# Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity

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

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) is characterized by a decline in forced expiratory volume in 1 s ($FEV_1$) and, in many advanced patients, by arterial hypoxemia with or without hypercapnia. Spirometric and gas exchange abnormalities have not been found to relate closely, but this may reflect a narrow range of severity in patients studied. Therefore, we assessed the relationship between pulmonary gas exchange and airflow limitation in patients with COPD across the severity spectrum. Ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch was measured using the multiple inert gas elimination technique in 150 patients from previous studies. The distribution of patients according to the GOLD stage of COPD was: 15 with stage 1; 40 with stage 2; 32 with stage 3; and 63 with stage 4. In GOLD stage 1, $AaPO_2$ and $\dot{V}_A/\dot{Q}$ mismatch were clearly abnormal; thereafter, hypoxemia, $AaPO_2$, and $\dot{V}_A/\dot{Q}$ imbalance increased, but the changes from GOLD stages 1–4 were modest. Postbronchodilator $FEV_1$ was related to $Pa_{O_2}$ ($r = 0.62$) and $Pa_{CO_2}$ ($r = -0.59$) and to overall $\dot{V}_A/\dot{Q}$ heterogeneity ($r = -0.48$) ($P < 0.001$ each). Pulmonary gas exchange abnormalities in COPD are related to $FEV_1$ across the spectrum of severity. $\dot{V}_A/\dot{Q}$ imbalance, predominantly perfusion heterogeneity, is disproportionately greater than airflow limitation in GOLD stage 1, suggesting that COPD initially involves the smallest airways, parenchyma, and pulmonary vessels with minimal spirometric disturbances. That progression of $\dot{V}_A/\dot{Q}$ inequality with spirometric severity is modest may reflect pathogenic processes that reduce both local ventilation and blood flow in the same regions through airway and alveolar disease and capillary involvement.

airflow limitation; arterial blood gases; chronic respiratory failure; global initiative for COPD; pulmonary gas exchange

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 ($\dot{V}_A/\dot{Q}$) 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 $\dot{V}_A/\dot{Q}$ 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 $Pa_{O_2}$ was the only clinical variable that correlated with forced expiratory volume in 1 s ($FEV_1$), it is widely held that arterial blood gas abnormalities relate poorly to the severity of airflow limitation (39) and also that the pattern of $\dot{V}_A/\dot{Q}$ 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 $FEV_1$- to- forced vital capacity ($FEV_1$/FVC) ratio $< 0.7$ with $FEV_1 \geq 80\%$ predicted]? Second, how does the relationship between spirometry and $\dot{V}_A/\dot{Q}$ mismatch progress across the entire spectrum of COPD severity?

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## 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 ($DL_{CO}$) and arterial blood gases and minute ventilation were measured at rest and while breathing ambient air, and $AaPo_2$ and MIGET were used to measure the distributions of $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ distribution so that it is possible to estimate the distribution of both pulmonary blood flow and alveolar ventilation, computed as Log SDQ and Log SDV, respectively, to characterize parametrically the amount of $\dot{V}_A/\dot{Q}$ dispersion [95% upper confidence limits are 0.60 and 0.65 (dimensionless), respectively (10)]. Severe $\dot{V}_A/\dot{Q}$ inequality sufficient to produce life-threatening arterial hypoxemia ($Pa_{O_2} < 40$ mmHg) leads to Log SD values of the order of 2.00–2.50 (42). A complementary, more global index of $\dot{V}_A/\dot{Q}$ inequality, named DISP R-E*, includes the combined effects of the Log SDQ and Log SDV. It is the root mean square difference between measured retentions and excretions of the six inert gases (normal values, 1.0–3.0). If $\dot{V}_A/\dot{Q}$ inequality leads to Log SD values of 2.50, DISP R-E* is ~20–30 (19). 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 $\dot{V}_A/\dot{Q}$ distributions.

Results are expressed as means $\pm$ SD, and 95% confidence interval, unless otherwise stated. Mean variables between GOLD stages were analyzed using either one-way ANOVA for parametric variables or the Kruskal-Wallis test for nonparametric data. When significant differences were observed, post hoc comparisons were made using an $\alpha$ correction to $< 0.0083$ (Bonferroni) where appropriate. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used for checking distribution normalcy. Pearson's and Spearman's correlation coefficients were applied to assess the strength of relationship for normally and nonnormally distributed data, respectively.

