Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity

Robertino Rodríguez-Roisin,1,3 Mitra Drakulovic,2 Diego A. Rodríguez,2 Josep Roca,1,3 Joan Albert Barberà,1,3 and Peter D. Wagner4

1Servei de Pneumologia (Institut del Tórax), Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer, 2Fundació Clinic de Recerca Biomèdica, and 3Ciber Enfermedades Respiratorias, Universitat de Barcelona, Barcelona, Spain; and 4Division of Physiology, University of California, San Diego, California

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Rodríguez-Roisin R, Drakulovic M, Rodríguez DA, Roca J, Barberà JA, Wagner PD. Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. J Appl Physiol 106: 1902–1908, 2009. First published April 26, 2009; doi:10.1152/japplphysiol.00085.2009.—Chronic obstructive pulmonary disease (COPD) has emerged as a major worldwide public health challenge (26, 28). It is characterized by airflow limitation, the major site of which is the small airways. Airway obstruction and pulmonary emphysema are thought to cause this airflow limitation through persistent inflammation, as immune cells are present at all pulmonary sites (20–22). The inflammatory response leads to increased airway wall thickness, lumen reduction, and mucus secretion, all directly obstructing airways. Emphysematous alveolar destruction reduces radial traction on airways, further contributing to airflow limitation, and causes remodeling of the gas exchange zone with extensive loss of alveolar surface area and pulmonary capillaries.

COPD is the most common chronic respiratory disease state associated with chronic and/or acute respiratory insufficiency (26, 28). Uneven distribution of both alveolar ventilation and pulmonary blood flow, namely ventilation-perfusion (VA/Q) mismatch, remains the most important cause of arterial hypoxemia, with or without hypercapnia, in both stable and exacerbated COPD (3, 7, 27, 43). However, the progression of VA/Q imbalance in stable COPD remains to be examined, and no overview analysis with conclusive results is available to comprehensively understand the relationships between pulmonary gas exchange abnormalities and the spectrum of COPD, from mild to very severe stages.

While a recent meta analysis by Franciosi et al. (18) concluded that PaO2 was the only clinical variable that correlated with forced expiratory volume in 1 s (FEV1), it is widely held that arterial blood gas abnormalities relate poorly to the severity of airflow limitation (39) and also that the pattern of VA/Q mismatch is at best only weakly related to arterial blood gases (24, 39). This has been explained not only by the variability in the underlying anatomical and physiological components of airflow limitation and pulmonary gas exchange, but also by variability in the modulating effects of extrapulmonary factors governing arterial blood gases (i.e., minute ventilation, cardiac output, and oxygen consumption), which are not necessarily related to the degree of airflow limitation (39).

Over the past 10 years, the Global Initiative for COPD (GOLD) has made a major effort to increase awareness of all facets related to COPD (26, 28). Indeed, the GOLD spirometric staging classification, based on measurements of airflow limitation during forced spirometry and also analysis of arterial blood gases, has become widely accepted as one of the best standards for COPD diagnosis and management, and also as the stratifying tool for research studies concerned with COPD severity. Here we summarized the relationships between the progression of COPD, as reflected by its GOLD classification, and that of alveolar ventilation to pulmonary blood flow inequalities, using the multiple inert gas elimination technique (MIGET) (16, 33, 41), in a total of 150 patients. More specifically, we addressed two questions. First, what is the degree of gas exchange abnormalities at GOLD stage 1 [mild COPD; i.e., postbronchodilator FEV1/ forced vital capacity (FEV1/FVC) ratio < 0.7 with FEV1 ≥ 80% predicted]? Second, how does the relationship between spirometry and VA/Q mismatch progress across the entire spectrum of COPD severity?
METHODS

