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## **ECHOCARDIOGRAPHIC ABNORMALITIES IN PATIENTS WITH COPD AT THEIR FIRST HOSPITAL ADMISSION**

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## SUMMARY

Cardiovascular disease accounts for significant morbidity and mortality in COPD. Its prevalence and mechanisms of association have not been elucidated. The study aimed to assess the prevalence of echocardiographic abnormalities and potential risk factors in patients with COPD at their first exacerbation requiring hospital admission.

Transthoracic echocardiography was prospectively performed in 342 patients ( $FEV_1$   $52 \pm 16\%$  predicted) 3 months after discharge. Significant cardiac alterations were present in 64% of patients: 27% left- and 48% right-heart disorders. The most common were right ventricle enlargement (30%) and pulmonary hypertension (19%). Left ventricle (LV) enlargement was present in 6%, LV systolic dysfunction in 13%, LV diastolic impairment in 12% and left atrial dilatation in 29%. Echocardiographic abnormalities were unrelated to COPD severity and were more frequent in patients with self-reported cardiac disease. They were also observed in 63% of patients with no known cardiac disease or cardiovascular risk factors other than smoking.

We conclude that cardiac abnormalities are highly prevalent in COPD patients at the time of their first severe exacerbation, even in the absence of established cardiac disease or cardiovascular risk factors. Considering the prognostic and therapeutic implications of cardiac comorbidity, echocardiography should be considered in the assessment of patients with clinically significant COPD.

## INTRODUCTION

Cardiovascular disease is a frequent comorbidity and cause of death in chronic obstructive pulmonary disease (COPD).[1,2] Both conditions share cigarette smoking as a major risk factor for their development, although smoking alone does not fully explain the frequency of this association.[3] Different explanations have been suggested, including systemic inflammation,[4] vascular dysfunction[5] and lung hyperinflation.[6] Furthermore, pulmonary hypertension (PH), which is a frequent complication of COPD,[7] and the resulting right ventricular (RV) dysfunction, are both predictive of survival in COPD.[8]

Given the prognostic implications of cardiovascular disease in COPD, its detection could serve as a guide to appropriate treatment and eventually improve survival. The prevalence, development and evolution of cardiovascular comorbidity in the natural history of COPD have not been fully elucidated. This lack of information could be explained by the fact that studies have generally been conducted in small and selected series of cases,[6,9,10] restricted either to the right or left chambers,[11,12] or by technical difficulties in the echocardiographic assessment of COPD patients.

We hypothesized that a high proportion of COPD patients might present clinically silent echocardiographic abnormalities, and that these cardiac alterations could constitute a clinically relevant trait in COPD.

The present study was addressed to investigate the prevalence and characteristics of cardiac abnormalities in a large and representative cohort of COPD patients, assessed at a specific clinical time-point of their natural history: their first hospital admission due to an exacerbation episode. Accordingly, we evaluated the participants in the *Phenotype and Characterization of COPD* (PAC-COPD) study, which is a prospective multicentre study that investigated the phenotypic heterogeneity of COPD in a cohort of 342 patients recruited during their first hospital admission due to an exacerbation.[13]

## **METHODS**

### **Subjects**

Participants were prospectively recruited from January 2004 to March 2006 in 9 hospitals in Spain, during their first admission for COPD exacerbation. The assessments and flow-chart of patient recruitment have been described elsewhere.[14] Briefly, of all the patients admitted to the participating hospitals with a diagnosis of COPD exacerbation, 342 (57% of those eligible) participated in the study. The diagnosis of COPD was confirmed by forced spirometry at least 3 months after hospital discharge, when patients were clinically stable. COPD severity was defined according to the European Respiratory Society-American Thoracic Society consensus criteria.[15]

The protocol was approved by the Ethics Committees of all the participating hospitals and written informed consent was obtained from all the subjects.

### **Assessments**

Assessments were performed on clinical stability, at least 3 months after discharge. Patients were asked to complete a questionnaire that included: 1) socio-demographic data; 2) lifestyle information; 3) previous treatments and diagnoses; and 4) quality of life (St. George Respiratory Questionnaire). The Charlson index of comorbidity and all previous diagnoses were obtained from medical records.