## RESULTS

*Anthropometric and pulmonary functional characteristics.* The means $\pm$ SD of demographic and usual lung function variables for all participants are shown in Table 1 as a function of GOLD stage. There was no difference in age, smoking history, or body mass index across the four stages. In this study over all 150 patients, the residual sum of squares values corresponding to the corresponding $\dot{V}_A/\dot{Q}$ distributions (Table 2) were 2.92 $\pm$ 3.49 (95% confidence interval, 2.49–3.34) and indicated data of good quality.

*Values at GOLD stage 1.* Table 1 shows that postbronchodilator $FEV_1$ was 87% predicted, and $FEV_1/FVC$ was 0.65. Figure 1 shows that at stage 1, residual volume and single-breath diffusing capacity for carbon monoxide ($DL_{CO}$) were within normal limits without lung hyperinflation [i.e., inspiratory capacity-to-total lung capacity ($IC/TLC$) $> 0.25$ (11)]. So too were arterial blood gases (Fig. 1), but the $AaPo_2$ was already quite abnormal at 26 mmHg as were the MIGET-derived indexes of $\dot{V}_A/\dot{Q}$ inequality shown in Fig. 1 and Table 2. The increase in the overall $\dot{V}_A/\dot{Q}$ dispersion index (DISP R-E*, Fig. 1, *bottom*) is explained mostly by the increase in the dispersion of pulmonary blood flow (Log SDQ, Fig. 1, *top*). Both the $AaPo_2$ and the Log SDQ were about twice as large as

Table 1. *Anthropometric and functional characteristics of the patients grouped according to the GOLD stage of COPD*

| Characteristic | GOLD Stage 1, Mild | GOLD Stage 2, Moderate | GOLD Stage 3, Severe | GOLD Stage 4 , Very Severe | P Value |
|---|---|---|---|---|---|
| No. of patients, male/female | 14:1 | 39:1 | 30:2 | 59:4 | |
| Age, yr | 64±5 | 62±9 | 63±6 | 61±8 | NS[a] |
| Smoking history, pack-years | 42±3 | 63±5 | 55±6 | 54±4 | NS[a] |
| Body mass index, m/kg² | 27±3 | 25±4 | 27±3 | 25±4 | NS[b] |
| FEV₁, liters | 2.80±0.40 | 2.10±0.45[c] | 1.27±0.26[d,f] | 0.80±0.2[e,g,h] | < 0.001[a] |
| FEV₁, % of predicted | 87±6 | 63±8[c] | 39±6[d,f] | 25±8[e,g,h] | < 0.001[a] |
| FVC, liters | 4.08±0.62 | 3.66±0.90[c] | 3.00±0.86[d,f] | 2.40±0.68[e,g,h] | < 0.001[a] |
| FVC, % of predicted | 98±8 | 84±14[c] | 67±8[d,f] | 56±16[e,g,h] | < 0.001[a] |
| FEV₁/FVC ratio | 0.65±0.26 | 0.54±0.15[c] | 0.40±0.07[d,f] | 0.32±0.10[e,g,h] | < 0.001[a] |
| TLC, % of predicted, n =127 | 104±6 | 105±18 | 112±12 | 123±30[i,j] | < 0.01[b] |
| FRC, % of predicted, n = 127 | 115±14 | 132±28 | 159±28[d,f] | 191±50[e,g,h] | < 0.001[a] |
| RV, % of predicted, n = 127 | 121±23 | 141±52 | 183±54[f] | 260±100[e,g,h] | < 0.001[a] |
| IC/TLC ratio, n = 127 | 0.43±0.04 | 0.33±0.06[c] | 0.27±0.04[d,f] | 0.20±0.07[e,g,h] | < 0.001[a] |
| DL_CO, % of predicted, n =146 | 86±22 | 82±21 | 72±22 | 46±20[j,k] | < 0.001[b] |
| Pa_O2, mmHg | 81±9 | 78±11 | 73±9 | 59±9[j,k,l] | < 0.001[b] |
| Pa_CO2, mmHg | 37±3 | 38±4 | 40±5 | 45±6[j,k,l] | < 0.001[b] |
| AaPo₂, mmHg | 26±11 | 29±9 | 32±9 | 36±8[m,n] | < 0.001[b] |

