Right Ventricular Dysfunction and Remodeling in Chronic Obstructive Pulmonary Disease Without Pulmonary Hypertension

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Objectives
The aim of the present study was to elucidate right ventricular (RV) function and structure in patients with chronic obstructive pulmonary disease (COPD) without pulmonary hypertension (PH).

Background
There is little knowledge of RV function and remodeling in COPD without PH.

Methods
Thirty-four controls and 98 patients with COPD were included. The study patients were divided into 2 groups by right heart catheterization: no PH (mean pulmonary artery pressure [mPAP] < 25 mm Hg) and PH (mPAP ≥ 25 mm Hg). The echocardiographic tissue Doppler imaging variables of RV isovolumic acceleration, peak systolic strain, and RV myocardial performance index were measured at the basal free wall, and RV wall thickness and RV internal dimension were measured in the RV outflow tract.

Results
The increases in RV wall thickness and RV dimension were more evident when comparing controls with the no PH group (3.5 ± 0.5 mm to 5.5 ± 1.0 mm [p < 0.01] and 1.5 cm ± 0.2 to 2.0 ± 0.5 cm [p < 0.01]) than comparing the no PH group with the PH group (5.5 ± 1.0 mm to 6.6 ± 1.1 mm [p < 0.01] and 2.0 cm ± 0.5 to 2.1 ± 0.3 cm [p = NS]), respectively. Similarly, RV isovolumic acceleration, performance index, and strain deteriorated significantly when comparing controls with the no PH group and comparing the no PH group with the PH group (p < 0.01). Significant correlations were observed between mPAP and RV isovolumic acceleration, performance index, strain, and RV wall thickness (p < 0.01). RV impairment and increased RV wall thickness and RV dimensions were present even at slight elevations of mPAP (18 ± 3 mm Hg) in the no PH group.

Conclusions
The present study showed that impaired RV systolic function, hypertrophy, and dilation were present even at a slight increase of mPAP, which indicates an early impact on RV function and structure in patients with COPD. RV isovolumic acceleration, performance index, and strain could detect subclinical disease and separate controls from those with no PH. (J Am Coll Cardiol 2013;62:1103–11) © 2013 by the American College of Cardiology Foundation

The development of right heart failure in patients with chronic obstructive pulmonary disease (COPD) is linked to worse outcomes with an increased risk of hospital readmissions and mortality (1,2). Thus, noninvasive imaging modalities that provide an accurate measurement of right ventricular (RV) function are crucial in a clinical setting. Several studies have investigated RV function in patients with COPD who have pulmonary hypertension (PH) (3–5). However, little information is available on RV function in patients with COPD who do not have PH.

COPD is associated with structural and mechanical changes in the pulmonary vascular bed that increase RV afterload. Pulmonary vascular remodeling occurs not only in patients with advanced COPD but also in patients with mild disease and even in smokers with normal lung function (6,7). This narrowing and stiffening process occurs in both the proximal and distal pulmonary arteries and results in increased...
RV Dysfunction and Remodeling in COPD

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Abbreviations and Acronyms

CI = confidence interval
COPD = chronic obstructive pulmonary disease
GOLD = Global Initiative for Chronic Obstructive Lung Disease
LV = left ventricular
mPAP = mean pulmonary artery pressure
PA = pulmonary artery
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
PWP = pulmonary wedge pressure
RV = right ventricular
TDI = tissue Doppler imaging

Thus, the present study sought to identify subclinical RV systolic dysfunction at rest, before hemodynamic decompensation, by applying modern echocardiographic imaging in a cohort of patients with stable COPD. We hypothesized that remodeling of the pulmonary arteries, increased steady state, and pulsatile RV afterload would have a secondary impact on RV geometry and function in patients with COPD who had a mean pulmonary artery pressure (mPAP) below the current guideline definition of PH.

Methods

Study patients. Ninety-eight outpatients with stable COPD of varying severity and free of overt cardiovascular disease were consecutively included in this study from 2006 to 2010 (Table 1). The diagnosis of COPD was based on a history of cigarette smoking of at least 10 pack-years and spirometric irreversible airway obstruction according to current guidelines (9). Spirometry, diffusion capacity for carbon monoxide, and measurement of arterial blood gases were performed according to guidelines. Patients were classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (9).

