Pulmonary Hemodynamics in Advanced COPD Candidates for Lung Volume Reduction Surgery or Lung Transplantation*

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Study objectives: To assess the pulmonary hemodynamic characteristics in COPD candidates for lung volume reduction surgery (LVRS) or lung transplantation (LT).

Design: Retrospective study.

Setting: One center in France.

Patients: Two hundred fifteen patients with severe COPD who underwent right-heart catheterization before LVRS or LT.

Results: Mean age was 54.6 years. Pulmonary function test results were as follows: FEV1, 24.3% predicted; total lung capacity, 128.3% predicted; residual volume, 259.7% predicted. Mean pulmonary artery pressure (PAPm) was 26.9 mm Hg. Pulmonary hypertension (PAPm > 25 mm Hg) was present in 50.2% and was moderate (PAPm, 35 to 45 mm Hg) or severe (PAPm > 45 mm Hg) in 9.8% and in 3.7% of patients, respectively. Cardiac index was low normal. PAPm was related to PaO2 and alveolar-arterial oxygen gradient in multivariate analysis. Cluster analysis identified a subgroup of atypical patients (n = 16, 7.4%) characterized by moderate impairment of the pulmonary mechanics (mean FEV1, 48.5%) contrasting with high level of pulmonary artery pressure (PAPm, 39.8 mm Hg), and severe hypoxemia (mean PaO2, 46.2 mm Hg).

Conclusion: While pulmonary hypertension is observed in half of the COPD patients with advanced disease, moderate-to-severe pulmonary hypertension is not a rare event in these patients. We individualized a subgroup of patients presenting with a predominant vascular disease that could potentially benefit from vasodilators. (CHEST 2005; 127:1531–1536)

Key words: COPD; hemodynamics; pulmonary hypertension

Abbreviations: CI = cardiac index; IC = inspiratory capacity; iPVR = indexed pulmonary vascular resistance; LT = lung transplantation; LVRS = lung volume reduction surgery; (A-a)O2 = alveolar-arterial oxygen gradient; PAPm = mean pulmonary artery pressure; Pw = pulmonary artery wedge pressure; RAP = right atrial pressure

Secondary pulmonary hypertension is a well-known possible feature in patients with advanced COPD.1,2 3 The studies4 - 5 that have focused on this topic have shown that pulmonary hypertension is frequent during exacerbations or exercise but is not constant when the subjects are studied in a stable state of their disease. When present at rest, pulmonary hypertension is in general of moderate severity, but the range of mean pulmonary artery pressures (PAPms) that may be observed is very wide.6,7 The studies on pulmonary hemodynamics in COPD have constant when the subjects are studied in a stable state of their disease. When present at rest, pulmonary hypertension is in general of moderate severity, but the range of mean pulmonary artery pressures (PAPms) that may be observed is very wide.6,7 The studies on pulmonary hemodynamics in COPD have in general included patients of various severities; however, little is known about the particular case of patients with very advanced form of the disease. In a study reporting the results of right-heart catheterization in patients considered for lung volume reduction surgery (LVRS), Scharf and coworkers7 showed that a mild pulmonary hypertension was present in

For editorial comment see page 1480
most cases. However, only a few patients (5%) exhibited PAPm > 35 mm Hg. Unfortunately, because of the very stringent selection criteria applied to the patients recruited in this study, the enrolled patients represented a very selected subset of all patients with emphysema. For instance, selection criteria excluded patients with PaO2 < 45 mm Hg or PaCO2 > 60 mm Hg.

For > 15 years, our center has developed a lung transplant program, and more recently an LVRS program. For that reason, COPD patients are frequently referred to our center for consideration of either lung transplantation (LT) or LVRS, and all of them undergo right-heart catheterization during the selection process, thus giving us the opportunity to study the pulmonary hemodynamics in a large cohort of patients with advanced COPD. The aim of this study is to describe the pulmonary hemodynamics at rest in a large cohort of patients with severe COPD during a 14-year period, and to look for correlations between hemodynamic and pulmonary functional parameters.

**Materials and Methods**

All COPD patients referred to our center for consideration of either LT or LVRS from 1988 to 2002 and who underwent right-heart catheterization were screened for potential inclusion in the study. Right-heart catheterization is not performed routinely for COPD but is a mandatory component of a thorough cardiorespiratory assessment before LT or LVRS.

