Mechanisms of Gas-exchange Impairment in Idiopathic Pulmonary Fibrosis\textsuperscript{1-4}

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Introduction

Patients with idiopathic pulmonary fibrosis (IPF) generally exhibit an abnormal gas-exchange response to exercise as shown by a dramatic fall in arterial oxygenation and a lack of improvement in the efficiency of alveolar ventilation [no change in the dead space–tidal volume ratio (Vd/Vt)] \textsuperscript{(1)}). The fall in arterial \( P_O_2 \) was originally attributed to failure in the diffusion of \( O_2 \) from the alveoli to the capillary blood (the so-called alveolar-capillary block syndrome) \textsuperscript{(2)}. However, two different studies showed subsequently that it was basically due to ventilation-perfusion (VA/Q) mismatching and that the diffusion of \( O_2 \) limited gas exchange only partially \textsuperscript{(3, 4)}. These two studies included patients with a wide variety of interstitial lung diseases \textsuperscript{(3, 4)}. It has been demonstrated that the pattern of pulmonary gas-exchange response to exercise may vary markedly among different interstitial lung diseases \textsuperscript{(5-7)}. Therefore it may well be that the mechanisms leading to \( O_2 \) desaturation during exercise also differ among them. On the other hand, the lack of improvement in the Vd/Vt ratio during exercise in IPF \textsuperscript{(1)} is at variance with the normal decline seen in healthy subjects \textsuperscript{(8)} but agrees perfectly with that seen in patients with pulmonary vascular disease \textsuperscript{(9)}. This suggests that the pulmonary circulation plays an important role in modulating the efficiency of gas exchange during exercise in IPF. It is generally believed that pulmonary arterial hypertension in patients with interstitial lung disease basically reflects the destruction of blood vessels caused by the fibrotic process \textsuperscript{(10)}, but several reports have claimed that pulmonary vasoconstriction elicited by alveolar hypoxia (hypoxic pulmonary vasoconstriction) can also be of importance \textsuperscript{(11-13)}. To our knowledge the interaction between pulmonary vascular tone and gas exchange during exercise in IPF has not been previously assessed. Finally, a reduction in the diffusion capacity for carbon monoxide (DL\textsubscript{CO}) is a common functional hallmark of IPF \textsuperscript{(1)}. However, its relationship to the mechanisms of hypoxemia in IPF remains uncertain.

The present investigation sought first, to define the mechanisms that govern gas exchange during exercise in patients with “lone” IPF, a disease classically considered the paradigm of the vast group of interstitial lung diseases \textsuperscript{(1)}; second, to analyze the role of pulmonary vascular tone in modulating such response; and, finally, to delineate the relationships between DL\textsubscript{CO} and the preceding pathophysiologic phenomena. Given that both resting DL\textsubscript{CO} and gas-exchange measurements during exercise are commonly performed in patients with IPF to stage and follow the severity of the interstitial process \textsuperscript{(14)}, the results of the present investigation may be of clinical relevance.

Methods

Population

We studied 15 patients (11 men and 4 women) with a mean age of 55 ± 3 (SEM) yr (range 27 to 69 yr). The diagnosis of lone IPF was established according to Fulmer and coworkers \textsuperscript{(14)}: (1) progressive exertional dyspnea of unknown origin (patients with exposure to any substance known to induce pulmonary fibrosis or with an associate collagen vascular disease were specifically excluded); (2) diff
fuse interstitial pattern on the chest X-ray film without left ventricular enlargement; and (3) reduction in lung volumes and/or low DLCO. An open-lung biopsy confirmed the diagnosis of IPF in eight patients, another individual had a familial form of IPF, and a transbronchial biopsy showed morphologic changes consistent with IPF and ruled out any granulomatous process in two other subjects (table 1). When we analyzed separately the results of the nine patients with a positive diagnosis of IPF (proved by open-lung biopsy) or with a familial form of IPF (1), our results were basically unchanged. Therefore from this point we report the results of the whole population of 15 patients studied. Whenever an open-lung biopsy was available we calculated a total pathologic score of interstitial fibrosis following the scoring system proposed by Watters and coworkers (15).