Presence of cardiovascular risk factors was defined as any of the following: hypertension (self-reported), hypercholesterolemia (>240 mg/dL) or medical diagnosis of diabetes. Previous cardiac disease was established by patient self-reporting and classified as myocardial infarction, congestive heart failure or non-specified cardiac disorder.

#### *Lung Function Testing and Exercise Capacity*

Assessment of pulmonary function included forced spirometry and bronchodilator testing, total body plethysmography, measurement of CO diffusing capacity (DLco) and arterial blood gas analysis. All the procedures were standardized according to current recommendations.[16]

### *Echocardiography*

Doppler echocardiography was performed following a standard protocol. Echocardiograms were recorded in the participating hospitals and sent to the core centre (Hospital Clínic, Barcelona), where uniform reading and analysis were carried out. Standard views were used to obtain parasternal, apical and subcostal views. Each study was classified into three categories, according to the quality of the registry (good, intermediate and poor). The protocol included the measurements recommended by the European Society of Cardiology.[17]

1. Right ventricle (RV) dimensions, measured in apical view.
2. Left ventricle (LV) size and wall thickness, measured in parasternal view.
3. Left atrial (LA) diameter, measured in parasternal view.
4. Aortic root diameters, measured at the sinuses of Valsalva.
5. Left ventricular ejection fraction (LVEF), assessed by Simpson's rule when adequate 2- and 4-chamber views were available. In other cases we applied visual estimation ('eye-balling').
6. Evaluation of LV and RV diastolic function, which included: A) Maximal peak velocity of early diastolic flow ( $E_{max}$ ), maximal peak velocity of atrial contraction ( $A_{max}$ ), and their ratio ( $E_{max}/A_{max}$ ), measured over the mitral and tricuspid valves. B) Tissue Doppler imaging (TDI) measured in the mitral and tricuspid lateral annulus at early diastole ( $Ea$ ), atrium systole ( $Aa$ ), and their ratio ( $Ea/Aa$ ). C) The  $E_{max}/Ea$  ratio.[18]

Diastolic function of LV was classified into four categories: I, normal or II, mild; III, moderate; and IV, severe diastolic dysfunction following the classification proposed by Bursi et al [19].

7. Mitral, aortic, tricuspid and pulmonary valvular evaluation.
8. Tricuspid regurgitant velocity (TRV) recorded by continuous-wave Doppler. Pulmonary hypertension was considered when TRV was  $\geq 2.8$  m/sec,[20] and subsequently graded as mild (2.8-3.4 m/sec) or moderate-severe ( $>3.4$  m/sec).

## Data analysis

Results are expressed as mean $\pm$ SD for continuous variables and as n (%) for categorical ones. Comparisons between groups were performed using unpaired t-test for continuous variables and Chi-square and Fisher's exact test for categorical variables. Results were stratified according to the presence of previously diagnosed cardiac disease and cardiovascular risk factors. As a sensitivity analysis, we repeated all the computations, this time excluding subjects with poor quality echocardiography. Results were considered statistically significant at a p-value <0.05. Statistical analyses were performed using the STATA package version 10.1 (College Station, Texas 77845 USA).

## RESULTS

A total of 342 patients were included in the study. Mean age was 67.9 $\pm$ 8.6 years and 318 patients (93%) were males. A wide range of COPD severity was found, although the majority of patients had moderate-to-severe disease, with a mean post-bronchodilator FEV<sub>1</sub> of 52.4 $\pm$ 16.2% of predicted. Characteristics of the subjects and lung function measurements are shown in Table 1.

### Echocardiographic abnormalities

The prevalence and characteristics of left and right echocardiographic defects are shown in Table 2.

#### *Left heart*

Dilatation of left atrium (LA), followed by hypertrophy of left ventricle (LV), were the most frequent left heart abnormalities. Impaired LV systolic function (LVEF <50%) was present in 13.3% of subjects, although most frequently (8.9%) it was only mildly impaired (LVEF, 40-50%). In the remaining 4.4% it ranged between 30 and 40%. Abnormal LV segmentary wall motion was detected in 4.1% of patients and only one-third of patients with this abnormality reported previous ischemic cardiopathy. Normal or grade I LV diastolic dysfunction was seen in only 37.9% of patients.