White patients who were 40 to 75 years of age with spirometric confirmed COPD in GOLD stages II to IV were included. They had to be free of exacerbations of COPD for the 2 months before inclusion in the study. A small number of these patients were treated with supplemental oxygen, administered as long-term treatment with oxygen in 8 patients and as ambulatory oxygen support in 4 patients. All participants underwent preinclusion screening, including resting electrocardiogram and a dynamic exercise test on a cycle ergometer. Patients with left ventricular (LV) disease, treated arterial hypertension with blood pressure >160/90 mm Hg, arrhythmias (including atrial fibrillation), other acute or

Table 1 Demographics, LV Systolic/Diastolic Functional Indices, and Pulmonary Function in Patients With COPD With and Without PH Compared With Healthy Controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy Controls (n = 34)</th>
<th>No PH (n = 72)</th>
<th>PH (n = 26)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63 ± 7</td>
<td>64 ± 6</td>
<td>62 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Female (n)</td>
<td>19</td>
<td>34</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 3</td>
<td>24 ± 5</td>
<td>25 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.9 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66 ± 11</td>
<td>87 ± 14*</td>
<td>95 ± 18*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120 ± 17</td>
<td>139 ± 22*</td>
<td>140 ± 18*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>76 ± 12</td>
<td>69 ± 12*</td>
<td>68 ± 13*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>N-terminal pro-hormone of brain natriuretic peptide (pmol/l)*</td>
<td>N/A</td>
<td>9.3 (2.1-40.4)</td>
<td>9.9 (1.4-68.7)</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>61 ± 5</td>
<td>57 ± 4*</td>
<td>58 ± 5*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV transmitral early diastolic velocity/late diastolic velocity ratio</td>
<td>1.07 ± 0.29</td>
<td>1.04 ± 0.25</td>
<td>1.03 ± 0.26</td>
<td>NS</td>
</tr>
<tr>
<td>LV transmitral early diastolic velocity/septal mitral annular early diastolic tissue velocity</td>
<td>7.7 ± 1.5</td>
<td>8.6 ± 2.1</td>
<td>10.3 ± 2.2*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left atrial volume (ml/m²)</td>
<td>21 ± 4</td>
<td>24 ± 5*</td>
<td>21 ± 5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking habits (n)</td>
<td>2/13/19</td>
<td>23/49/0*</td>
<td>8/18/0*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>8 ± 9</td>
<td>41 ± 19*</td>
<td>39 ± 20*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>98 ± 10</td>
<td>46 ± 15*</td>
<td>32 ± 12*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>105 ± 11</td>
<td>76 ± 20*</td>
<td>61 ± 16*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>76 ± 4</td>
<td>49 ± 11*</td>
<td>43 ± 13*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diffusion capacity for carbon monoxide of the lungs % predicted</td>
<td>100 ± 15</td>
<td>57 ± 19*</td>
<td>36 ± 20*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Residual volume % predicted</td>
<td>119 ± 16</td>
<td>192 ± 59</td>
<td>241 ± 60*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Inspiratory capacity/total lung capacity</td>
<td>0.44 ± 0.08</td>
<td>0.32 ± 0.11</td>
<td>0.23 ± 0.12*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>6-min walk distance (m)</td>
<td>N/A</td>
<td>489 ± 113</td>
<td>343 ± 149</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n. *Significantly different from controls. †Significantly different from no PH. Geometric mean (95% confidence interval). Current, former, and never smokers, respectively.

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; LV = left ventricular ejection fraction; N/A = not measured; PH = pulmonary hypertension.
chronic pulmonary disease, malignancy, metabolic conditions, hyperthyroidism, systemic inflammatory diseases, and renal failure were excluded. Patients treated with beta-blockers, warfarin, or clopidogrel were also excluded. A detailed study design and COPD baseline characteristics of the entire study group were reported previously (10).

The patients with COPD were compared with a group of 34 controls with a similar age and sex distribution and determined to be healthy based on clinical, spirometric, biochemical, and imaging investigations (Table 1). The healthy volunteers were recruited from the hospital staff and their relatives. The study complied with the Declaration of Helsinki and was approved by the local research ethics committee. Written informed consent was obtained from all subjects.