Patients were excluded if a factor that could influence pulmonary hemodynamics was present. In particular, the exclusion criteria were as follows: (1) acute or chronic pulmonary embolism, (2) left-heart disease, (3) portal hypertension, (4) collagen vascular disease, (5) HIV infection, (6) use of appetite-suppressant drugs, (7) recent exacerbation, and (8) sleep-related respiratory disturbances. All included patients underwent a CT scan of the thorax displaying some degree of pulmonary emphysema, and echocardiography showing the absence of left-heart systolic dysfunction (left ventricular end-diastolic diameter < 32 mm/m² and left ventricular ejection fraction > 50%). Right-heart catheterization (Swan-Ganz catheter; Edwards Lifesciences LLC; Irvine, CA) was performed on patients at rest, in stable condition, and in a supine position. Oxygen was administered if required in order to maintain blood oxygen saturation > 90%, but the patients did not receive any vasodilators at the time of evaluation. Right atrial pressure (RAP), pulmonary artery pressure (systolic, diastolic, mean), and pulmonary artery wedge pressure (Pw) were measured at end expiration. Cardiac output and cardiac index (CI) were calculated by thermodilution. Indexed pulmonary vascular resistance (iPVR) was calculated as follows: iPVR = [(PAPm – Pw)/CI] × 79.9 (dyne · sec · cm⁻⁵ · m²).

In addition to hemodynamic results, the results of lung perfusion scans and pulmonary function tests obtained in each patient at the time of right-heart catheterization were retrieved. Pulmonary function testing consisted of FEV1, obtained by spirometry and lung volumes obtained by plethysmography; inspiratory capacity (IC), total lung capacity, functional residual capacity, and residual volume, all expressed as percentage of predicted. The value of the Fletcher dyspnea score at the time of the evaluation and the results of measurements of gas tensions in arterial blood drawn on room air were also retrieved. The alveolar-arterial oxygen gradient [Pa(O2) - PaO2] was calculated using the measured PaO2 and Pao2, and alveolar oxygen tension was calculated from the alveolar gas equation assuming standard respiratory exchange ratio of 0.8.

**Statistical Analysis**

The primary statistical goal of this study was to estimate the prevalence of pulmonary hypertension in this population and determine which factors are associated with it. Pulmonary hypertension was defined as a PAPm > 25 mm Hg at rest, and was classified as mild (PAPm, 26 to 35 mm Hg), moderate (PAPm, 36 to 45 mm Hg), or severe (PAPm > 45 mm Hg). Continuous data are expressed as mean (SD), and categorical data are presented as count and proportions. Univariate analyses were made by Student t test and χ² test. Pearson correlation coefficient was used to assess the relationship between continuous variables. Multiple linear regression models were built to assess the relationship between PAPm and variables found to be significant at the 0.2 level in univariate analyses, or thought to be of clinical importance. Underlying models assumptions were checked graphically. We used cluster analysis as an explanatory analysis to find homogeneous groups of patients. The data set was treated (after standardization of data) by the k-means partition cluster analysis, with Euclidian distance as measure of similarity. The Calinski stopping rule was used to find the optimal number of clusters. Analysis was performed using software (Stata Statistical Software, Release 8.0; Stata Corporation; College Station, TX).

**Results**

**Characteristics of the Studied Population**

Two hundred forty-seven patients fulfilled the selection criteria for the study. Although they had no evidence of cardiac dysfunction, 32 patients with a Pw > 15 mm Hg were excluded from the analysis because pulmonary hypertension, when present, has a postcapillary component. Thus, 215 patients form the basis of this study.

In this cohort, pulmonary hemodynamics was assessed as a preoperative evaluation before LVRS in 123 patients and before LT in 92 patients. The demographic and respiratory function characteristics of the patients according to the considered surgical procedure are shown in Table 1. There were 169 male (78.6%) and 46 female (21.4%) patients.

**Pulmonary Hemodynamics**

The hemodynamic data are given in Table 2. Figure 1 displays the distribution of PAPm in our population. The mean PAPm of the whole cohort was 26.9 ± 8.1 mm Hg (range, 8 to 63 mm Hg). Pulmonary hypertension as defined by a resting PAPm > 25 mm Hg was present in 108 of 215 patients (50.2% of cases) and was considered as mild in 79 patients (36.7%), moderate in 21 patients...
By multiple linear regression analysis, only $P_{\text{Pa}}/H_11005$ of FEV1 and $P_{\text{Pa}}$ (14%) is characterized by moderately lowered values, as summarized in Table 3. Group 1, consisting of 30 patients (9.8%), and severe in 8 patients (3.7%). Only 15 patients (7%) had a CI < 2.2 L/min/m².