The present paper includes data from 10 previously published studies (number of subjects, n = 105) (1, 4, 6–9, 27, 31, 35, 38) and three others: two reported preliminarily (n = 30) (14, 15) and one reported here for the first time (n = 5). Ten GOLD stage 1 patients were also additionally included to increase the small number of patients of the original stage 1 subgroup. All involved patients were in stable condition (i.e., at least 3 mo distant from the last exacerbation) without significant comorbidities, including cardiac failure, diabetes mellitus, or other coexisting respiratory disease (Table 1). All were current (n = 30) or past heavy (n = 120) smokers and, as can be seen, virtually all were male (142/150). The distribution was 15 with stage 1 (mild); 40 with stage 2 (moderate); 32 with stage 3 (severe); and 63 with stage 4 (very severe). Protocols for these studies were approved by the Ethics Review Board at Hospital Clinic, and all patients gave written informed consent.

Forced spirometry (using only postbronchodilator values) and static lung volumes (model CPF-S; Medical Graphics, St. Paul, MN) were measured according to American Thoracic Society/European Respiratory Society recommendations, using our own predicted equations (29, 30, 32). Diffusing capacity for carbon monoxide (DLCO) and arterial blood gases and minute ventilation were measured at rest and while breathing ambient air, and AaPo2 and MIGET were used to measure the distributions of V˙A/Q˙ ratios calculated, as previously described (16, 33, 41). The quantitative degree of pulmonary elimination of the six inert gases of MIGET is determined by the V˙A/Q˙ inequality shown in Fig. 1 and Table 1. Inert gas data quality is explored by compiling the summed squared errors, named residual sum of squares, found in fitting the inert gas data to the corresponding V˙A/Q˙ distributions.
Table 2. Ventilation-perfusion distributions of the patients grouped according to the GOLD stage of COPD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GOLD Stage 1, Mild</th>
<th>GOLD Stage 2, Moderate</th>
<th>GOLD Stage 3, Severe</th>
<th>GOLD Stage 4, Very Severe</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunt, % Q̇T</td>
<td>1±1</td>
<td>1±1</td>
<td>1±2</td>
<td>2±28</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Low, V̇A/Q, % Q̇T</td>
<td>1.4±3.3</td>
<td>2.8±4.8</td>
<td>4.1±7.0</td>
<td>3.1±7.0</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Q</td>
<td>0.83±0.23</td>
<td>0.72±0.23</td>
<td>0.68±0.30</td>
<td>0.65±0.27</td>
<td>NS</td>
</tr>
<tr>
<td>Log SDQ</td>
<td>0.83±0.32</td>
<td>0.87±0.30</td>
<td>0.98±0.24</td>
<td>1.00±0.26</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>High, V̇A/Q, % Q̇T</td>
<td>0.9±2.8</td>
<td>7.4±14.4</td>
<td>5.1±10.7*</td>
<td>6.8±11.5*</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean V̇</td>
<td>1.60±0.54</td>
<td>1.54±0.73</td>
<td>1.80±0.52</td>
<td>2.0±0.97§§</td>
<td>§ 0.01</td>
</tr>
<tr>
<td>Log SDV</td>
<td>0.72±0.25</td>
<td>0.79±0.24</td>
<td>0.98±0.26*‡</td>
<td>1.04±0.28§§</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DISPR-E*</td>
<td>8.12±4.43</td>
<td>9.02±4.11</td>
<td>13.22±6.08*‡‡</td>
<td>14.20±4.57§§</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dead space, % V̇E</td>
<td>21±12</td>
<td>28±15</td>
<td>31±12</td>
<td>34±14†</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>V̇E, l/min</td>
<td>0.50±4.00</td>
<td>0.05±2.3</td>
<td>0.8±2.0</td>
<td>8.4±2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Qt, l/min</td>
<td>5.8±1.8</td>
<td>6.0±1.3</td>
<td>5.6±1.5</td>
<td>5.3±1.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD. Shunt, perfusion-to-alveolar units with V̇A/Q ratios <0.005; low V̇A/Q, ratios between 0.005 and 0.1 (excluding shunt); Q̇T, cardiac output; mean Q, the mean V̇A/Q ratio of the blood flow distribution; Log SDQ, dispersion of pulmonary blood flow; mean V̇, the mean of V̇A/Q ratio of the ventilation distribution; Log SDV, dispersion of pulmonary blood flow, V̇A/Q ratio between 10 and 100; DISPR-E*, dispersion of retention minus excretion of inert gases corrected by dead space; dead space, V̇A/Q ratios >100; V̇E, minute ventilation. mean Q, mean V̇, Log SDQ, Log SDV, and DISPR-E* are dimensionless. P values were determined by the Kruskal-Wallis test: *P < 0.0083, GOLD stage 1 vs. 3; ‡P < 0.0083, GOLD stage 1 vs. 4; §P < 0.0083, GOLD stage 2 vs. 3; §§P < 0.0083, GOLD stage 2 vs. 4.