**Doppler echocardiography.** All study patients underwent a comprehensive Doppler echocardiographic examination during breath hold in end-expiratory phase within 2 h of right heart catheterization using a Vivid7 and stored for offline analyses (GE Vingmed Ultrasound, Horten, Norway). The recordings were performed from left parasternal long- and short-axis and apical 4-chamber views, adjusted to acquire the RV-focused view. TDI was performed using a high frame rate (median of 175 [range of 143 to 268] frame rate per second). The RV free wall basal segment and tricuspid annulus were considered the most reliable imaging regions of the right ventricle, and a region of interest was placed at these 2 sites to measure peak TDI velocities and peak systolic longitudinal strain. LV systolic function was estimated by LV ejection fraction (11), and LV diastolic function was estimated by transmitral pulsed Doppler early velocity/early TDI at the septal annular mitral leaflet and left atrial volume, respectively (12). All results were the average of 3 measurements, and analyses were performed without knowledge of clinical status.

**RV size and wall thickness.** RV end-diastolic area and RV end-systolic area were assessed by manual planimetry and divided by body surface area. Basal, midcavity, and longitudinal dimensions were obtained at end diastole and indexed for body surface area. RV outflow tract proximal dimensions were measured in end diastole and end systole by M-mode imaging. RV wall thickness was obtained from the short-axis window by either M-mode imaging or 2-dimensional echocardiography in end diastole. RV hypertrophy was defined by an RV anterior wall thickness ≥0.55/0.60 cm in female/male subjects, respectively (13).

**RV systolic function.** Maximal longitudinal tricuspid annular displacement was measured, and RV fractional area change and RV outflow tract fractional shortening were derived (14). RV myocardial performance index was estimated using the pulsed tissue Doppler method with the region of interest (5 mm) at the lateral tricuspid annulus. Myocardial acceleration during isovolumic contraction was obtained by color-coded tissue Doppler with the region of interest (6/4 mm) at the RV free wall basal segment (15). Real-time 3-dimensional echocardiography was used to acquire full-volumetric datasets of the right ventricle from 4 electrocardiography-triggered subvolumes. Post-processing

**Hemodynamic measurements.** Pressure transducers were balanced against atmospheric pressure, and the zero reference level for recording was 5 cm below the sternal angle (10). An electrocardiogram and heart rate were recorded continuously, and cardiac output was determined by thermodilution technique. All pressures, including mPAP, right atrial pressure, pulmonary wedge pressure (PWP), and RV pressures, were measured at end expiration. PVR was calculated as: (mPAP – mean PWP)/cardiac output in Wood units. PA compliance was calculated as RV stroke volume/pulse pressure in milliliters per millimeters of mercury. Patients were categorized as having PH if the mPAP was ≥25 mm Hg and as having no PH if the mPAP was <25 mm Hg (16). No PH was further divided into an mPAP ≤20 mm Hg and an mPAP of 21 to 24 mm Hg.

**Statistical analysis.** Continuous variables are expressed as mean ± SD. For comparison of continuous data between controls and COPD subgroups, analysis of variance with Bonferroni correction was used. Independent-sample t test was used for comparison of continuous hemodynamic data between the COPD subgroups. The distribution of N-terminal pro-hormone of brain natriuretic peptide was skewed and hence log transformed before statistical analyses, and results are reported in original scale in Table 1 as geometric mean and 95% confidence interval (CI). The relationship of PVR and PA compliance was assessed by regression analyses and curve fittings (Sigma Plot version 12.0). Multivariate regression analyses were performed to determine independent predictors of RV systolic function indices. Variables for final analyses were chosen by automatic stepwise forward selection with p values set to <0.05. Pearson correlation coefficient was used to evaluate the relationship between forced expiratory volume in 1 s percent predicted and RV function and remodeling, and partial correlation with adjustment for PaO2 was performed. A p value <0.05 was considered statistically significant. Reproducibility data were tested by intraclass correlation coefficient in 10 random participants for 3 RV systolic indices, one RV dimension, and wall thickness (J.M.H. and K.S.). Results are presented as intraclass correlation with 95% CI. The statistical analyses were performed using SPSS version 20.

**Results**

**Patient characteristics.** Table 1 shows the clinical data for the healthy age- and sex-matched controls and the patients with COPD. All participants had sinus rhythm. Type 2 diabetes mellitus and treated systemic hypertension were present in 9% and 31% of subjects, respectively, equally distributed in COPD subgroups. Seven patients were being treated with single loop diuretics (20 to 40 mg/day) and 14 with hydrochlorothiazide (12.5 mg/day).
Invasive hemodynamics. Table 2 summarizes the hemodynamic and arterial blood gas data at rest for 98 patients with COPD who underwent right heart catheterization.