Overall, of the 278 patients in which the left ventricle could be fully assessed, 74 (27%) presented significant abnormalities (Table 3). There were no differences with respect to socio-demographic or clinical variables between these 278 patients and those in which the left ventricle could not be fully assessed.

#### *Right heart*

Right ventricular enlargement was the most common echocardiographic disorder (29.9% of patients). Transtricuspid flow recorded by pulsed wave Doppler showed signs of RV diastolic dysfunction, as depicted by the higher  $E_{\max}$ , higher  $A_{\max}$ , and lower  $E_{\max}/A_{\max}$  ratio than those found in healthy subjects.[21] Moreover, measurements of lateral tricuspid tissue Doppler imaging were also consistent with RV diastolic impairment with low  $E_a$ , high  $A_a$ , and low  $E_a/A_a$  ratio.

Maximal TRV could be assessed in 62% of patients, showing an abnormal value ( $\geq 2.8$  m/sec) in 19%, consistent with PH, although of those patients 16.2% had slightly elevated values, whereas moderate or severe values ( $> 3.4$  m/sec) were observed in only 2.8%.

Of the 181 patients in which the right heart could be adequately assessed, 87 (48%) presented abnormalities (Table 3).

#### *Valvular disease*

Moderate or severe left valvulopathy was present in 8.7% of patients: mitral regurgitation in 3.1%, aortic regurgitation in 5.5% and aortic stenosis in 1.2%. Only 3 of the 8 patients with mitral insufficiency presented functional mitral regurgitation..

### **Echocardiographic abnormalities and cardiovascular risk factors**

To investigate whether echocardiographic findings were associated with previous cardiac disease and/or cardiovascular risk factors, we assessed the proportion of patients with major echocardiographic disorders according to the presence/absence of cardiovascular risk factors (except smoking, since 99% of patients were current or former smokers), and/or self-reported previous cardiac disease.

As anticipated, patients with previous cardiac disorders had greater prevalence of left heart

abnormalities detected by echocardiography, whereas the prevalence of right heart abnormalities did not differ between the subgroups (Table 3). Forty-three (63%) patients with COPD without previously diagnosed heart disease and free of cardiovascular risk factors other than cigarette smoking had significant echocardiographic abnormalities; in 27% these affected the LV and in 44% the right heart.

### **Echocardiographic abnormalities and COPD severity**

The potential association between echocardiographic abnormalities and COPD severity was also analysed. Table 4 shows the percentage of patients with echocardiographic abnormalities according to COPD severity. No association was observed between the degree of airflow obstruction, the distance covered in the 6-min walk test or the St. George Respiratory Questionnaire and the presence of echocardiographic abnormalities. Furthermore, we did not find any significant association between PaO<sub>2</sub> and the presence of LV impairment ( $74.2 \pm 1.2$  and  $74.4 \pm 0.8$  mmHg, in patients with and without LV impairment;  $p=0.88$ ). Pulmonary hypertension was more prevalent in patients with severe airflow obstruction ( $FEV_1 \leq 50\%$  pred.) (32.9%) than in patients with  $FEV_1 > 50\%$  pred. (7.2%) ( $p<0.001$ ). Patients with PH had greater RV diameter ( $33.9 \pm 4.5$  mm) than those without PH ( $31.2 \pm 3.4$  mm;  $p<0.001$ ).

A total of 229 (67.7%) and 262 (77.5%) patients had been previously treated with anticholinergic or beta-agonist bronchodilators, respectively. No relationship was found between echocardiographic abnormalities and previous use of these agents.

Sensitivity analysis excluding subjects with poor quality echocardiography yielded similar results.

## **DISCUSSION**

The results of the present study, conducted in one of the largest cohorts of COPD patients assessed by echocardiography to date, show an elevated prevalence of both left and right cardiac disorders at the time of their first hospital admission due to an exacerbation episode.