### Procedures

In each patient we measured forced spirometry and inspiratory capacity (HP 47804A Pulmonary System Desk®; Hewlett-Packard, Palo Alto, CA), thoracic gas volume (body test; E. Jaeger, Wurzburg, FRG), and the single-breath DLCO (Respirometer® Model A; PK Morgan, Ltd., Chatham, Kent, UK) corrected for hemoglobin concentration (16); Kco was calculated as the ratio between DLCO (ml/min/mm Hg, STPD) and alveolar volume (VA, L BTPS; Kco = DLeo/VA). Reference values were from our own laboratory (17, 18).

On the day of the study a polyethylene catheter (Plastimed, Saint Leu La Foret, France) was inserted in the radial artery, and in 12 of the 15 patients a 7F transvenous balloon-tipped catheter was advanced into the pulmonary artery under pressure-wave monitoring (HP 78303A). Cardiac output was determined by the thermodilution technique (9520A; Edwards Laboratories, Santa Ana, CA) in the three patients without a pulmonary artery catheter, the inert gas concentrations in the mixed venous blood were derived from the Fick principle using the measured mixed expired and arterial inert gas samples and cardiac output measured by the green dye technique (19). The solubilities of inert gases were measured in each patient. The V/Q distributions were estimated from inert gas data using a least-squares algorithm with enforced smoothing (23). The duplicate samples of each set of measurements were treated separately, resulting in two V/Q distributions in each set, the final data being the average of variables determined from both distributions (22).

### Protocol

The protocol was approved by the Research Committee on Human Investigations of the Hospital Clinic, Universitat de Barcelona. Consent was obtained after the purposes, risks, and potential of the investigations were explained to and understood by each patient. Patients were always studied in a semirecumbent position, first at rest (breathing room air or 100% O2 in random order) and afterward while cycling under steady-state conditions (breathing room air) at approximately 60% of their maximum tolerated workload (determined during the course of a maximal incremental exercise test performed on a previous day; Jaeger). Heart rate, tidal volume, minute ventilation, and mixed expired O2 and CO2 were monitored on-line to assure steady-state conditions. Measurements included systemic (n = 15) and pulmonary hemodynamics (n = 12) and respiratory and inert gas-exchange variables (n = 15). In the eight patients with open-lung biopsy all measurements were done during the month before the surgical procedure.

### Safety Precautions

Patients were instructed to stop exercise should unusual symptoms other than discomfort develop, but none of them did. Three physicians were present at all times, with one directing his attention exclusively to the patient. Systemic and pulmonary hemodynamics, EKG (HP-7830A), and ear O2 saturation (Biox® II; Ohmeda-BOC, ProClinic, Barcelona) were continuously monitored. Oxygen therapy (35% delivered through a Venturi mask [Ohmeda-BOC]) was started immediately after having obtained all exercise measurements.

### Statistical Analysis

Data are expressed as mean ± SEM.

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### Table 1

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* Patient with a familial form of IPF.
Hyperoxic and exercise data were compared to baseline values (i.e., at rest, breathing room air) using the paired Student's t test (two-tailed). Linear regression was used when appropriate. A p value < 0.05 was considered significant.

Results

General Characteristics

Of the patients studied, five had never smoked, seven were exsmokers, and three were current smokers. Most subjects exhibited mild-to-moderate restrictive ventilatory impairment and a low DC_{CO}, but the KCO was lower than 80% of predicted in only seven individuals (table 1).

