± 3 days. After a 30-minute rest, an arterial blood sample was obtained for gas analysis. The pulmonary volumes and capacity of pulmonary diffusion were measured with adequate spirometric devices (Collins/GS; Milwaukee, USA) according to the recommendations of the ATS^{15,16}.

Pulmonary hypertension was quantified by using Doppler echocardiography (ATL – HDI 3000 or 5000 model; Bothell, WA, USA). The mean pulmonary artery pressure (MPAP) was quantified through the time of acceleration of the pulmonary flow (TAC) on Doppler¹⁷⁻¹⁹. The systematic calculation of the pulmonary artery systolic pressure through acquisition of the velocity of tricuspid regurgitation was not routinely used, due to the difficulty of obtaining the echocardiographic window in patients with pulmonary hyperinflation.

Coronary artery disease, as a cause of left ventricular dysfunction, was excluded due to the lack of history of precordial pain and of alterations in myocardial scintigraphy and in the pharmacological dobutamine stress test.

A previous history of systemic arterial hypertension and the presence of right bundle-branch block on the electrocardiogram, which could influence the interpretation of ventricular function, were recorded.

Considering that the irregular rhythm may hinder the measurement of cardiac chambers on magnetic resonance imaging, patients with atrial fibrillation or frequent ectopic beats were excluded from the study protocol.

The 1.5T Horizon (GE) model was used for magnetic resonance imaging. To determine the anatomy and future planning of the images, 3 spin-echo sequences were obtained in the coronal, transverse, and sagittal planes. The gradient-echo technique was used with the following parameters: mean repetition time of 9 ms, echo time of 4 ms, cut thickness of 10 mm, field of view of 320° , tilt angle of 35 mm, and matrix of 128×256 . The temporal resolution was 12 to 16 phases per cardiac cycle.

The following parameters were analyzed for each ventricle: ejection fraction (Simpson formula), systolic volume, cardiac output, thickening of the interventricular septum, percentage of septal thickening during systole, thickness of the lateral ventricular wall, percentage of thickening of the lateral ventricular wall during systole, diameter of the long and short ventricular axes during diastole and systole, and the ratio between the diameters of the long and short ventricular axes during both diastole and systole^{20,21}.

The percentage of systolic parietal thickening was obtained based on the equation²²:

$$\% \text{ parietal thickening} = \frac{(ST - DT)}{DT} \cdot 100\%$$

where, ST = systolic parietal thickness, DT = diastolic parietal thickness.

The ratio between the short axis diameter and the long axis diameter (SA/LA) of the left ventricle during diastole and systole is used for observing the change in ventricular geometry during the cardiac cycle. The difference between the SA/LA ratios during

diastole and systole was used as a method for quantifying, in absolute values, the systolic motion of the interventricular septum towards the left ventricle. Therefore, the percentage of interventricular septal motion towards the left ventricle during systole (%LSD) was obtained based on the equation:

$$\% \text{ LSD} = \frac{(SA/LA_{\text{diastole}} - SA/LA_{\text{systole}})}{SA/LA_{\text{diastole}}} \cdot 100\%$$

According to the literature^{23,24}, the patients with right ventricular ejection fraction (RVEF) below 45% on magnetic resonance imaging were classified as having right ventricular dysfunction. Therefore, the patients with COPD were divided into the following 2 groups: COPD_s group = without RV dysfunction; COPD_c group = with RV dysfunction; group C = control (healthy).

The characteristics of the groups studied were compared using the Fisher exact test and the Student *t* test. The ANOVA and the Kruskal-Wallis test were used for assessing the differences between the parameters of the LV and RV obtained on magnetic resonance imaging. The Pearson test assessed the existence of linear correlations between the ejection fractions of the LV and RV, between the LV diameter during diastole and its systolic volume, and between the pulmonary parameters and MPAP. All calculations were performed using a system of statistical analysis (SSA). A *P* value < 0.05 was considered significant.

Results

The control, COPD_s, and COPD_c groups comprised 11, 16, and 11 individuals, respectively. The characteristics of the 3 groups are shown in table I. Fifteen patients with chronic obstructive pulmonary disease were continuous users of O₂ according to the national and international consensus of continuous O₂ inhalation therapy²⁵⁻²⁸.

Table II shows the results of arterial gas analysis and of the pulmonary function tests of the COPD_s and COPD_c groups. Statistical differences were not observed between both groups (*P* = NS). A linear correlation was observed between the predicted percentage of the forced expiration volume in the first second (%FEV₁) and the partial pressure of arterial oxygen (PaO₂) (*r* = 0.32; *P* < 0.01).