The proportion of patients presenting cardiac disorders remained high even after excluding those with cardiovascular risk factors, and it was unrelated to COPD severity.

Cardiovascular disease is a frequent cause of mortality in COPD. Roughly 30% of patients die from a cardiovascular cause.[1,2,22] A better understanding of the association between COPD and cardiovascular disease should help improve the outcome, particularly if cardiovascular disease could be identified earlier and/or prevented.[23] Previous echocardiographic studies in COPD present limitations because of their retrospective design, their reduced number of subjects, their partial echocardiographic analysis or their potential selection biases.[9,11,12,24] To overcome these difficulties, we prospectively explored COPD patients in a well-defined and relevant time-point of their clinical evolution -first hospital admission due to an exacerbation-, selecting them from the population admitted in 9 hospitals during a defined period of time and performing a comprehensive echocardiographic assessment.[14] Thus, the results of the present study are representative of patients with clinically relevant COPD.

The study shows a high prevalence (64%) of significant echocardiographic abnormalities, in 27% of cases affecting the left heart and in 48% the right heart.

#### *Left heart impairment*

Enlargement of left atrium and LV hypertrophy were present in 20-30% of patients, whereas LV systolic dysfunction (LVSD) was identified in 13.3%, albeit generally of mild intensity. The prevalence of left heart abnormalities previously reported in COPD patients varies widely, from 0 to 32%,[11,12] depending on whether the study was performed on “selected” patients with no history of coronary artery disease or on unselected subjects. The prevalence of LVSD in our cohort was similar to that recently reported by Macchia et al[12] (13.7%) and is in keeping with the emerging evidence that unrecognized left heart failure is common in stable COPD patients, as shown by Rutten et al.[25] Our study complements these previous observations by showing them in a cohort of patients with COPD who already required hospitalization for an exacerbation episode. Since most of the detected cardiac abnormalities

were of mild severity, the clinical implications of these findings are unclear. Although a potential lower threshold for congestive heart failure in patients with systolic or diastolic dysfunction might be anticipated, the progression of echocardiographic abnormalities, the need for specific management and the impact on clinical outcome in COPD patients warrant future evaluation.

In our study almost 30% of patients with LVSD presented LV wall motion abnormalities, strongly suggesting ischemic heart disease as the underlying mechanism, even though the disease had only been previously diagnosed in one third of those patients. Another important finding was the high prevalence of LV diastolic dysfunction (62%) in the present cohort. Although the age and characteristics of the population might explain the high prevalence of mild dysfunction (50%),[26] it is worth noting that 12% of patients presented moderate (Grade 3) or severe (Grade 4) diastolic impairment.

Recent studies have suggested potential mechanisms that may explain the association between LV dysfunction and COPD. First, the vascular dysfunction of systemic arteries, assessed by means of flow-mediated vasodilatation,[27] arterial stiffness[5] or carotid intima-media thickness,[28] is more prevalent in COPD and could explain the association with subclinical LV abnormalities. Second, the presence of emphysema has been related to impaired LV filling.[29] It is conceivable that hyperinflation and increased intrathoracic pressures produced by emphysema may impair cardiac function by decreasing biventricular preload and increasing LV afterload.[30] Third, chronic hypoxemia might also affect myocardial relaxation,[24] although in our study no relationship was shown between  $\text{PaO}_2$  and LV impairment. Finally, the influence of chronic RV pressure overload on the interventricular septum may also jeopardize LV filling as a result of abnormal LV torsion and impaired longitudinal and circumferential strain.[31] Whatever the mechanism, it is apparent that the presence of LV dysfunction has a negative impact on COPD survival.[11] Accordingly, the early identification of such comorbidity might help improve patient outcome. In fact, a subgroup of COPD patients who combined mild airflow obstruction with a high proportion of obesity, cardiovascular disorders and diabetes was identified in the PAC-COPD

cohort. Interestingly, these patients required more hospital admissions as a result of cardiovascular disease during the follow-up.[13]

### *Right heart impairment*

We observed RV enlargement in 30% of patients, and this was more pronounced in those with PH. Assessment of RV is important in COPD because its enlargement or dysfunction is associated with limited exercise capacity and a poorer prognosis.[8] Subclinical RV dysfunction detected by echocardiography might be present in patients with mild airflow obstruction,[10] while RV hypertrophy, assessed by magnetic resonance, has been shown in COPD patients without PH.[32] Overall, these observations suggest that RV morphological and functional changes could be early signs of pressure overload developing at the initial disease stages.