Typically seen in health, despite only minor abnormalities in FEV1/FVC ratio (and normal FEV1).

More importantly, in addition to the behavior of group mean values, Table 3 shows that almost all (14 of 15) stage 1 patients displayed abnormal overall V̇A/Q inequality (i.e., DISPR-E*), and all but two showed an abnormal AaPO2 equal to or greater than 15 mmHg (normal range in our laboratory, 4–6 mmHg). On the other hand, PaO2 was <80 mmHg in only 40%, and PaCO2 was increased (≥45 mmHg) in none.

In summary, almost all patients at stage 1 show considerable V̇A/Q inequality and an increased AaPO2, despite mild airflow limitation. Of note is that a decrease in FEV1/FVC ratio of just 0.07 from the fixed value of 0.7 was associated with an increase of 38% over the upper limit of normal in the Log SDQ (Fig. 1).

Progression of spirometry and gas exchange according to the GOLD stage: group findings. As shown in Fig. 2, mild-to-moderate hypoxemia (<80 mmHg to ≥ 60 mmHg) was observed in six patients (40%) with stage 1, 24 (60%) with stage 2, 23 (72%) with stage 3, and 22 (35%) with stage 4; severe hypoxemia (<60 mmHg) was recorded in 39 (62%) with stage 4; hypercapnic respiratory failure (partial pressure of carbon dioxide ≥50 mmHg) was present in 1 (1%) and 13 (21%) patients at stages 3 and 4, respectively. Low DLCO (<80% predicted) was observed in seven patients (47%) with stage 1, 18 (45%) with stage 2, 23 (61%) with stage 3, and 58 (92%) with stage 4.

The severity of spirometric and arterial blood gas abnormalities significantly increased across the spectrum of the GOLD classification (Table 1). As shown in Fig. 1 and Table 1, residual volume increased progressively, while the IC/TLC ratio remained almost constant. Mean DLCO remained normal until stage 2 and then decreased, paralleling the changes in residual volume. Figs. 1 and 2 and Table 1 show that both PaO2 and Paco2 changed little over the first two stages, but then changed rapidly with further severity (stages 3 and 4) of COPD. Since AaPo2 increased only modestly, and linearly, over the entire range, this rapid change in PaO2 and Paco2, at stages 3 and 4 reflects not only V̇A/Q worsening but also insufficient alveolar ventilation in relation to carbon dioxide production. Figure 1 shows that all indexes of V̇A/Q inequality worsened linearly with GOLD stage. There are some important trends, however, in that, at stage 4, the Log SDQ (reflecting mostly low V̇A/Q ratio areas) was not much higher than at stage 1, and nowhere near the values of 2.00–2.50 observed in life-threatening clinical conditions, such as COPD severe exacerbation (5, 7, 27, 36, 37) or acute severe asthma (2, 17, 34). In contrast, the Log SDV (reflecting mostly high V̇A/Q regions) increased more with GOLD stage and significantly at stage 3. However, this greater increase occurred because the values at stage 1 were closer to normal than was the case for the Log SDQ. Thus, by stage 4, absolute values of Log SDQ and Log SDV were not different from each other, and again had not reached values anywhere near those observed during acute severe COPD and bronchial asthma.