Values are means $\pm$ SD. Forced spirometric results refer to postbronchodilator values. In 23 patients, bronchodilator test data were not available. Millimeters of mercury $\times$ 0.133 = kilopascals. GOLD, global initiative for chronic obstructive pulmonary disease (COPD); $FEV_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; FRC, xxx; RV, residual volume; IC, inspiratory capacity; TLC, total lung capacity; $DL_{CO}$, diffusing capacity for carbon dioxide. [a]Kruskal-Wallis test; [b]1-way independent ANOVA. [c]$P < 0.0083$, GOLD stage 1 vs. 2; [d]$P < 0.0083$, GOLD stage 1 vs. 3; [e]$P < 0.0083$, GOLD stage 1 vs. 4; [f]$P < 0.0083$, GOLD stage 2 vs. 3; [g]$P < 0.0083$, GOLD stage 2 vs. 4; [h]$P < 0.0083$, GOLD stage 3 vs. 4; [i]$P < 0.05$, GOLD stage 1 vs. 4; [j]$P < 0.001$, GOLD stage 1 vs. 4; [k]$P < 0.001$, GOLD stage 2 vs. 4; [l]$P < 0.001$, GOLD stage 3 vs. 4; [m]$P < 0.01$, GOLD stage 1 vs. 4; [n]$P < 0.01$, GOLD stage 2 vs. 4; NS, not significant.

Table 2. *Ventilation-perfusion distributions of the patients grouped according to the GOLD stage of COPD*

| Characteristic | GOLD Stage 1, Mild | GOLD Stage 2, Moderate | GOLD Stage 3, Severe | GOLD Stage 4, Very Severe | P Value* |
|---|---|---|---|---|---|
| Shunt, %$\dot{Q}_T$ | $1 \pm 1$ | $1 \pm 1$ | $1 \pm 2$ | $2 \pm 2\S$ | $< 0.01$ |
| Low, $\dot{V}_A/\dot{Q}$, %$\dot{Q}_T$ | $1.4 \pm 3.3$ | $2.8 \pm 4.8$ | $4.1 \pm 7.0$ | $3.1 \pm 7.0$ | NS |
| Mean Q | $0.83 \pm 0.23$ | $0.72 \pm 0.23$ | $0.68 \pm 0.30$ | $0.65 \pm 0.27$ | NS |
| Log SDQ | $0.83 \pm 0.32$ | $0.87 \pm 0.30$ | $0.98 \pm 0.24$ | $1.00 \pm 0.26$ | $< 0.05$ |
| High, $\dot{V}_A/\dot{Q}$, %$\dot{V}_E$ | $0.9 \pm 2.8$ | $7.4 \pm 14.4$ | $5.1 \pm 10.7*$ | $6.8 \pm 11.5\dagger$ | $< 0.05$ |
| Mean $\dot{V}$ | $1.60 \pm 0.54$ | $1.54 \pm 0.73$ | $1.80 \pm 0.52$ | $2.00 \pm 0.97\S$ | $\S\ 0.01$ |
| Log SDV | $0.72 \pm 0.25$ | $0.79 \pm 0.24$ | $0.98 \pm 0.26*\ddagger$ | $1.04 \pm 0.28\S$ | $< 0.001$ |
| DISP R-E* | $8.12 \pm 4.43$ | $9.02 \pm 4.11$ | $13.22 \pm 6.08*\ddagger$ | $14.20 \pm 4.57\S$ | $< 0.001$ |
| Dead space, %$\dot{V}_E$ | $21 \pm 12$ | $28 \pm 15$ | $31 \pm 12$ | $34 \pm 14\dagger$ | $< 0.01$ |
| $\dot{V}_E$, l/min | $9.0 \pm 4.0$ | $9.0 \pm 2.3$ | $8.3 \pm 2.0$ | $8.4 \pm 2.0$ | NS |
| $\dot{Q}_T$, l/min | $5.8 \pm 1.8$ | $6.0 \pm 1.3$ | $5.6 \pm 1.5$ | $5.3 \pm 1.5$ | NS |