Tricuspid regurgitation may not always be present in COPD, limiting the possibility of estimating systolic pulmonary artery pressure (PAP). In our cohort we were able to determine TRV and hence estimate systolic PAP in 62% of cases, which is within the best range reported in the literature.

The prevalence of PH in the whole cohort was 19%, being much more prevalent in patients with severe disease (33%) than in those with mild disease (7%). Although PH is a frequent complication in the natural history of COPD, its prevalence in the whole spectrum of the disease remains unclear because the majority of studies have been conducted in patients with advanced disease.[7] The magnitude of PH was mild in the majority of cases and only in 3% of patients did TRV exceed 3.4 m/s -equivalent to systolic PAP >55 mmHg, a value close to the estimated prevalence of out-of-proportion PH in COPD.[33]

### *Influence of cardiovascular risk factors and disease severity*

As anticipated, a previous diagnosis of cardiac disease was associated with greater prevalence of echocardiographic abnormalities in the left heart, but the lack of association between the presence of cardiovascular risk factors and echocardiographic abnormalities was unexpected. In this cohort the proportion of cardiac impairment remained high even after

excluding patients with cardiovascular risk factors or previous cardiac disease. This observation suggests that COPD *per se* could be a risk factor for the development of heart disorders. Smoking, a risk factor for both COPD and cardiovascular disease, could explain such an association. However, as discussed above, increasing evidence suggests that COPD may induce vascular damage by mechanisms independent of cigarette smoking[3,4] and that lung hyperinflation may directly affect ventricular function.[6,29]

In the present cohort the severity of airflow obstruction was not associated with the prevalence of heart disease. This finding concurs with the lack of association between COPD severity and cardiac comorbidity reported in the large ECLIPSE cohort[34] and could lead to the hypothesis that it is the presence of COPD, rather than its severity, that favours the development of cardiovascular disease. In contrast, the presence of echocardiographic abnormalities did not appear to modify exercise tolerance or quality of life. Furthermore, we did not find any association between the use of bronchodilators and echocardiographic abnormalities, in line with recent reanalyses of large clinical trials.[35]

The study has some limitations. First, the absence of a control group limits a definite assessment of the role of COPD in the pathogenesis of cardiac disorders. Second, the range of COPD severity is somewhat restricted, limiting the extrapolation of current findings to the whole disease spectrum. Yet, we prospectively assessed patients at a very specific and clinically relevant time-point -first hospital admission due to an exacerbation- and carefully screened patients who satisfied the diagnosis of COPD in a number of hospitals with different clinical practices. This allowed us to avoid potential selection biases that could arise from other methods of recruitment. Third, the study had a cross-sectional design, so no causal relationships with clinical outcomes could be established. Fourth, as a result of a suboptimal echocardiographic window, the right ventricle was only measurable in 234 patients. Fifth, LA diameters and not LA indexed volumes were measured. Despite the greater diagnostic accuracy of indexed volumes, LA diameters provide valuable information and might be less prone to misevaluation in patients with a suboptimal echocardiographic

window. Finally, the presence of previous cardiovascular disease was dependent on patient self-reporting, thus we cannot exclude the under-reporting of pre-existing cardiovascular disorders.

In conclusion, this large, prospective, multicentre, comprehensive echocardiographic study shows that cardiac disorders are highly prevalent in patients with moderate-to-severe COPD, even among those without cardiovascular risk factors other than cigarette smoking. Whereas right heart abnormalities could be anticipated, such a high prevalence of left heart abnormalities is a novel and unexpected finding that was unrelated to disease severity. Accordingly, the implementation of echocardiography in the evaluation of COPD patients should be considered, since it might help detect unrecognized cardiac disorders and establish adequate treatment that may potentially improve patient prognosis.