The mean PVR in the no PH group was 2.0 ± 0.9 Wood units. Fifty patients (69%) in the no PH group had a PVR >1.5 Wood units, and the majority of patients with GOLD stage II had an elevated PVR >1.5 Wood units at rest (Fig. 1). Mean PA compliance in the no PH group was 4.1 ± 1.3 ml/mm Hg. GOLD distribution showed a similar pattern as observed for PVR; patients with GOLD stage II had PA compliance ranging from below 2.0 to above 6.0 (Fig. 1). Figure 2 displays the hyperbolic relationship of PVR and PA compliance (R² = 0.55; p < 0.001). Invasive measurements identifying RV dysfunction revealed significant differences between no PH and PH, but the values were within the range of normal RV function in both groups (Table 2). However, 14 (14%) of the 98 patients had a cardiac index <2.5 l/min/m², including 11 (15%) in the no PH group and 3 (12%) in the PH group. None had a severely reduced cardiac index below 2.0 l/min/m².

RV systolic function. All 9 echocardiographic parameters describing RV systolic function and the RV myocardial performance index were significantly impaired in both patients with no PH and patients with PH compared with controls (Table 3). RV myocardial performance index, RV isovolumic acceleration, and strain showed the largest differences between controls and those with no PH (Fig. 3). These 3 indices were still significantly impaired as compared with controls even in those with an mPAP ≤20 mm Hg, which again showed no difference compared with those with an mPAP of 21 to 24 mm Hg (Table 4). Significant correlations (p < 0.01) were observed between mPAP and RV myocardial performance index (r = 0.5), RV isovolumic acceleration (r = −0.5), and strain (r = −0.5). RV myocardial performance index, RV isovolumic acceleration, and strain correlated with forced expiratory volume in 1 s percent predicted (r = −0.36, r = 0.34, and r = −0.30 [p < 0.01 for all], respectively), but not when adjusted for PaO₂.

RV size and wall thickness. Parameters describing RV geometry are presented in Table 3. RV wall thickness was significantly increased by 57% and 89% when comparing controls with the no PH group and the PH group, respectively (Table 3). Due to RV dilation in both groups, the RV relative wall thickness increased less than than RV wall thickness (15% and 33%, respectively). There was a similar large and significant increase in the 3 RV and the 2 RV outflow tract dimensions when comparing the controls with those in the no PH group, but it was clearly less when comparing the no PH group with the PH group (Table 3, Fig. 3). Table 4 shows that the increase in RV size and wall thickness has already occurred in those patients with mPAP below 20 mm Hg. RV wall thickness correlated well with myocardial performance index (r = 0.7; p < 0.01) and mPAP with RV wall thickness and PaO₂ (r = 0.4 and r = −0.6; p < 0.01 for both), respectively. RV basal dimension did not correlate with forced expiratory volume percent predicted; RV wall thickness did (r = −0.44; p < 0.01), but with lower strength (r = −0.30; p < 0.01) when adjusted for PaO₂. Forced expiratory volume percent predicted explains only 8% of the variance in RV wall thickness. A nonlinear relationship was shown between RV
wall thickness and PA compliance ($r^2 = 0.3$; $p < 0.01$) and PVR ($r^2 = 0.3$; $p < 0.01$), respectively.

Multiple regression analysis. RV myocardial performance index, systolic strain, and RV isovolumic acceleration were dependent variables and age, sex, body mass index, forced expiratory ventilation percent predicted, PaO$_2$, inspiratory capacity/total lung capacity ratio, RV wall thickness, PWP, and mPAP were independent variables in multiple regression analysis. This resulted in RV wall thickness and mPAP as independent determinants of RV myocardial performance index (RV wall thickness: $\beta = 0.492$ [95% CI: 0.263 to 0.720; $p = 0.000$]; mPAP: $\beta = 0.010$ [95% CI: 0.006 to 0.012; $p = 0.000$]) and systolic strain (RV wall thickness: $\beta = 7.600$ [95% CI: 1.079 to 14.122; $p = 0.023$]; mPAP: $\beta = 0.240$ [95% CI: 0.113 to 0.368; $p = 0.000$]). RV isovolumic acceleration was predicted by RV wall thickness ($\beta = -0.965$ [95% CI: $-1.827$ to $-0.103$; $p = 0.029$]) and PaO$_2$ ($\beta = 0.116$ [95% CI: 0.050 to 0.181; $p = 0.001$]).