Baseline Measurements (at Rest, Breathing Room Air)

Cardiac output was normal, and mean pulmonary artery pressure values ranged between 13 and 40 mm Hg (table 2). There was no average mild arterial hypoxemia (PaO$_2$ values ranging from 57 to 96 mm Hg). Arterial PCO$_2$ was normal in all but one patient (patient RRD, 47 mm Hg). Overall, the aAPO$_2$ and the VA/VT ratio were increased (table 2). The VA/Q distributions were minimally altered, with 2 and 4% of cardiac output perfusing poorly ventilated and completely unventilated lung units (shunt), respectively (table 3 and figure 1). As a result the dispersion of the blood flow distribution (log$_{10}$ Q, 0.93 ± 0.09) was moderately abnormal [table 3; upper limit of normal, 0.6 (24)]. An overall index of the degree of VA/Q mismatching directly obtained from raw retention and excretion data (DISP R-E*, 7.2 ± 0.7) was also higher than normal (< 3) (25).

Measurements Breathing 100% O$_2$ (at Rest)

Pulmonary hemodynamics and cardiac output did not change while breathing 100% O$_2$. Minute ventilation (and arterial PCO$_2$) did not change, either (table 2). As expected, the arterial and mixed venous Po$_2$ and the aAPO$_2$ increased significantly while breathing 100% O$_2$. The shunt fraction determined using the multiple inert gas technique did not change, but the percentage of cardiac output perfusing low VA/Q units increased almost twofold (table 3 and figure 1). Because of this latter effect the dispersion of the blood flow distribution (log$_{10}$ Q) increased (from 0.93 ± 0.09 to 1.26 ± 0.10, p < 0.01). Expressed as the percentage change from baseline (at rest, breathing room air), this increase represented 48 ± 13% and ranged from −13 to 143%.

Measurements During Exercise (Breathing Room Air)

Oxygen uptake increased fourfold during exercise (table 2) and averaged 58 ± 4% of the maximal predicted value (26). This moderate amount of exercise was indeed substantial for these patients, as shown by the fall in base excess (−0.4 ± 0.3 to −2 ± 0.5 mmol/L, p < 0.01) and arterial pH (7.41 ± 0.01 to 7.37 ± 0.01, p < 0.05) and the increase in the respiratory exchange ratio (0.84 ± 0.02 to 0.93 ± 0.03, p < 0.01). During exercise both cardiac output and mean pulmonary artery pressure increased (table 2). The latter reached extremely high values in some individuals (i.e., patient JSS, 75 mm Hg). As previously reported in IPF patients, the mean pulmonary vascular resistance did not increase during exercise (table 2), but the change in pulmonary artery pressure per unit change in flow (4.2 ± 0.7 mm Hg/L/min) was much higher than normal (0.9 mm Hg/L/min) (27). Arterial Po$_2$ fell (and the aAPO$_2$ increased) in all but three subjects (patients JFA, MRG, and HRF). As a result the mean PaO$_2$ during exercise was lower than at rest (table 2) but ranged from very low (39 mm Hg) to normal (108 mm Hg). Arterial PCO$_2$ did not change, and mixed venous Po$_2$ fell (table 2). The latter reached values as low as 20 mm Hg.
in some patients. The Vd/Vt ratio did not decrease with exercise. There were minor changes in the area of high VA/Q units, without physiologic significance, but overall the VA/Q distributions did not change with exercise (table 3) except in those three patients who improved Pao₂ (and VA/Q inequality; figure 1).