**Correlates of PAPm**

PAPm was found inversely correlated with $P_{\text{PaO}}_2$ ($r = -0.55$, $p = 0.0001$), IC ($r = -0.26$, $p = 0.002$), and FEV1 ($r = -0.17$, $p = 0.005$), and directly correlated with $P_{\text{PW}}$ ($r = 0.28$, $p = 0.0001$), $P_{(A-a)O}_2$ ($r = 0.53$, $p = 0.0001$), RAP ($r = 0.38$, $p = 0.0001$), and dyspnea score ($r = 0.40$, $p = 0.0001$). By multiple linear regression analysis, only $P_{\text{PaO}}_2$, $P_{(A-a)O}_2$, and $P_{\text{PW}}$ remained significantly associated with PAPm (partial correlation coefficient $[r] = -0.37$, $p = 0.001$; $r = 0.22$, $p = 0.003$; and $r = 0.28$, $p = 0.001$, respectively).

**Cluster Analysis**

Cluster analysis suggests the existence of four groups of patients, whose characteristics are summarized in Table 3. Group 1, consisting of 30 patients (14%) is characterized by moderately lowered values of FEV1 and $P_{\text{PaO}}_2$ and a normal level of PAPm. All these patients had been referred to our institution as potential candidates to LVRS. Group 2 is characterized by severe airflow obstruction attested by a profound FEV1 impairment, and by moderate hypoxemia and pulmonary hypertension ($n = 106$; 49.3%). Two thirds of these patients were assessed for LVRS, whereas the remaining patients were considered for LT. Group 3 includes 63 patients (29.3%) with severe spirometric impairment associated with severe hypoxemia and high pulmonary artery pressure. Most of these patients were evaluated for LT. Group 4 ($n = 16$; 7.4%) consists of patients characterized by moderate airflow obstruction (mean FEV1, 48.5 ± 11.8%), contrasting with moderate-to-severe pulmonary hypertension (mean PAPm, 39.8 ± 10.2 mm Hg) and by severe hypoxemia (mean PaO2, 46.2 ± 15.7 mm Hg). Group 4 patients were referred for either LT or LVRS. Figure 2 illustrates the main profile of each of the four groups. When compared to the three other groups, group 4 patients were characterized by a higher FEV1, a lower PaO2, and a higher level of PAPm. Moreover, $P_{\text{PaCO}}_2$ was significantly lower and the $P_{(A-a)O}_2$ was significantly higher than in the other groups. None of the group 4 patients had a right-to-left shunt identified on lung perfusion scan.

**Discussion**

The salient results of our study are the following: (1) while half of the patients with severe COPD had mild-to-moderate pulmonary hypertension, a subset of patients (3.7%) exhibit severe pulmonary hypertension; and (2) we identified a subgroup of patients characterized by a moderate impairment of the pulmonary mechanics contrasting with the severity of pulmonary hypertension.

Pulmonary hypertension is a well-known complication of COPD. Its presence is associated with a worse survival11 and an increased risk of hospitalization for exacerbation.12 To date, the therapeutic strategies have been disappointing. Several mechanisms may be involved in the pathogenesis of pulmonary hypertension in this setting: reduction of the pulmonary vascular bed, effects of abnormal pulmonary mechanics (pleural pressure, alveolar pressure), inflammation-induced vascular remodeling related to smoking, hyperviscosity, elevated Pw, and chronic alveolar hypoxia with subsequent vascular remodeling, the latter being considered the most significant mechanism.

The actual prevalence of pulmonary hypertension in patients with COPD is not precisely known. According to the series3,7,11,13 in which pulmonary artery pressure has been measured via right-heart catheterization, the prevalence of pulmonary hyper-

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**Table 1—Demographics and Respiratory Function Data of the Patients (n = 215) According to Surgical Procedure**