Interobserver and intraobserver variability. Intraclass correlation coefficients of interobserver variability for RV acceleration during isovolumic contraction, strain, myocardial performance index, RV basal dimension, and wall thickness were 0.99 (0.99 to 1.00), 0.94 (0.74 to 0.98), 0.99 (0.95 to 0.99), 0.91 (0.64 to 0.98), and 0.95 (0.79 to 0.98) and of intraobserver variability were 0.91 (0.70 to 0.98), 0.94 (0.80 to 0.98), 0.99 (0.97 to 0.99), 0.99 (0.98 to 0.99), and 0.97 (0.92 to 0.99), respectively ($p < 0.001$ for all).

Discussion

The present study showed that reduced RV systolic function, RV hypertrophy, and dilation were present even in patients with COPD who did not have PH compared with controls. These findings suggest that cardiac complications on the right side start early in the course of the pulmonary vascular disease, are incremental, and lead to RV impairment even at subclinical levels of elevated mPAP, PVR, and reduced PA compliance.

Impact of increased afterload on RV remodeling and function. One of the key findings in the present study is the observation that a small increase in mPAP at rest, even slightly above the considered normal level of 14.7 ± 4.0 mm Hg (17) and below 20 mm Hg (18), contributed to a significant and substantial adaptive increase in RV wall thickness and dilation.
and impaired function. The rise in resting mPAP above 25 mm Hg is a late marker of the remodeling process, and >50% of the pulmonary vascular bed is at this point already destroyed with a pronounced impact on the right ventricle (19). Although this is a new finding in patients with COPD, similar results have been documented in an early phase of patients prone to developing pulmonary arterial hypertension (20).

A polynomial relationship between PVR and PA compliance was shown, both of which are considered essential for RV afterload during slight exercise, which corresponds to daily life activities in patients with COPD, could partly in concert with nocturnal desaturation and a subsequent increase in PA pressure explain the presence of right heart abnormalities observed in the present study.

Other mechanisms for RV remodeling and dysfunction. The dissociation between PH and RV remodeling and impaired function in the early stages of COPD (mPAP <20 mm Hg) suggests that additive mechanisms to increased afterload, such as lung hyperinflation, systemic inflammation, and endothelial dysfunction, might have a direct and negative impact on the right ventricle. This may also in part explain the poor association between RV function and remodeling and forced expiratory flow per second, indicating that this important parameter of COPD severity is more connected to obstruction than to hypoxemia. The strong correlation between PaO2 and mPAP also reflects the important role of chronic hypoxemia in vascular remodeling; even at early stages of COPD, there was a slight reduction of PaO2 compared with normal values (Table 4).

The augmented right atrial pressure in COPD-PH is probably caused by intrinsic impairment of RV function in concert with the increased afterload leading to diastolic over-load. Inappropriate treatment with diuretics might increase this problem. The hypoxemic-induced hyperkinetic circulation by a cardiac index in the upper normal range, particularly evident in those with PH but also in those with no PH, may also play a role in diastolic overload. In addition, the relative chronic hypercapnia in COPD that leads to HCO3⁻ and Na⁺