Quantification of the pulmonary artery pressure was technically possible in 20 patients with COPD (74%). The systolic pulmonary artery pressure (SPAP) and MPAP of the COPD_s and COPD_c groups were similar, 57 ± 14 mmHg versus 59 ± 17 mmHg, and 40 ± 9 mmHg versus 40 ± 11 mmHg, respectively (*P* = NS). An MPAP ≥ 35 mmHg was observed in 13 patients with COPD, 8 in the COPD_s group, and 5 in the COPD_c group. A linear and significant correlation was observed between PaO₂ and MPAP (*r* = 0.45; *P* < 0.01) (fig. 1). No correlation was observed between %FEV₁ and MPAP. Moreover, no correlation was observed between MPAP and the RV ejection fraction (RVEF), and between PaO₂ and the LV ejection fraction (LVEF).

Table III shows the parameters derived from the analyses of the right ventricle on magnetic resonance imaging in the 3 groups. The RVEF of the control, COPD_s, and COPD_c groups were, respectively, $54 \pm 8\%$, $53 \pm 6\%$, and $32 \pm 8\%$. These differences between the RVEF were already expected, because the COPD_c group was selected as that with RVEF < 45%, and the COPD_s group as that with RVEF > 45%. The COPD_c group had a lower right ventricular

Table I – Characteristics of the control, COPD_s, and COPD_c groups

	Group C (n = 11)	COPD _s group (n = 16)	COPD _c group (n = 11)	p
Age (years)*	60±11	65±8	57±11	NS
Male sex (%)	9 (82)	13 (81)	7 (73)	NS
BSA (m ²)*	1.63±0.20	1.78±0.25	1.59±0.19	NS
Arterial hypertension (%)	-	7 (44)	4 (36)	NS
Right bundle-branch block (%)	0 (0)	4 (25)	2 (18)	NS
Continuous use of O ₂ (%)	-	8 (50)	7 (64)	NS

* Results presented as mean ± standard deviation. BSA = body surface area. NS = P > 0.05; COPD = chronic obstructive pulmonary disease.

Table II – Arterial gas analysis and pulmonary function of the COPD* groups

	COPD _s group	COPD _c group	p
PaO ₂ (mmHg)	66±14	63±17	NS
PaCO ₂ (mmHg)	48±13	50±7	NS
FEV ₁ (previewed %)	39±20	27±12	NS
RV (previewed %)	191±61	204±59	NS
TLC (previewed %)	115±21	104±29	NS
RV/TLC (previewed %)	167±33	185±26	NS
DLCO (previewed %)	42±29	53±16	NS

* Results presented as mean ± standard deviation. PaO₂ = partial pressure of arterial oxygen; PaCO₂ = partial pressure of carbon dioxide; FEV₁ = forced expiration volume in the first second; RV = residual volume; TLC = total lung capacity; DLCO = diffusing lung capacity for carbon monoxide; COPD = chronic obstructive pulmonary disease. NS = P > 0.05.

Table III – Parameters of right ventricular function*

	Group C	COPD _s group	COPD _c group	p
RVEF (%)	54±8	53±6	32±8	
RVSV (mL)	58±28	66±19	40±21	†
RVCO (L/min)	4±2	5±2	3±2	NS
RVLWT (mm)	5±1	8±2	9±3	‡, §
%RVLWT	86±89	86±82	41±35	NS
RVSA (mm)	30±6	29±8	31±7	NS

* Results presented as mean ± standard deviation. †P < 0.01, COPD_s versus COPD_c; ‡P < 0.01, group C versus COPD_s group; §P < 0.01, group C versus COPD_c group. RVEF = right ventricular ejection fraction; RVSV = right ventricular systolic volume; RVCO = right ventricular cardiac output; RVLWT = right ventricular lateral wall thickness; %RVLWT = percentage of systolic right ventricular lateral wall thickness; RVSA = diameter of the right ventricular short axis at the end of diastole; COPD = chronic obstructive pulmonary disease. NS = P > 0.05.

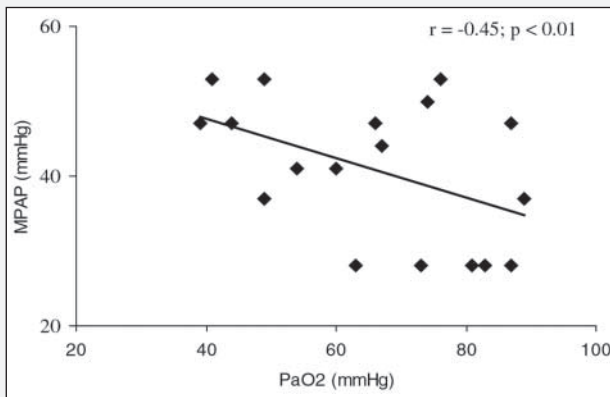


Fig.1 - Graph of dispersion showing the linear correlation between the partial pressure of arterial oxygen (PaO₂) and mean pulmonary artery pressure (MPAP).