Values are means ± SD. Shunt, perfusion-to-alveolar units with $\dot{V}_A/\dot{Q}$ ratios <0.005; low $\dot{V}_A/\dot{Q}$, ratios between 0.005 and 0.1 (excluding shunt); $\dot{Q}_T$, cardiac output; mean Q, the mean $\dot{V}_A/\dot{Q}$ ratio of the blood flow distribution; Log SDQ, dispersion of pulmonary blood flow; mean $\dot{V}$, the mean of $\dot{V}_A/\dot{Q}$ ratio of the ventilation distribution; Log SDV, dispersion of pulmonary blood flow, $\dot{V}_A/Q$ ratio between 10 and 100; DISP R-E*, dispersion of retention minus excretion of inert gases corrected by dead space; dead space, $\dot{V}_A/\dot{Q}$ ratios >100; $\dot{V}_E$, minute ventilation. mean Q, mean $\dot{V}$, Log SDQ, Log SDV, and DISP R-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 $FEV_1/FVC$ ratio (and normal $FEV_1$).

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 $\dot{V}_A/\dot{Q}$ inequality (i.e., DISP R-E*), and all but two showed an abnormal $AaPo_2$ equal to or greater than 15 mmHg (normal range in our laboratory, 4–6 mmHg). On the other hand, $Pa_{O_2}$ was < 80 mmHg in only 40%, and $Pa_{CO_2}$ was increased (≥ 45 mmHg) in none.

In summary, almost all patients at stage 1 show considerable $\dot{V}_A/\dot{Q}$ inequality and an increased $AaPo_2$, despite mild airflow limitation. Of note is that a decrease in $FEV_1/FVC$ 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 $DL_{CO}$ (<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 decreased linearly. Mean $DL_{CO}$ remained normal until stage 2 and then decreased, paralleling the changes in residual volume. Figs. 1 and 2 and Table 1 show that both $Pa_{O_2}$ and $Pa_{CO_2}$ changed little over the first two stages, but then changed rapidly with further severity (stages 3 and 4) of COPD. Since $AaPo_2$ increased only modestly, and linearly, over the entire range, this rapid change in $Pa_{O_2}$ and $Pa_{CO_2}$ at stages 3 and 4 reflects not only $\dot{V}_A/\dot{Q}$ worsening but also insufficient alveolar ventilation in relation to carbon dioxide production.

Figure 1 shows that all indexes of $\dot{V}_A/\dot{Q}$ inequality worsened linearly with GOLD stage. There are some important trends,