### Table 3

Echocardiographic Data for 98 Patients With COPD With and Without PH and 34 Healthy Controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Healthy Controls (n = 34)</th>
<th>Patients With COPD (n = 98)</th>
<th>p Value (Analysis of Variance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV global function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV myocardial performance index</td>
<td>0.33 ± 0.05</td>
<td>0.50 ± 0.12*</td>
<td>0.67 ± 0.15*</td>
</tr>
<tr>
<td>RV myocardial performance index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV basal longitudinal strain (%)</td>
<td>-31 ± 4</td>
<td>-22 ± 4*</td>
<td>-18 ± 3*</td>
</tr>
<tr>
<td>TDI RV isovolumic acceleration (m/s²)</td>
<td>3.1 ± 0.7</td>
<td>2.0 ± 0.4*</td>
<td>1.6 ± 0.5*</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>27 ± 3</td>
<td>22 ± 3*</td>
<td>19 ± 4*</td>
</tr>
<tr>
<td>TDI tricuspid annular displacement (mm)</td>
<td>26 ± 5</td>
<td>22 ± 3*</td>
<td>18 ± 4*</td>
</tr>
<tr>
<td>RV fractional area change (%)</td>
<td>47 ± 8</td>
<td>39 ± 8*</td>
<td>34 ± 8*</td>
</tr>
<tr>
<td>RV fractional shortening (%)</td>
<td>50 ± 13</td>
<td>40 ± 14*</td>
<td>38 ± 10*</td>
</tr>
<tr>
<td>TDI tricuspid annular systolic velocity (cm/s)</td>
<td>15.2 ± 3.1</td>
<td>12.8 ± 2.2*</td>
<td>12.8 ± 2.6*</td>
</tr>
<tr>
<td>RV basal systolic velocity (cm/s)</td>
<td>11.5 ± 1.6</td>
<td>9.1 ± 1.1*</td>
<td>8.5 ± 0.7*</td>
</tr>
<tr>
<td>Three-dimensional RV ejection fraction (%)</td>
<td>58 ± 4</td>
<td>50 ± 5*</td>
<td>46 ± 6*</td>
</tr>
<tr>
<td>RV geometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV outflow tract wall thickness (mm)</td>
<td>3.5 ± 0.5</td>
<td>5.5 ± 1.0*</td>
<td>6.6 ± 1.1*</td>
</tr>
<tr>
<td>RV outflow tract 1 proximal (cm/m²)</td>
<td>1.47 ± 0.2</td>
<td>2.00 ± 0.47*</td>
<td>2.09 ± 0.33*</td>
</tr>
<tr>
<td>RV outflow tract 2 distal (cm/m²)</td>
<td>1.24 ± 0.11</td>
<td>1.39 ± 0.18*</td>
<td>1.42 ± 0.19*</td>
</tr>
<tr>
<td>RV hypertrophy (%)</td>
<td>0</td>
<td>42*</td>
<td>92*</td>
</tr>
<tr>
<td>RV dimension 1 base (cm/m²)</td>
<td>1.45 ± 0.15</td>
<td>1.95 ± 0.30*</td>
<td>2.13 ± 0.39*</td>
</tr>
<tr>
<td>RV dimension 2 mid (cm/m²)</td>
<td>1.15 ± 0.17</td>
<td>1.42 ± 0.31*</td>
<td>1.52 ± 0.34*</td>
</tr>
<tr>
<td>RV dimension 3 base apex (cm/m²)</td>
<td>4.04 ± 0.29</td>
<td>4.56 ± 0.43*</td>
<td>4.69 ± 0.57*</td>
</tr>
</tbody>
</table>

Values are mean ± SD or %. *Significantly different (p < 0.01) from controls. †Significantly different (p < 0.01) from no PH. Indexed for body surface area.

TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; other abbreviations as in Tables 1 and 2.
Retention at the kidney level, along with the osmotic result of H₂O reabsorption, may contribute to the increased circulating blood volume and diastolic overload as well (27).

Nine percent of our patients with COPD had diabetes, all were current or former smokers, many had slightly increased systemic blood pressure, and mean PWP and the echo estimated LV filling pressure in the PH group were in the upper part of normal limits. Subclinical coronary heart disease also could not be excluded. Moreover, there was a slight impairment of LV ejection fraction, although it was well within normal limits. LV diastolic heart failure with preserved LV ejection fraction in some of our patients with COPD can thus not entirely be excluded. On the other hand, none had large left atrial volumes, PWP of more than 15 mm Hg, or echo estimated LV filling pressure above 15. Conversely, LV function can also be influenced by hypertension (28) (Table 1) and by ventricular interdependency caused by the increased right ventricle (size and wall thickness) through the common ventricular septum (29).

**Echocardiographic indices to assess RV function.** The RV myocardial performance index combines measures of systolic and diastolic RV function and is thus presumed to reflect global RV function (30). This index has been validated in patients with PH and has the advantages of good
trophy had basal RV free wall strain of 34, patients with COPD who had PH and RV hyper-
value of group, we had a similar RV wall thickness but an RV strain
models (30). The RV myocardial performance index
reproducibility, quick calculation, and no need for geometric
models (30). The RV myocardial performance index find-
ings in the present study also support results from previous
noninvasive studies (31,32). Longitudinal strain was ob-
tained from the basal RV free wall, which previously has been
reported as more sensitive compared with mid or apical
levels in COPD (33). In a comparable study by Park et al.
(34), patients with COPD who had PH and RV hyper-
trophy had basal RV free wall strain of −13%. In our PH
group, we had a similar RV wall thickness but an RV strain
value of −18%. The discrepancy in strain is probably due to
lower overall RV function in the group from Park et al (34).