Table 3 shows that PaO2 was reduced in only 60% of patients at stage 2, despite almost universally abnormal V̇A/Q relationships and AaPo2. Even at stage 3, only in 72% of patients was PaO2 <80 mmHg, and it was not until stage 4 that essentially all patients exhibited arterial hypoxemia. Similarly, Paco2 was within normal limits in (essentially) all patients across the first three GOLD stages.

In summary, in all GOLD stages, essentially all patients presented abnormal V̇A/Q relationships reflected in an increased AaPo2, with many fewer patients demonstrating arterial hypoxemia with or without hypercapnia until stage 4. In addition, indexes of V̇A/Q inequality by stage 4 are surprisingly only modestly worse than at stage 1. As a result, the progression of V̇A/Q mismatch from GOLD stage 1 to stage 4 is not nearly as rapid as the loss of FEV1, and the rapid deterioration in PaO2 at stage 4 is not fully explained by further V̇A/Q worsening.

Progression of spirometry and gas exchange according to the GOLD stage: correlations. Over the entire range, most gas exchange variables were significantly related to postbronchodilator FEV1. These included PaO2 (r = 0.62) and Paco2 (r = −0.59), AaPo2 (r = −0.30) (Fig. 2), Log SDV (r = −0.49), and DISPR-E* (r = −0.48) (P < 0.001 each); however, there was not a significant correlation between Log SDQ and FEV1. These correlations show that spirometric variation explains no more than 40% of the changes in any of the gas exchange variables on a per-patient basis. There were other significant, but less marked, correlations between Log SDQ, Log SDV, and DISPR-E* and Paco2 (r = 0.57, 0.36, and 0.37), and between the latter two V̇A/Q.
descriptors (Log SDV and DISP R-E*) and the AaPO2 (r = 0.28 and 0.53), respectively (P < 0.001 each).

Functional residual capacity and Log SDV (r = 0.46) and DISP R-E* (r = 0.50) (P < 0.001 each) were linearly correlated, but the correlation with Log SDQ (r = 0.21; P < 0.05) was weak. Likewise, there was a negative association between both the Log SDV (r = −0.46) and also the DISP R-E* (r = −0.45) and the IC/TLC ratio (P < 0.001 each), a parameter that expresses lung hyperinflation and is an excellent predictor of all-cause and respiratory mortality (11). Moreover, FRC (%predicted) was negatively associated with PaO2 (r = −0.52), while the IC/TLC ratio correlated positively with PaO2 (r = 0.54) and negatively with PaCO2 (r = −0.50) and the AaPo2 (r = −0.33) (P < 0.001 each); PaO2 and DLCO were also correlated (r = 0.50) (P < 0.001 each). No correlations were observed between VA/Q descriptors and body mass index.

**DISCUSSION**

**General findings.** The present perspective of pulmonary gas exchange disturbances across the GOLD classification is the most comprehensive analysis that has so far assessed the association between airflow limitation and VA/Q imbalance in
COPD being based on 150 patients. It identifies three major findings and complements and extends previous investigations. First, pulmonary gas exchange, as assessed by the A\(A_{\text{O2}}\) and V\(\dot{A}/Q\) inequality as assessed by the MIGET’s indicators of inequality, is disproportionately abnormal at stage 1 before FEV\(_1\) decline, and, in particular, is relatively more abnormal than the spirometric variables. The Log SDQ, reflecting mostly low V\(\dot{A}/Q\) ratio areas, is more abnormal than the Log SDV, reflecting mostly high V\(\dot{A}/Q\) ratio areas.

Second, there is a steady progression of arterial blood gas disturbances and V\(\dot{A}/Q\) mismatch from stage 1 (postbronchodilator FEV\(_1/FVC\) ratio < 0.7 with FEV\(_1 \approx 80\%\)) through stage 4 (postbronchodilator FEV\(_1 < 30\%\) and/or chronic respiratory failure). This is reflected by increases in the Log SDV but not in the Log SDQ, which is already highly abnormal by stage 1.