however, in that, at stage 4, the Log SDQ (reflecting mostly low $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ 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 $Pa_{O_2}$ was reduced in only 60% of patients at stage 2, despite almost universally abnormal $\dot{V}_A/\dot{Q}$ relationships and $AaPo_2$. Even at stage 3, only in 72% of patients was $Pa_{O_2}$ < 80 mmHg, and it was not until stage 4 that essentially all patients exhibited arterial hypoxemia. Similarly, $Pa_{CO_2}$ 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 $\dot{V}_A/\dot{Q}$ relationships reflected in an increased $AaPo_2$, with many fewer patients demonstrating arterial hypoxemia with or without hypercapnia until stage 4. In addition, indexes of $\dot{V}_A/\dot{Q}$ inequality by stage 4 are surprisingly only modestly worse than at stage 1. As a result, the progression of $\dot{V}_A/\dot{Q}$ mismatch from GOLD stage 1 to stage 4 is not nearly as rapid as the loss of $FEV_1$, and the rapid deterioration in $Pa_{O_2}$ at stage 4 is not fully explained by further $\dot{V}_A/\dot{Q}$ 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 $FEV_1$. These included $Pa_{O_2}$ ($r = 0.62$) and $Pa_{CO_2}$ ($r = -0.59$), $AaPo_2$ ($r = -0.30$) (Fig. 2), Log SDV ($r = -0.49$), and DISP R-E* ($r = -0.48$) ($P < 0.001$ each); however, there was not a significant correlation between Log SDQ and $FEV_1$. 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 DISP R-E* and $Pa_{CO_2}$ ($r = 0.57$, 0.36, and 0.37), and between the latter two $\dot{V}_A/\dot{Q}$