RV isovolumic acceleration, TDI strain from the basal RV
free wall, and RV myocardial performance index were the 3 of
10 indices that best could discriminate between healthy controls, patients with COPD without PH, and patients with COPD
who had PH. However, by applying 2 SDs in the group of
controls, only strain and RV myocardial performance index
could separate healthy controls from those with COPD without PH. The cardiologist should therefore consider reduced RV
function in these patients when the RV myocardial performance
index and basal RV strain are above 0.43 and below −23%,
respectively. We also consider that our results emphasize more
frequent use of echocardiography in the evaluation of RV
function in COPD, not only because it is inexpensive and
noninvasive, but also because it provides additional information
as compared with invasive right heart catheterization.

**Study limitations.** Our control group did not undergo
invasive hemodynamic measurements for ethical reasons. However, noninvasively estimated mPAP was normal and
consistent with reported mPAP values of healthy subjects
older than 50 years of age (17).

Echocardiography and right heart catheterization were not performed simultaneously. However, because the echo-
cardiographic examinations were comprehensive and there
was a risk of suboptimal patient positioning during these
recordings, we decided to perform the 2 examinations
separately in the patients, which also provided similar
conditions as the controls.

The duration of RV isovolumic acceleration is short (20
to 40 ms). The median frame rate was 175 frames/s (i.e., data
are acquired every 5 to 6 ms), which may result in a slight
underestimation of peak velocity. The acceleration time of RV
isovolumic acceleration is also angle dependent, and dif-
ferences in beam alignment could represent a source of error.

An important issue of the present study was to evaluate the
impact of pre-capillary pulmonary vascular alterations

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### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 34)</th>
<th>Normal (n = 51)</th>
<th>Borderline (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right heart catheterization hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>17 ± 2</td>
<td>23 ± 1*</td>
<td></td>
</tr>
<tr>
<td>Pulmonary wedge pressure (mm Hg)</td>
<td>8 ± 4</td>
<td>10 ± 4*</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance (Wood units)</td>
<td>1.8 ± 0.7</td>
<td>2.4 ± 1.1*</td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery compliance (ml/mm Hg)</td>
<td>4.3 ± 1.3</td>
<td>3.7 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.2 ± 1.0</td>
<td>5.2 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>9.9 ± 1.2</td>
<td>9.5 ± 1.1</td>
<td></td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV myocardial performance index</td>
<td>0.33 ± 0.05</td>
<td>0.50 ± 0.13</td>
<td>0.48 ± 0.08*</td>
</tr>
<tr>
<td>RV isovolumic acceleration (cm/s²)</td>
<td>3.1 ± 0.7</td>
<td>2.1 ± 0.4</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>RV basal strain (%)</td>
<td>−31 ± 4</td>
<td>−22 ± 4</td>
<td>−21 ± 3</td>
</tr>
<tr>
<td>RV outflow tract wall thickness (mm)</td>
<td>3.5 ± 0.5</td>
<td>5.4 ± 1.0</td>
<td>5.8 ± 0.9</td>
</tr>
<tr>
<td>RV01 dimension (cm/m²)</td>
<td>1.5 ± 0.2</td>
<td>1.9 ± 0.3</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>RV outflow tract 1 dimension (cm/m²)</td>
<td>1.5 ± 0.2</td>
<td>1.9 ± 0.04</td>
<td>2.1 ± 0.6</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *Significantly different (p < 0.01) between borderline and normal. | Standard conversion: 1 kPa = 7.501 mm Hg. | Significantly different (p < 0.01) between normal and borderline versus controls. Abbreviations as in Tables 1 and 2.
on RV function. Our findings are thus not generalizable to all patients with COPD.

Conclusions

The present study has shown, in a group of outpatients with COPD who had the post-capillary impact thoroughly excluded, impaired RV systolic function along with RV hypertrophy and dilation. The majority of these patients did not have PH, which emphasizes that even minor elevations in mPAP have important consequences for RV function and structure; however, the dissociation to PH at early stages of COPD indicates other mechanisms as well. RV isovolumic acceleration, RV basal strain, and RV myocardial performance index seem to be the echocardiographic indices that best can identify patients with COPD who have subclinical reduced RV function.

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Key Words: COPD • echocardiography • pulmonary circulation • right ventricular function.