Third, and more importantly, the changes in V\(\dot{A}/Q\) inequality from stage 1 through stage 4 are modest and, by stage 4, the dispersions are nowhere near values that are observed during acute severe conditions, such as exacerbation in COPD (5, 7, 27, 36, 37) and bronchial asthma (2, 17, 34).

Stage 1 and pulmonary gas exchange abnormalities. Although not completely new, the considerable severity of gas exchange disturbances at stage 1 needs to be highlighted, given the minimal degree of spirometrically detected airflow limitation. The average amount of V\(\dot{A}/Q\) mismatch, as assessed by the Log SDQ is quite above the upper limit of normal, while airflow limitation, as assessed by postbronchodilator FEV\(_1/FVC\) ratio, is just 0.07 below the value of the fixed ratio of 0.7. This is reflected not just in average values, but by the finding that almost all (Table 3) patients at this stage showed V\(\dot{A}/Q\) mismatch and half of them, abnormal conventional gas exchange (hypoxemia and/or low DL\(_{CO}\)). Hence the observation cannot be ascribed to a few outliers. The most plausible explanation for the disproportionate dissociation between pulmonary gas exchange and spirometry at stage 1 is that FEV\(_1\) reflects mostly large and medium airways function, whereas alveolar gas exchange in a diffusely distributed disease like COPD is more likely determined by events in much smaller airways, alveolar spaces, and blood vessels. Furthermore, it suggests that spirometry is not as sensitive in detecting early COPD as is gas exchange, but an important caveat must be made. The present data show that gas exchange in the present context is not sufficiently assessed by just Pa\(O_2\) and/or Pa\(CO_2\) measurements, but may benefit of calculation of the A\(A_{O2}\), a contention reinforced in the presence of a normal or mildly elevated cardiac output, which, others things being equal, raises the mixed venous Po\(2\), hence increasing Pa\(O_2\) (40).

MIGET-based outcome variables help to understand the pathophysiology but are not all necessary for such an analysis. That the Log SDQ was more abnormal than that of the Log SDV in stage 1 is evidence that low V\(\dot{A}/Q\) areas are more prominent than are high V\(\dot{A}/Q\) areas at this early stage of disease. This finding is compatible with underlying small airway abnormalities (12, 13, 21, 22) and dysfunction (25) known to be present in early COPD, that can lead to the presence of poorly ventilated but still well-perfused alveolar units, along with the abnormally increased Log SDV also coupled with changes in pulmonary precapillary arteries (3) that may further contribute to impair the vascular regulation of V\(\dot{A}/Q\) matching. At stages 1 and 2, morphometric pulmonary emphysema severity was shown to be the best correlate of pulmonary gas exchange abnormalities (4).

There is concern regarding the use of a fixed FEV\(_1/FVC\) ratio < 0.7 to diagnose stage 1 GOLD, because of the risk of overdiagnosis and false-positive cases, leading to inappropriate
misclassification and treatment, especially in the elderly (23). Our finding of relatively greater gas exchange than spirometric disturbances at stage 1 would seem to substantially mitigate that risk, although the number of patients at stage 1 in our cohort is modest, and whether or not these findings can be extended to larger COPD populations with mild COPD remains unsettled. The finding that arterial hypoxemia at stage 1 is less prevalent than \( V_{A}/Q \) inequality itself can be explained by mildly increased ventilation, which increases the alveolar Po2, and mildly high cardiac output, which raises the mixed venous Po2, other things being equal (40). Together these “extrapulmonary” influences on arterial oxygenation serve to improve arterial oxygen tension for a given degree of \( V_{A}/Q \) imbalance.

Progression of pulmonary gas exchange abnormalities with GOLD stage. As noted, there is a steady progression of most arterial blood gas disturbances and \( V_{A}/Q \) mismatch from stage 1 through stage 4. Most work to date has failed to find such a clear relationship between gas exchange and spirometric severity. However, most of these correlations are not too strong, a finding most likely explained by deliberate selection of patients at the GOLD stage 3–4 level in most prior studies, including our own (1, 4, 6–9, 14, 15, 27, 31, 35, 38), which had been designed mostly for other purposes. Within a relatively narrow band of spirometric variation, it is not so surprising that significant relationships have not been uncovered (24, 39). This is underscored by the large individual variance in both gas exchange and spirometry shown in Figs. 1 and 2. Visual inspection of these illustrations suggests that without studying a wide range of severity, the variance would preclude finding such associations.