A reversible perfusion defect in the inferoseptal area was observed in 5 patients in the COPD_c group and in 3 patients in the COPD_s group on thallium myocardial scintigraphy and a pharmacological dobutamine stress test. The LVEF values for individuals with and without these reversible perfusion defects were 52±15% and 66±11%, respectively (P < 0.01). The RVEF values for those with and without inferoseptal ischemia were 38±14% and 47±11%, respectively (P=0.07). The percentages of septal thickening during systole (%ST) for those with and without inferoseptal ischemia were 14±10% and 24±17%, respectively (P=NS). During the study, 2 patients in the COPD_c group with

systolic volume (RVSV) than the COPD_s group (40±21 mL vs 66±19 mL; P = 0.006). No statistical difference was observed for right ventricular systolic volume (RVSV) between the COPD_s and control groups. Although the COPD_c group had a lower RVSV, the diameter of the right ventricle short axis during diastole (RVSA) was similar for the 3 groups. Patients with COPD had a greater right ventricular lateral wall thickness (RVLWT), which were comparable in the COPD_s and COPD_c groups (8±2 mm and 9±3 mm, respectively); group C had a lower mean value (5±1 mm) (P<0.004, C vs COPD_s, and P<0.004, C vs COPD_c). No difference regarding the percentage of systolic right ventricular lateral wall thickening (%RVLWT) was observed in the 3 groups: C (86±89%), COPD_s (86±82%), and COPD_c (41±35%) (P = NS).

Table IV shows the results derived from the assessment of left ventricular function on magnetic resonance imaging. The left ventricular ejection fraction (LVEF) was different in the 3 groups. The lowest LVEF was observed in the COPD_c group.

Table IV – Parameters of left ventricular function*

	Group C	COPD _s group	COPD _c group	p
LVEF (%)	76±6	69±9	55±16	†, ‡, §
LVSV (ml)	70±22	50±17	52±20	†, xx
LVCO (L/min)	5±2	4±1	5±1	NS
ST (mm)	11±2	10±4	10±1	NS
%ST	46±63	38±44	24±20	NS
LVLWT (mm)	10±2	12±4	12±2	NS
%LVLWT	83±72	58±31	65±64	NS
LVSA (mm)	44±5	40±8	44±7	NS

* Results presented as mean ± standard deviation. †P < 0.02, group C versus COPD_s group; ‡P < 0.01, group C versus COPD_c group; §P < 0.05, COPD_s versus COPD_c; xxP < 0.05, group C versus COPD_c group; LVEF = left ventricular ejection fraction; LVSV = left ventricular systolic volume; LVCO = left ventricular cardiac output; ST = interventricular septum thickness; %ST = percentage of systolic interventricular septum thickness; LVLWT = left ventricular lateral wall thickness; %LVLWT = percentage of systolic left ventricular lateral wall thickness; LVSA = diameter of the left ventricular short axis during diastole; COPD = chronic obstructive pulmonary disease. NS = P > 0.05.



inferoseptal ischemia underwent cine coronary angiography. The coronary arteries were normal.

A positive and significant linear correlation was observed between LVEF and RVEF ($r = 0.58$) and between the diameter of the left ventricular short axis during diastole (LVSA) and its systolic volume (LVSV) ($r = 0.72$), figures 2 and 3, respectively.

The percentage of septal motion of the left ventricle during systole (%LSD) was similar in the 3 groups, C, COPD_s, and COPD_c, 7 ± 12 , 13 ± 13 , and 11 ± 13 , respectively ($P = \text{NS}$).

Discussion

Our population sample comprised patients with the advanced form of chronic obstructive pulmonary disease characterized by the following parameters: %FEV₁, 34 ± 18 ; %RV/TLC (TLC = total lung capacity), 175 ± 31 ; and %DLCO (DLCO = diffusing lung capacity for carbon monoxide), 47 ± 24 . Although PaO₂ of 65 ± 15 mmHg may be considered high for such patients, it is worth noting that the arterial blood sample was obtained under continuous use of O₂ in some patients. No correlation was observed between the degree of pulmonary impairment and the presence or absence of right ventricular dysfunction.