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Table 1

**Characteristics of the Study Population\***

Age (years), m±SD	67.9±8.6
Gender:	
Males, n (%)	318 (93)
Females, n (%)	24 (7)
BMI (kg/m <sup>2</sup> ), m±SD	28.2±4.7
Smoking status:	
Current smokers, n (%)	109 (33)
Former smokers, n (%)	220 (66)
Never smokers, n (%)	2 (1)
Systemic hypertension (self-reported), n (%)	123 (36)
Hypercholesterolemia (>240 mg/d), n (%)	78 (23)
Diabetes mellitus (physician-diagnosed), n (%)	62 (18)
Myocardial Infarction (physician-diagnosed), n (%)	36 (11)
Stroke (physician-diagnosed), n (%)	12 (4)
Peripheral vascular disease (physician-diagnosed), n (%)	37 (11)
Renal insufficiency (physician-diagnosed), n (%)	20 (6)
COPD severity	
I: Mild (FEV <sub>1</sub> ≥80% pred), n (%)	19 (6)
II: Moderate (FEV <sub>1</sub> 50-79% pred), n (%)	164 (48)
III: Severe (FEV <sub>1</sub> 30%-49% pred), n (%)	132 (39)
IV: Very severe (FEV <sub>1</sub> <30% pred), n (%)	27 (8)
PostBD FVC (% pred), m±SD	68.7±16.2
PostBD FEV <sub>1</sub> (% pred), m±SD	52.4±16.2
PostBD FEV <sub>1</sub> /FVC (% pred), m±SD	53.4±11.9
DLco (%), m±SD	65.2±20.7
PaO <sub>2</sub> (mmHg), m±SD	74.3±10.6
PaCO <sub>2</sub> (mmHg), m±SD	41.8±5.3
TLC(%), m±SD	100.4± 18.4
IC (%), m±SD	62.8± 18.5
IC/TLC, m±SD	0.31±0.10

\* N=342 patients.

*Definition of abbreviations:* BMI, Body Mass Index; FVC, forced vital capacity; BD, bronchodilator; FEV<sub>1</sub>, forced expiratory volume in the 1<sup>st</sup> second; DLco, diffusing capacity of the lung for carbon monoxide; PaO<sub>2</sub>, partial pressure of arterial oxygen; PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide; TLC, total lung capacity; IC, inspiratory capacity.

Table 2

**Echocardiographic measurements and prevalence of abnormalities**

Characteristic	No.	
LEFT HEART		
Dimensions		
Left atrium		
Diameter (mm) <sup>a</sup>	279	37.8±6.4
Abnormal value (≥40 mm) <sup>b</sup>		29% (24-35%)
Left ventricle (LV)		
End-diastolic diameter (mm) <sup>a</sup>	293	50.6±5.6
Abnormal value <sup>b,c</sup>		6% (3-8%)
Wall thickness (mm) <sup>a</sup>	291	10.7±1.5
Abnormal value (≥12 mm) <sup>b</sup>		26% (21-31%)
Ventricular function		
Systolic function <sup>d</sup>	294	
LV ejection fraction (%)		59.1±8.9
Abnormal value (≤50%)		13% (9-17%)
Diastolic Function	282	
Normal or Grade I <sup>b</sup>		107 (38%)
Grade II <sup>b</sup>		141 (50%)
Grade III <sup>b</sup>		23 (8%)
Grade IV <sup>b</sup>		11 (4%)
RIGHT HEART		
Dimensions		
Right ventricle (RV)		
Mid end-diastolic diameter (mm) <sup>a</sup>	234	31.6±3.8
Abnormal value (>33mm) <sup>b</sup>		30% (24-36%)
Inferior cava vein (ICV)		
Mid diameter at rest (mm) <sup>a</sup>	191	12.4±4.0
Abnormal value (≥20 mm) <sup>b</sup>		6% (4-8%)
Ventricular function		
Diastolic function		
E <sub>max</sub> tric (cm/sec) <sup>a</sup>	270	48.6±12.9
A <sub>max</sub> tric (cm/sec) <sup>a</sup>	265	51.4±15.9
E/A tricuspid <sup>a</sup>	265	1.0±0.45
E/Ea <sub>max</sub> tricuspid <sup>a</sup>	211	5.0±2.30
Ea <sub>max</sub> tric (cm/sec) <sup>a</sup>	224	11.3±4.7
Aa <sub>max</sub> tric (cm/sec) <sup>a</sup>	215	17.3±6.9
Ea/Aa tricuspid <sup>a</sup>	215	0.7±0.5
Assessment of pulmonary hypertension		
Transtricuspid regurgitant velocity (m/sec) <sup>a</sup>	179	2.39±0.55
Abnormal value (≥2.8 m/sec) <sup>b</sup>		19% (13-25%)
Estimated systolic pulmonary artery pressure (mmHg)		34.0±10.1