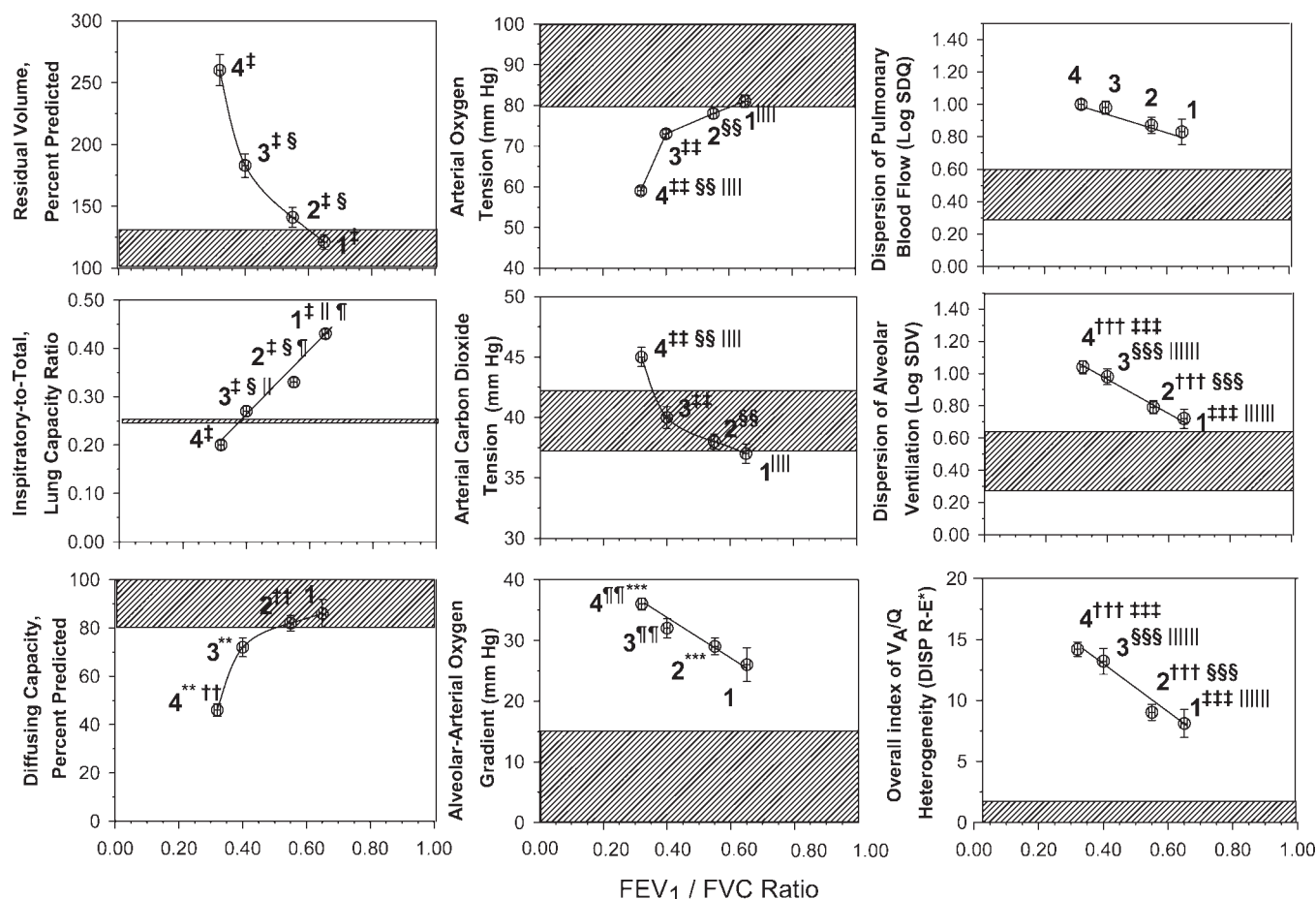
Fig. 1. Relationship between the forced expiratory volume in 1 s and forced vital capacity (FEV$_1$/FVC) and means ± SE for residual volume, inspiratory capacity-to-total lung capacity (IC/TLC) ratio, diffusing capacity for carbon dioxide (DL$_{CO}$), Pa$_{O_2}$, Pa$_{CO_2}$, AaPo$_2$ (expressed in mmHg), dispersion of pulmonary blood flow (Log SDQ) and alveolar ventilation (Log SDV), and an overall index of ventilation-perfusion heterogeneity (DISP R-E*) (all measured at rest and while breathing ambient air) are shown. Spirometric results refer to postbronchodilator values. Data are grouped according to the global initiative for COPD (GOLD) stage of chronic obstructive pulmonary disease (COPD). Symbols denote statistical differences between stages. Normal limits are indicated by the hatched areas, except for the IC/TLC ratio, whose best cutoff point for death from any cause corresponds to 0.25. ‡$P < 0.0083$, GOLD stage 1 vs. 2; §$P < 0.0083$, GOLD stage 1 vs. 3; ‖$P < 0.0083$, GOLD stage 1 vs. 4; **$P < 0.0083$, GOLD Stage 2 vs. 4; ††$P < 0.0083$, GOLD Stage 3 vs. 4; ‡‡$P < 0.05$, GOLD stage 1 vs. 4; §§$P < 0.001$, GOLD stage 1 vs. 4; ‖‖$P < 0.001$, GOLD stage 2 vs. 4; ¶¶$P < 0.001$, GOLD stage 3 vs. 4; ***$P < 0.01$, GOLD stage 1 vs. 4; †††$P < 0.01$, GOLD stage 2 vs. 4; ‡‡‡$P < 0.0083$, GOLD stage 1 vs. 4; §§§$P < 0.0083$, GOLD stage 2 vs. 3; ‖‖‖$P < 0.0083$, GOLD stage 1 vs. 3.