No differences in %RVLWT were observed between the groups. Although a lower %RVLWT was observed in the COPD_c group, it did not reach statistical significance. On the other hand, the number of patients studied may have been too small to evidence differences between the groups. In addition, the fact that the RVLW thickens during systole suggests that right ventricular dysfunction may still be reverted in those with RVEF < 45% after

lung transplantation or lung volume reduction surgery (LVRS). This may be an advantage of magnetic resonance imaging over the other methods, such as echocardiography and computed tomography, which do not provide a detailed analysis of the right ventricular lateral wall. Moreover, pulmonary hyperinflation, which is usually present in these patients, hinders echocardiographic performance²⁸⁻³¹. Measurement of the regional ventricular function is important information for the analysis of myocardial feasibility. Certainly, a myocardial region that thickens during systole contains, at least, some viable tissue. The contrary, however, is not true – the absence of systolic parietal thickening does not necessarily implicate the absence of myocardial viability. However, still in these cases, the presence of viability may be assessed by using the contractile reserve test with dobutamine³¹. Both the COPD_s and the COPD_c groups showed right ventricular hypertrophy with preserved %RVLWT.

The COPD_s group had a greater RSV than that in the COPD_c group; however, the end-diastolic diameters of the right ventricle were similar. One explanation could be the restriction to right ventricular filling due to pulmonary hyperinflation.

Pulmonary artery pressure (PAP) in the COPD_s and COPD_c groups were similar on Doppler echocardiography. Considering that PAP is the result of the product of RSV by pulmonary vascular resistance, one may infer that pulmonary vascular resistance is greater in the COPD_c group. Therefore, patients with the advanced form of chronic obstructive pulmonary disease may or may not have right ventricular dysfunction, depending on the degree of pulmonary vascular resistance. In 120 patients with emphysema who participated in the National Emphysema Treatment Trial, no correlation was observed between the ventilatory parameters and PAP³². In our study, no correlation was observed between %FEV₁ and MPAP. Only a linear correlation was observed between PaO₂ and MPAP. This, however, does not explain why patients with similar PaO₂ may develop different values of pulmonary vascular resistance. Certainly, factors other than PaO₂ and pulmonary function seem to be involved, and these factors may be partially related to the individual genetic expression of pulmonary receptors for endothelin. The lungs account not only for the production, but also for the extraction of circulating endothelin, a peptide with potent vasoconstricting and proliferative action. In animals with pulmonary hypertension, a reduction in the expression of ET_B receptors has been observed^{33,34}. Endothelin, when bound to ET_B receptors, causes pulmonary vasodilation, while in the presence of only ET_A receptors, it causes vasoconstriction.

Patients with chronic obstructive pulmonary disease showed lower LVEF as compared with that of controls. Factors considered risky for coronary artery disease, such as arterial hypertension and smoking, were observed in both COPD groups. Therefore, the possibility of coronary artery disease as a cause of left ventricular dysfunction had to be eliminated. Thus, all patients underwent myocardial scintigraphy with dobutamine, which showed reversible defects of radioisotope uptake in the inferoseptal region in 8 patients. This finding may be a common artifact obtained in the perfusion images, occurring in approximately 25% of the patients³⁵. These defects are usually caused by attenuation of the radioisotopic activity of the inferior wall due to elevation of the left diaphragmatic cupula, as observed in obese patients.

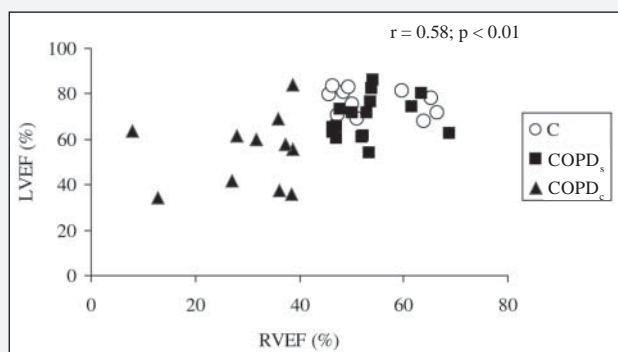


Fig. 2 - Graph of dispersion showing the linear correlation between the right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) of all groups. Circle = control group; square = COPD_s group; triangle = COPD_c group.