**Assessment of O₂ Diffusion Limitation**

The multiple inert gas elimination technique allows computation of the arterial Pao₂ value ("predicted Pao₂") that corresponds to the observed degree of VA/Q mismatching on the explicit assumption that no diffusion limitation is present (19). In this manner the diffusion limitation of O₂ transfer from the alveoli to the capillary blood is evident as a significantly higher predicted than measured Pao₂ (19). At rest our patients showed higher predicted than measured Pao₂ (81 ± 3 versus 74 ± 3 mm Hg, respectively, p < 0.005; figure 2A). The mean difference between these two variables (i.e., the component of hypoxemia due to O₂ diffusion limitation) was 6 mm Hg. Expressed as a percentage of aAPO₂, this difference represented 19 ± 6%. Thus 81% of the aAPO₂ at rest was due to both the VA/Q inequality and shunt and 19% to O₂ diffusion limitation. During exercise the predicted Pao₂ (80 ± 4 mm Hg) was considerably higher than that measured simultaneously in the arterial blood (59 ± 5 mm Hg, p < 0.0001; figure 2A). The difference of 21 mm Hg represented 40 ± 5% of the exercise aAPO₂. These observations suggest that O₂ transfer during exercise in IPF is partially limited by the rate of diffusion equilibration both at rest and during exercise. However, the severity of this limitation was much greater during exercise (21 mm Hg) than at rest (6 mm Hg, p < 0.005). Interestingly, those patients with more O₂ diffusion limitation at rest also showed more O₂ diffusion limitation during exercise (r = 0.67, p = 0.006) (figure 2B).

**Relevance of Hypoxic Pulmonary Vasoconstriction**

The increase in the dispersion of the blood flow distribution (log V/Q) during 100% O₂ breathing (expressed as the percentage change from baseline) presumably represents the degree of release of hypoxic pulmonary vasoconstriction in each patient (19, 22). We found that it was related to the severity of pulmonary hypertension during exercise (p < 0.05) (figure 3A), to the overall degree of VA/Q mismatching seen both at rest (r = −0.72, p < 0.005) and during exercise (p < 0.0025) (figure 3B), and to the Pao₂ measured during exercise (p = 0.01; figure 3C).

**Relationship Between DLCO and the Mechanisms of Gas-exchange Impairment**

DLCO corrected for alveolar volume (Kco) and expressed as percentage of predicted was related to the amount of O₂ diffu-
and diffusion components (8) of arterial hypoxemia. (For further explanations, see text.)

AaPo" against Kco the greater is the gas-exchange impairment evaluated either globally (A), less VA/Q mismatch (B), and higher arterial oxygenation (C) during exercise. (For further explanations, see text.)

Fig. 3. Dispersion of the blood flow distribution (log10 Q) while breathing 100% O2 (percentage change from baseline), indicating release of hypoxic pulmonary vasoconstriction, plotted against the exercise values of mean pulmonary artery pressure (A), overall degree of VA/Q mismatching (DISP R-E*), and measured PacO2 (C). Note that those subjects with more release of hypoxic vasoconstriction showed less pulmonary hypertension (A), less VA/Q mismatch (B), and higher arterial oxygenation (C) during exercise. (For further explanations, see text.)

Fig. 4. CO diffusing capacity [corrected for alveolar value (Kco)] and expressed as percentage of predicted] plotted against AaPo2, amount of O2 diffusion limitation [i.e., difference between predicted PacO2 (inert gases) and measured PacO2] and overall degree of VA/Q mismatching (DISP R-E*) during exercise. Note that the lower the Kco the greater is the gas-exchange impairment evaluated either globally (A) or after separating the VA/Q (C) and diffusion components (B) of arterial hypoxemia. (For further explanations, see text.)

Importance of O2 Diffusion Limitation

At rest the main cause of hypoxemia in our patients was VA/Q mismatching (81% of AaPo2) (figure 1), but 19% of AaPo2 was due to O2 diffusion limitation (figure 2). The observation of some O2 diffusion limitation at rest is at variance with earlier reports, which included patients with a wide variety of interstitial lung diseases (3, 4), but in accordance with a very recent study in patients with sarcoidosis (stage 2 and 3) (28) and can probably be explained by the more careful selection of our patients (all of them with lone IPF; table 1). During exercise the PacO2 fell in most of our patients (table 2), but VA/Q mismatch did not increase (table 3 and figure 1). This apparent paradox is explained by more limitation in the diffusion of O2 while exercising than at rest (figure 2). It is known that for a given degree of VA/Q mismatch the lower the input Pao2 to the lungs (in mixed venous blood) the lower is the Pao2 at the outlet (in arterial blood) (19). Further, a fall in mixed venous Pao2 and/or a reduction in the time that the erythrocyte spends in the pulmonary capillary (transit time) theoretically increases