<sup>a</sup> Values are mean±SD; <sup>b</sup> values are % (95%CI); <sup>c</sup> >59 mm for males and >53 mm for females; <sup>d</sup> LV ejection fraction assessed by Simpson's rule in 243 patients (82.6%) and corrected by visual estimation in 51 (17.3%).

Table 3

**Presence of echocardiographic disorders according to previous cardiac disease or presence of cardiovascular risk factors**

	All subjects n=342	Previous cardiac disease <sup>a</sup>		Cardiovascular risk factors		Comparisons	
		Group 1 n=80	No				
				Yes	No		
						Present (group 2) n=139	Absent (group 3) n=114
<b>Left Ventricle</b>							
Enlarged end-diastolic diameter <sup>b</sup> [293 <sup>c</sup> ]	17 (6%)	9 (14%)	5 (4%)	3 (3%)	0.001	0.700	
Diastolic dysfunction ≥Grade 3 [282 <sup>c</sup> ]	34 (12%)	8 (14%)	11 (9%)	15 (15%)	0.632	0.127	
Ejection fraction ≤50% [294 <sup>c</sup> ]	39 (13%)	17 (27%)	10 (8%)	12 (12%)	0.000	0.291	
Global left ventricle impairment (any of the above) [278 <sup>c</sup> ]	74 (27%)	27 (47%)	22 (19%)	25 (27%)	0.000	0.166	
<b>Right heart</b>							
Mid end-diastolic right ventricle diameter >33mm [234 <sup>c</sup> ]	70 (30%)	20 (39%)	31 (31%)	19 (23%)	0.117	0.265	
Transtricuspid regurgitant velocity ≥2.8 m/sec [179 <sup>c</sup> ]	34 (19%)	7 (16%)	17 (24%)	10 (17%)	0.535	0.348	
Global right heart impairment (any of the above) [181 <sup>c</sup> ]	87 (48%)	22 (54%)	38 (50%)	27 (44%)	0.437	0.504	
<b>Global left and/or right Impairment [201<sup>c</sup>]</b>	129 (64%)	36 (77%)	50 (60)	43 (63%)	0.048	0.707	

Values are n and (%). <sup>a</sup> Myocardial infarction in 9.9%, chronic heart failure in 5%, and unspecified cardiac disorder in 8.8%. <sup>b</sup> >59 mm for males and >53 mm for females; <sup>c</sup> number of subjects assessed;

Table 4

**Patients with echocardiographic abnormalities according to COPD severity\***

		<b>Left heart abnormalities</b>	<b>Right heart abnormalities</b>	<b>Left and/or right heart abnormalities</b>
FEV <sub>1</sub>	≤50% pred	23 (30%)	40 (42%)	47 (62%)
	>50% pred	29 (30%)	41 (53%)	53 (55%)
6 min walk distance	≤440 m	22 (30%)	37 (49%)	45 (61%)
	>440 m	24 (29%)	37 (45%)	47 (57%)
St. George Respiratory Questionnaire	≤33	25 (28%)	44 (49%)	54 (60%)
	>33	27 (33%)	37 (45%)	46 (57%)

\* 173 patients who underwent complete echocardiographic assessment.

## Appendix 1

### List of investigators of the Phenotype and Course of COPD (PAC-COPD) Study

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