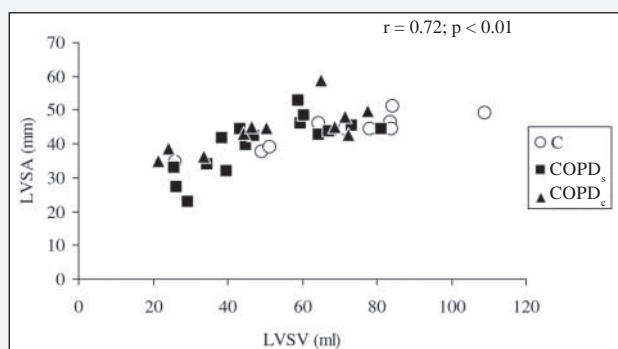


Fig. 3 - Graph of dispersion showing the linear correlation between the diameter of the left ventricular short axis (LVSA) and left ventricular systolic volume (LVSV) of all groups. Circle = control group; square = COPD_s group; triangle = COPD_c group.

During our study, 1 patient underwent LVRS. That patient had severe left and right ventricular dysfunction prior to surgery. As that patient was 1 of those with defective inferoseptal radioisotopic uptake in myocardial scintigraphy, he underwent a complete hemodynamic study, and the absence of coronary artery disease was confirmed. After LVRS, the patient significantly improved his pulmonary function and remained out of the protocol of continuous O₂ inhalation therapy. The major data of pulmonary and ventricular function before and 3 months after LVRS were, respectively: %FEV₁, 18% vs 42%; %VEF₁/FVC (FVC = forced vital capacity), 39% vs 43%; RVEF, 27% vs 64%; LVEF, 42% vs 53%; and MPAP, 50 mm Hg vs 33 mm Hg. As LVRS was performed in only 1 patient in our population sample, no inferences about the result of this surgery may be performed with the results of the present study.

Recently, Mineo et al⁹ reported the effect of LVRS on ventricular function. All patients underwent hemodynamic study before surgery, and 9 of the 12 patients had RVEF below 40% at rest. Those authors attributed the improvement in right ventricular function observed in the postoperative period to the Frank-Starling mechanism, because the increase in the right ventricular end-diastolic volume was accompanied by a parallel increase in RVSV. Those authors concluded that the reduction in the intrathoracic pressure may cause an increase in venous return, and, consequently, in ventricular filling. Other mechanisms include the decrease in pulmonary vascular resistance in the pulmonary regions that had previously undergone compression by the hyperinflated alveoli and improvement in the pulmonary elastic recoil³⁶⁻³⁸.

Although LVEF was different in the 3 groups, LVSV was similar in the COPD groups. The increase in intrathoracic pressure seems to reduce left ventricular transmural pressure and increase cardiac output in patients with heart failure, while in those with normal ventricular function, the increase in intrathoracic pressure is associated with a reduction in cardiac output³⁹.

The contribution of interventricular septal motion towards the left to the phenomenon of ventricular interdependence remains controversial. The present study, showed no difference in the %LSD in the groups. However, it is worth noting that %LSD was assessed at the end of systole. Some studies¹² have reported the presence of septal motion and its importance in restricting left ventricular

filling during the beginning of diastole. The presence of right ventricular hypertrophy and its smaller compliance cause a sudden increase in the right ventricular diastolic pressure with interventricular septal motion towards the left.

The presence of right bundle-branch block may contribute to loss of synchronism between the right and left ventricles and to a lower LVEF⁴⁰. In our study, a similar distribution of right bundle-branch block was observed in the COPD_s and COPD_c groups, which cannot explain the differences observed in LVEF.

Our results are similar to those reported by Marcus et al⁴¹, who found left ventricular filling restricted in patients with primary pulmonary hypertension.

A limitation of the present study is the noninvasive measurement of PAP. However, some studies have already shown a good correlation between MPAP obtained on Doppler echocardiography and the direct measurement through hemodynamics, and between TAC also obtained by use of Doppler and the invasive measurement of pulmonary vascular resistance⁴²⁻⁴⁴. However, future advances in magnetic resonance imaging may facilitate the noninvasive measurement of PAP. Recently, Saba et al⁴⁵ reported a noninvasive way of estimating PAP based on the ventricular mass index, and compared their results with those obtained on Doppler echocardiography and invasive measurements. The confidence interval for the ventricular mass index was shorter than that for echocardiography. The sensitivity and specificity for detecting pulmonary hypertension on magnetic resonance imaging were greater than those of echocardiography.

Another limitation was the fact that the diastolic function of the ventricles was not assessed, which could have provided additional data regarding ventricular compliance.

In conclusion, patients with the advanced form of chronic obstructive pulmonary disease may have a preserved %RLWT, regardless of the presence or absence of right ventricular dysfunction. Left ventricular function depends, in most cases, on RVSV. In the present study, no correlation was observed between pulmonary and ventricular functions. Whether a preserved %RLWT means a possible reversion to right ventricular dysfunction is still to be defined and requires further studies.

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