Most importantly, the other factor contributing to failure to find such relationships is probably the small degree of change in the \( V_{A}/Q \) indexes over the four stages. We find it remarkable that no statistically significant change in the Log SDQ can be found as FEV1 drops from normal limits to 20% of predicted, and even the change in the Log SDV, between most of the GOLD stages, although significant, is modest. Two coexisting explanations may be plausible. First, \( V_{A}/Q \) disturbances are extensively abnormal even at stage 1, leaving less room to deteriorate with advancing disease; and, second, \( V_{A}/Q \) mismatch at the most advanced COPD staging may be somewhat self-limiting in COPD. What we propose is that the underlying pathological processes that reduce ventilation in a lung region also reduce perfusion in the same region, possibly due to a remaining strong hypoxic vasoconstriction and active collateral ventilation. If ventilation and perfusion are both reduced, their ratio is somewhat buffered. This appears to be the case in COPD patients, undergoing lung volume reduction surgery, who exhibit nearly normal \( V_{A}/Q \) dispersions (14). Local airway obstruction would reduce ventilation, and emphysema in the same region would reduce blood flow by minimizing reducing blood flow and destroying capillaries. In this way, \( V_{A}/Q \) ratio changes might be buffered until, eventually, the local region became neither ventilated nor perfused and failed to take part at all in gas exchange. It is otherwise hard to explain how such a severe damage at stage 4 does not give rise to \( V_{A}/Q \) dispersion values higher than shown here when it is well-established that in acute severe airway disorders, such as exacerbation in COPD (5, 7, 36, 37) and in bronchial asthma (2, 17, 34), there can be twice as much \( V_{A}/Q \) inequality as in GOLD stage 4.

Strengths and limitations. There are several strengths and shortcomings in our analysis. First, all of the studies are united by a common author group, and more importantly for pulmonary gas exchange analyses, by common methodology (i.e., MIGET). Second, this is the most thorough study that has been able so far to assess the natural progression of \( V_{A}/Q \) imbalance in stable COPD, thus providing a unique, deeper insight into the difficult interplay between pulmonary gas exchange and airflow limitation in this airway disease state. We acknowledge, however, that this is a cross-sectional study, with the measurements averaged by GOLD stage, in which the number of patients studied at each GOLD stage is not uniform and that, compared with the other three GOLD stages, the number of patients included in state 1 is small, in part imposed by the difficult recruitment of this mild COPD cohort. Other limitations of our study are the lack of clinical and imaging characterization in terms of small airways dysfunction and/or regional emphysema such that no accurate phenotype discrimination could be made.

Conclusions. All in all, the present analysis highlights and extends what has been previously observed in individual COPD patients with different degrees of severity. In stable COPD, the AaPo2 is substantially increased due to \( V_{A}/Q \) mismatch already at GOLD stage 1, a finding observed in >90% of patients. The degree of this increase in the Log SDQ (by 38%) is out of proportion to the reduction in the postbronchodilator FEV1/FVC ratio (by 0.07), confirming that pulmonary gas exchange abnormalities develop early in the natural history of COPD as defined by spirometry. While further worsening of pulmonary gas exchange is observed with each GOLD stage, the severity of \( V_{A}/Q \) inequality by stage 4 is surprisingly modest, amounting to only about half of that shown in acute severe airway disease states. This may indicate that in affected regions of the lungs of COPD, alveolar ventilation and pulmonary blood flow are reduced together by the respective pathological airway, alveolar, and vascular processes as disease severity progresses, while hypoxic vasoconstriction and collateral ventilation still remain efficiently active.

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