<table>
<thead>
<tr>
<th>Variables</th>
<th>LT (n = 123)</th>
<th>LVRS (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>52.6 (7.3)</td>
<td>55.6 (9.8)</td>
</tr>
<tr>
<td>$P_{\text{PaO}}_2$, mm Hg</td>
<td>55.4 (12.2)</td>
<td>66.2 (12.5)</td>
</tr>
<tr>
<td>$P_{\text{PaCO}}_2$, mm Hg</td>
<td>50.1 (10.0)</td>
<td>40.6 (6.6)</td>
</tr>
<tr>
<td>$P_{(A-a)O}_2$, mm Hg</td>
<td>31.8 (14.5)</td>
<td>33.2 (12.8)</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>18.5 (9.6)</td>
<td>27.9 (12.9)</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>131.5 (20.7)</td>
<td>127.5 (20.1)</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>250.9 (67.6)</td>
<td>250.7 (67.9)</td>
</tr>
<tr>
<td>FRC, % predicted</td>
<td>205.7 (51.8)</td>
<td>184.8 (36.0)</td>
</tr>
<tr>
<td>IC, % predicted</td>
<td>3.2 (0.6)</td>
<td>3.0 (0.6)</td>
</tr>
<tr>
<td>Dyspnea score†</td>
<td>4.3 (0.9)</td>
<td>3.7 (1.0)</td>
</tr>
</tbody>
</table>

*Results are expressed as mean (SD). FRC = functional residual capacity; RV = residual volume.
†Fletcher’s dyspnea score.

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**Table 2—Hemodynamic Characteristics of the Patients (n = 215) According to Surgical Procedure**

<table>
<thead>
<tr>
<th>Variables</th>
<th>LT (n = 92)</th>
<th>LVRS (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPm, mm Hg</td>
<td>27.8 (7.3)</td>
<td>25.4 (7.7)</td>
</tr>
<tr>
<td>PAPs, mm Hg</td>
<td>39.3 (10.1)</td>
<td>36.4 (11.7)</td>
</tr>
<tr>
<td>PAPd, mm Hg</td>
<td>21.6 (5.5)</td>
<td>18.5 (6.3)</td>
</tr>
<tr>
<td>Pw, mm Hg</td>
<td>12.2 (3.2)</td>
<td>11.7 (3.2)</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>8.9 (4.1)</td>
<td>9.7 (3.9)</td>
</tr>
<tr>
<td>CI, L/min/m²²</td>
<td>3.2 (0.7)</td>
<td>3.0 (0.6)</td>
</tr>
<tr>
<td>iPVR, dyne * s * cm⁻³ * m²</td>
<td>390 (269)</td>
<td>365 (252)</td>
</tr>
</tbody>
</table>

*Results are expressed as mean (SD). PAPs = systolic pulmonary artery pressure; PAPd = diastolic pulmonary artery pressure.
tension (defined as a PAPm ≥ 20 mm Hg or ≥ 25 mm Hg in these studies) varies from 20 to 91%. These results are not surprising since the patients included in the different series were of various functional severity. Our data on a population of patients with severe functional impairment (mean FEV1, 23.9%) suggest that the prevalence of pulmonary hypertension in the advanced form of the disease is high. However, like the other studies on the same topic, our study is prone to a selection bias, since the population of patients referred for consideration of LVRS or LT is not a random subset of all COPD patients, precluding an unbiased estimate of the prevalence of pulmonary hypertension in the COPD population.

Whatever the prevalence of pulmonary hypertension in COPD patients may be, there is a general agreement on the fact that the level of pulmonary hypertension when present is usually mild to moderate and is far from the level observed in case of primary pulmonary hypertension.14–16 Our results contrast with this prevailing opinion, since a significant proportion (13.5%) of patients had moderate-to-severe pulmonary hypertension defined by a PAPm ≥ 35 mm Hg. In their study, Scharf and coworkers7 found a somewhat lower proportion (5%) of such patients, with only one patient with a PAPm > 45 mm Hg. This discrepancy could be explained by the higher degree of severity of airflow obstruction of our patients and by the selection criteria used in the study by Scharf and colleagues.7 A high value of RAP was found in our study. This result is in accordance with that of Scharf et al.,7 and could be related at least in part to the pleural pressure but we have no data to support this hypothesis.