Discussion

Our study describes the mechanisms of gas-exchange impairment in patients with lone IPF. In these patients VA/Q mismatching was the main cause of arterial hypoxemia at rest and during exercise, but the transfer of O2 was also partially limited by the rate of diffusion under both circumstances. Our results also highlight the role of pulmonary vascular tone in governing gas exchange in these patients and the relationship of DLCO to the mechanisms of hypoxemia.
the vulnerability of pulmonary gas exchange to become limited by diffusion (29). In keeping with this theoretical analysis we found that the percentage of \( \Delta P_{O_2} \) due to \( O_2 \) diffusion limitation increased from 19% at rest to 40% during exercise (p < 0.005), paralleling the fall in mixed venous \( P_{O_2} \) and the increase in cardiac output (table 2). As a result those patients with more \( O_2 \) diffusion limitation at rest also showed more \( O_2 \) diffusion limitation during exercise (p < 0.01) (figure 2B). Thus to some extent our results give further support to the classic concept of the "alveolar-capillary block" syndrome originally described by Austrian and colleagues more than 30 yr ago (2).

Patterns of Pulmonary Vascular Involvement

Pulmonary hypertension is common in patients with IPF, especially during exercise (1). It is generally believed that it basically reflects the destruction of blood vessels caused by the interstitial process (10). Several reports, however, have suggested a role for hypoxic pulmonary vasoconstriction (11-13). In our patients neither the pulmonary artery pressure nor the cardiac output changed significantly upon 100% \( O_2 \) breathing (table 2). At first glance this indicates the absence of a pulmonary vascular response to \( O_2 \). However, the mean dispersion of the blood flow distribution (log\( e \) Q) increased by 48% while breathing pure \( O_2 \), suggesting release of hypoxic pulmonary vasoconstriction (19). This apparent discrepancy is explained by the higher sensitivity of log\( e \) Q (22, 30-32), since such small absolute changes would never be seen in a standard pressure-flow plot. Yet the effect of \( O_2 \) upon pulmonary vascular tone was not uniform among patients. Some subjects (JAX) showed no evidence of release of hypoxic vasoconstriction [no increase in log\( e \) Q (= 13%)], but \( O_2 \) was a powerful stimulus to lower the pulmonary vascular tone and redistribute blood flow in other individuals (a 143% increase in log\( e \) Q in patient JPS). The former probably have predominantly anatomic (thus fixed) vascular changes; the latter probably have some functional (thus reversible by \( O_2 \)) derangement of the pulmonary circulation. In keeping with this hypothesis we found that those subjects with less vascular reactivity to \( O_2 \) showed more pulmonary hypertension during exercise (figure 3A) (indicating less vascular compliance) and more severe degrees of interstitial fibrosis (each p < 0.05). Interestingly, Crystal and colleagues (1) showed that the pulmonary arterial changes were more important in those IPF patients with more severe degrees of interstitial fibrosis. Thus, it may well be that these two patterns of vascular involvement actually correspond to two different evolutionary stages of the disease (functional changes earlier and anatomic derangement once the disease progresses).

Role of Pulmonary Vascular Tone in Governing Gas Exchange

In disease states other than IPF it has been shown that an enhanced pulmonary vascular tone facilitates better \( V_\text{A}/Q \) matching, as happens in patients with primary pulmonary hypertension (33), whereas an abnormally low vascular reactivity interferes with pulmonary gas exchange, as demonstrated in patients with liver cirrhosis (22, 34). In our patients with IPF we also found that a higher vascular reactivity to \( O_2 \), that is, a higher vascular tone, was associated with less \( V_\text{A}/Q \) mismatch at rest (p = 0.01) and during exercise (figure 3B). We speculate that the lack of anatomic derangement of the pulmonary vasculature at early stages of the disease may allow a good vasoconstrictor response to alveolar hypoxia, which in turn redistributes blood flow away from the poorly ventilated lung units and preserves relatively good \( V_\text{A}/Q \) matching. In contrast, once the fibrotic process evolves and the pulmonary circulation loses this ability, pulmonary gas exchange would worsen markedly. During exercise the effect of such a \( V_\text{A}/Q \) imbalance on arterial \( P_{O_2} \) would be further amplified because the abnormal pulmonary vasculature should induce a greater fall in mixed venous \( P_{O_2} \) and a shorter transit time, which by themselves would increase any \( O_2 \) diffusion limitation (figure 2) (29).