descriptors (Log SDV and DISP R-E*) and the AaPo$_2$ ($r = 0.28$ 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 corre-

Table 3. *Percentages of abnormalities of the principal pulmonary gas exchange descriptors according to the GOLD stage of COPD*

| Characteristic | GOLD Stages | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Pa$_{O_2}$, < 80 mmHg | 40% | 60% | 72% | 97% |
| Pa$_{CO_2}$, ≥ 50 mmHg | 0 | 0 | 1% | 21% |
| AaPo$_2$, ≥ 15 mmHg | 87% | 90% | 94% | 100% |
| Log SDQ, > 0.60 | 67% | 73% | 91% | 95% |
| Log SDV, > 0.65 | 60% | 90% | 100% | 95% |
| Log SDQ and/or Log SDV | 73% | 95% | 100% | 98% |
| DISP R-E*, > 3.0 | 93% | 95% | 100% | 100% |

Ventilation-perfusion indexes are dimensionless. To convert millimeters of mercury to kilopascals, multiply by 0.133.

lated, 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 Pa$_{O_2}$ ($r = -0.52$), while the IC/TLC ratio correlated positively with Pa$_{O_2}$ ($r = 0.54$) and negatively with Pa$_{CO_2}$ ($r = -0.50$) and the AaPo$_2$ ($r = -0.33$) ($P < 0.001$ each); Pa$_{O_2}$ and DL$_{CO}$ were also correlated ($r = 0.50$) ($P < 0.001$ each). No correlations were observed between V̇$_A$/Q̇ 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 V̇$_A$/Q̇ imbalance in
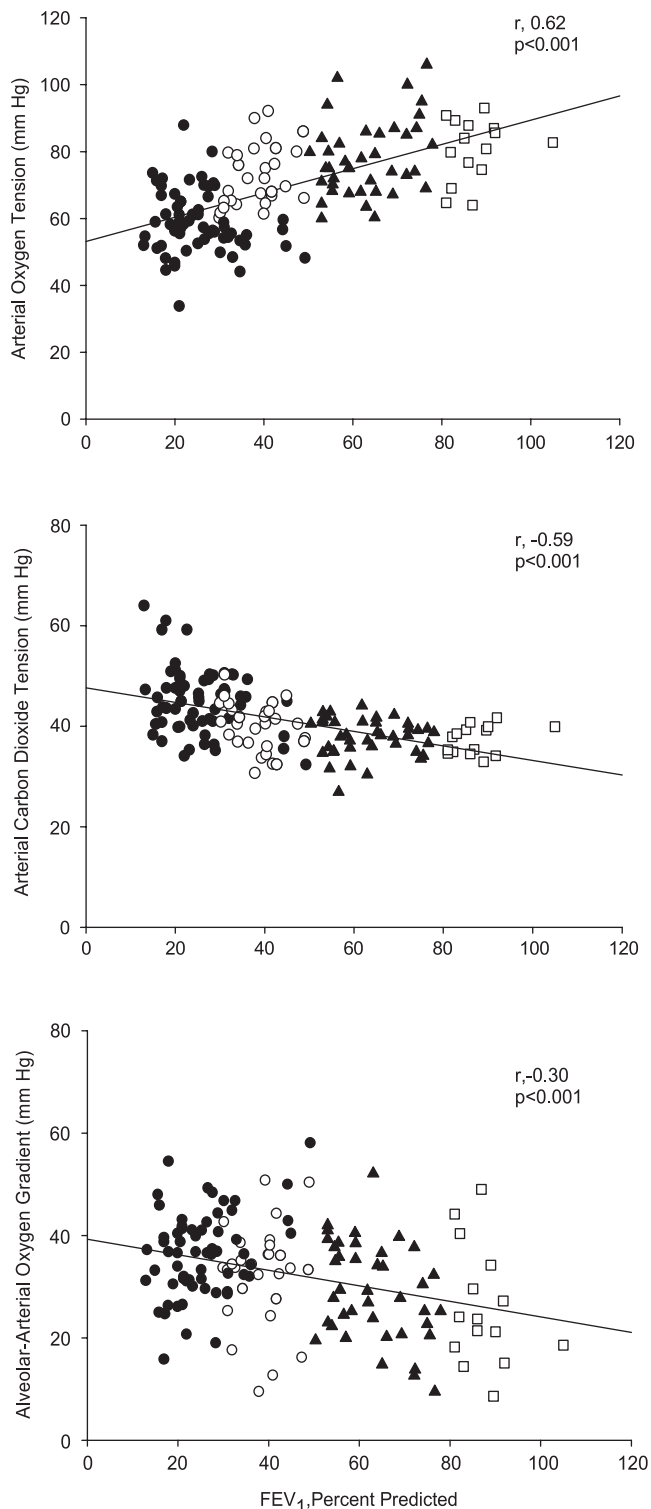
Fig. 2. Relationships between $FEV_1$ and $Pa_{O_2}$, $Pa_{CO_2}$, and $AaPo_2$, measured at rest and when breathing ambient air, from 150 patients (all expressed in mmHg; $FEV_1$ results refer to postbronchodilator values). □, stage 1, ▲, stage 2, ○, stage 3, and ●, stage 4.

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 $AaPo_2$ and $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ ratio areas, is more abnormal than the Log SDV, reflecting mostly high $\dot{V}_A/\dot{Q}$ ratio areas.

Second, there is a steady progression of arterial blood gas disturbances and $\dot{V}_A/\dot{Q}$ mismatch from stage 1 (postbronchodilator $FEV_1/FVC$ ratio $< 0.7$ with $FEV_1 \geq 80\%$) 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 $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ 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 $AaPo_2$, 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 $\dot{V}_A/\dot{Q}$ areas are more prominent than are high $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ inequality itself can be explained by mildly increased ventilation, which increases the alveolar $Po_2$, and mildly high cardiac output, which raises the mixed venous $Po_2$, other things being equal (40). Together these "extrapulmonary" influences on arterial oxygenation serve to improve arterial oxygen tension for a given degree of $\dot{V}_A/\dot{Q}$ imbalance.

*Progression of pulmonary gas exchange abnormalities with GOLD stage.* As noted, there is a steady progression of most arterial blood gas disturbances and $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ indexes over the four stages. We find it remarkable that no statistically significant change in the Log SDQ can be found as $FEV_1$ 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, $\dot{V}_A/\dot{Q}$ disturbances are extensively abnormal even at stage 1, leaving less room to deteriorate with advancing disease; and, second, $V_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ 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, $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ 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 $\dot{V}_A/\dot{Q}$ 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 $AaPo_2$ is substantially increased due to $\dot{V}_A/\dot{Q}$ 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 $FEV_1/FVC$ 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 $\dot{V}_A/\dot{Q}$ 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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