The negative correlations between PAPm and PaO2 and between PAPm and FEV1 have been already described by previous investigators.6,7,13 In particular, Scharf and colleagues7 found by multivariate analysis that PAPm was significantly related to

Table 3—Characteristics of the Four Groups of Patients According to Cluster Analysis*

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>PAPm (mmHg)</th>
<th>FEV1</th>
<th>PaO2</th>
<th>P(A-a)/O2</th>
<th>PaCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>19.0 (4.4)</td>
<td>41.5 (12.8)</td>
<td>80.1 (8.2)</td>
<td>20.7 (9.7)</td>
<td>39.3 (4.4)</td>
</tr>
<tr>
<td>2</td>
<td>106</td>
<td>24.5 (3.9)</td>
<td>20.3 (5.4)</td>
<td>65.3 (7.0)</td>
<td>30.7 (9.4)</td>
<td>43.1 (7.1)</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>31.3 (8.2)</td>
<td>17.0 (4.8)</td>
<td>48.0 (7.1)</td>
<td>37.1 (12.4)</td>
<td>51.9 (10.6)</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>39.8 (10.2)</td>
<td>48.5 (11.8)</td>
<td>46.2 (15.7)</td>
<td>53.9 (20.7)</td>
<td>39.7 (10.9)</td>
</tr>
</tbody>
</table>

*Results are expressed as mean (SD).
FEV$_1$ as well as to diffusion capacity for carbon monoxide but not to Pa$_{O_2}$. By contrast, in our study FEV$_1$ was related to PAPm by univariate but not by multivariate analysis. The only variable we found related to PAPm by multivariate analysis were Pa$_{O_2}$, P(A-a)O$_2$, and Pw. The fact that low Pa$_{O_2}$ was an exclusion criterion in the study by Scharf and co-workers$^7$ and that FEV$_1$ values of our cohort were lower could explain the discrepancy between the two studies.

We used cluster analysis to better define the hemodynamic profile of the patients. Cluster analysis is a generic term for a wide range of numerical methods for examining multivariate data with the aim to discover groups or clusters of homogeneous observations. The main aim of cluster analysis is grouping subjects into classes (clusters) so that patients within a class are similar to each other but different from those in other classes. It should be viewed as an explanatory tool able to indicate patterns of data. Cluster analysis identified several groups of patients according to their hemodynamic/respiratory function/gas exchange profile. One of these groups characterized by a high level of pulmonary artery pressure contrasting with moderate-to-mild airflow obstruction was very atypical. Compared to the remaining patients, this latter group consisted of 16 patients who differed significantly in terms of hypoxemia (more severe), hypercarbia (less severe), alveolar-arterial gradient (larger), and airflow obstruction (less severe). Although the number of patients in this group was relatively small, we think that they should be individualized since they represent a subset of COPD patients in whom the vascular disease seems to be predominant. Interestingly, Scharf and coworkers$^7$ failed to identify such a subgroup of patients. The stringent exclusion criteria of the National Emphysema Treatment Trial may explain this fact, since our group of patients is characterized by a low Pa$_{O_2}$, which was an exclusion criterion in the study by Scharf and co-workers.$^7$

The identification of such patients is important because of the potential therapeutic implications and in particular the use of vasodilators. Given the frequency of pulmonary hypertension as well as the relation between the latter and survival, there is a rationale to use vasodilators in patients with advanced COPD, but up to now the benefit offered by these agents in this setting is questionable.$^2$ However, one may hypothesize that the efficacy of vasodilators might be more pronounced in the subgroups of patients in whom the vascular disease seems to be predominant, such as those in group 4. The answer to that question should rely on a randomized controlled study.

Why does pulmonary hypertension develop in
some COPD patients with moderate airflow obstruction? The question remains unanswered, but some recent data from Eddahibi and coworkers\textsuperscript{17} suggest the role of a genetic predisposition. These authors have shown on a large cohort of COPD patients that pulmonary hypertension was associated with serotonin transporter gene polymorphism. For the same degree of airflow obstruction, the patients with LL genotype that is those with a high level of serotonin transporter gene transcription had a higher level of pulmonary artery pressure. Whether such a genetic susceptibility is involved in the pathogenesis of pulmonary hypertension in our group 4 patients remains to be studied.

In summary, pulmonary hypertension was present in a large subset of our patients with advanced COPD. Pulmonary hypertension was mild in most of them but was moderate to severe in a significant proportion of patients. By multivariate analysis, an inverse relationship was found between the level of pulmonary artery pressure and PaO\textsubscript{2}. The most striking result of our study is that we identified a subgroup of patients characterized by an elevated pulmonary artery pressure and a marked hypoxemia, contrasting with moderate impairment of FEV\textsubscript{1}. These patients with predominant vascular disease could be potential candidates for the testing of vasodilator agents.

**References**