Relevance of Airway Disease

In 1978 Carrington and coworkers reported that \( P_{A_{O_2}} \) can occasionally increase during exercise in IPF (35). This was explained in a simple manner by saying that this can only occur if the IPF patient also suffers concomitantly from chronic obstructive pulmonary disease (COPD) (13, 14). The improvement in \( V_\text{A}/Q \) mismatching that was supposed to occur with exercise in COPD could therefore explain a higher \( P_{A_{O_2}} \) while exercising. Although we have recently shown that \( V_\text{A}/Q \) mismatch can certainly be improved by exercise in COPD (36), the present results demonstrate that, contrary to what has been claimed (13, 14), the presence of airflow limitation is not required to explain an increase in \( P_{A_{O_2}} \) during exercise in IPF. In our series three patients (MRG, HRF, and JFA) improved \( P_{A_{O_2}} \) during exercise, but only one of them was a smoker or had any evidence of airflow limitation (JFA, table 1). In contrast, all three patients showed a substantial release by hypoxic vasoconstriction while breathing \( O_2 \), none developed severe pulmonary hypertension during exercise, and all reduced the degree of \( V_\text{A}/Q \) inequality while exercising (figure 1, bottom). The functional type of vascular involvement in these patients (high level of vascular reactivity to \( O_2 \)) probably led to a more homogeneous distribution of the blood flow distribution during exercise (less \( V_\text{A}/Q \) mismatch) by allowing substantial distention and/or recruitment of the pulmonary vasculature during exercise (no pulmonary arterial hypertension). This interpretation therefore further strengthens the key role of the pulmonary vasculature in modulating gas exchange in IPF. However, we were unable to demonstrate any significant difference between the severity of the interstitial involvement in the three patients who improved \( P_{A_{O_2}} \) during exercise and those five who became more hypoxemic and in whom an open-lung biopsy was available. Nonetheless, because of the small number of patients we compared, this may be still a working hypothesis to test in the future.

Relationship of \( D_{L_{CO}} \) to the Mechanisms of Gas-exchange Impairment

A low diffusing capacity for CO is one of the hallmarks of IPF (1). In these patients it may reflect either a reduction in the capillary surface area and/or a thickened alveolar-capillary membrane. We observed that the \( K_{CO} \) (percentage of predicted) was related both to the amount of \( O_2 \) diffusion limitation (at rest and during exercise) (figure 4B) and to the increase in pulmonary vascular resistance elicited by exercise. Since the latter reflects the degree of pulmonary vascular compliance, to some extent it is an estimate of the surface available for capillary perfusion. The finding that in IPF the \( K_{CO} \) appears to reflect both the amount of \( O_2 \) diffusion limitation and the involvement of the pulmonary vasculature may be explained by the close interaction between these two mechanisms of hypoxemia alluded to earlier. In fact, the \( K_{CO} \) (percentage of predict-
ed) was also related to the degree of \( \frac{V_{A}}{Q} \) mismatch and \( a aPO_{2} \) during exercise (figure 4). It should be noted that all these relationships were less strong when analyzed through \( DLCO \). Therefore from the clinical standpoint we recommend the routine correction of \( DLCO \) for alveolar volume (Kco) in the standard functional assessment of patients with IFP for a noninvasive estimate of the amount of \( O_{2} \) diffusion limitation, the severity of gas-exchange impairment during exercise, or the degree of pulmonary vascular involvement.

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