Chronic pulmonary diseases: chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis

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The multiple inert gas elimination technique (MIGET) was first described by Wagner et al in 1974. It allows quantitation of the ventilation-perfusion (VA/Q) distribution and a precise analysis of the intrapulmonary and extrapulmonary factors that govern gas exchange in humans. This review discusses how this technique has facilitated a better understanding of these mechanisms underlying gas exchange in two common chronic lung diseases – chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis. The methodological aspects of the MIGET are not discussed, and the interested reader is referred to the first review in this series (Thorax 1994;49:815–824) or to some comprehensive reviews published recently on this subject.

Chronic obstructive pulmonary disease (COPD)

Gas exchange abnormalities in COPD range from mild hypoxaemia to severe respiratory failure requiring mechanical ventilation. It was widely assumed that VA/Q mismatching probably was the major mechanism underlying such abnormalities. However, the MIGET has contributed to clarifying the following, previously unresolved, questions: (1) what are the basic mechanisms of abnormal gas exchange in COPD (VA/Q mismatch versus shunt versus oxygen diffusion limitation)? (2) what are the correlations (if any) between such mechanisms and lung structure? (3) what are the effects of exercise upon VA/Q mismatch in COPD? (4) how does oxygen breathing interact with the VA/Q distributions of these patients? (5) how do bronchodilators modify the baseline VA/Q distribution? and, finally (6) what are the effects of vasodilators upon VA/Q inequality?

MECHANISMS OF ABNORMAL GAS EXCHANGE

The MIGET has shown in COPD that, as anticipated, these patients have severe degrees of VA/Q mismatching. Interestingly, this mechanism of abnormal gas exchange accounts completely for the observed degree of arterial hypoxaemia. Conversely, it has been shown that true shunt and oxygen diffusion limitation do not generally play a significant part in the genesis of arterial hypoxaemia in these subjects. The type and severity of VA/Q mismatch has been found to differ among patients with COPD and to change with time, according to the evolution of the disease and the clinical state of the patient.

In a group of patients with severe COPD Wagner and coworkers’ described two different patterns of VA/Q mismatch. In some patients VA/Q inequality was mainly characterised by the presence of lung units with a very high VA/Q ratio (“high pattern”) (fig 1). By contrast, other patients exhibited a pattern of VA/Q distribution characterised by the presence of lung units with very low VA/Q ratios (“low pattern”) (fig 1). While the “high pattern” was more prevalent in patients fulfilling the criteria of the “emphysematous type” of COPD, according to the classification proposed by Burrows and coworkers, no other consistent association between the pattern of VA/Q inequality and the clinical picture could be established. Subsequent studies demonstrated that the degree of VA/Q inequality in patients with COPD does not correlate with the severity of airflow obstruction, since patients with mild to moderate airflow obstruction already exhibited a noticeable degree of VA/Q mismatch. However, the VA/Q distributions in these patients were usually less dispersed – that is, they exhibited less VA/Q mismatch – than those reported in patients with more advanced disease. This observation suggests that the amount of VA/Q mismatch changes according to the evolution of the disease and that the deterioration of the VA/Q distribution with time probably reflects the progressive structural derangement of the lung.

Likewise, during acute exacerbations the VA/Q distributions of patients with COPD worsen for a period of time. Using the MIGET, Ferrer and colleagues’ showed very severe VA/Q mismatch in patients with COPD and acute hypercapnic respiratory failure. The degree of VA/Q inequality improved as the clinical condition ameliorated and FEV1 recovered. This suggests that, at least in part, some of the VA/Q abnormalities observed in patients with
acute respiratory failure are related to reversible functional abnormalities (mucous impaction, bronchospasm, bronchial oedema).

CORRELATION OF VA/Q MISMATCH WITH LUNG STRUCTURE
As already mentioned, Wagner and coworkers observed that those patients with type A COPD ("emphysematous type") often had lung units with very high VA/Q ratio. They suggested that these high VA/Q areas were probably the functional counterpart of anatomical emphysema – that is, alveolar wall destruction and reduced capillary network. Supporting this notion, a recent report by Barberá and coworkers showed that the severity of anatomical emphysema, assessed morphometrically in resected lung specimens from patients with mild COPD and lung cancer, correlated with the dispersion of the ventilation distribution. The degree of anatomical emphysema also correlated with the dispersion of the blood flow distribution and Pao2 (fig 2). This observation was explained as follows. In emphysematous lungs the number of peribronchiolar alveolar attachments is reduced and causes distortion and narrowing of these airways. In conjunction with bronchiolar inflammation and fibrosis, such anatomical abnormalities may impair the ventilation of the dependent lung units and decrease the VA/Q ratio of these alveoli. The presence of lung units with low VA/Q ratios results in a higher dispersion of the blood flow distribution and contributes significantly to the decrease in arterial Pao2. Bronchiolar inflammation also produces a non-homogenous distribution of inspired air that results in a higher dispersion of ventilation distribution (fig 2). Interestingly, however, the presence of such abnormalities in small airways does not preclude an improvement of VA/Q distributions during exercise in patients with mild to moderate COPD. This suggests that changes on the ventilatory pattern that take place during exercise may overcome the effect of these anatomical abnormalities on gas exchange, at least in the early stage of the disease (see below).

EFFECTS OF EXERCISE
In patients with COPD Pao2 may fall, remain unchanged, or even rise during exercise. This different effect of exercise on Pao2 depends on the interplay between the intrapulmonary and extrapulmonary factors that govern gas exchange during exercise in human subjects. The
MIGET allows a precise dissection of the role of such factors in these patients. In advanced COPD several studies have shown that the resting degree of Va/Q inequality does not change (neither improve nor worsen) during exercise. By contrast, in patients with mild to moderate COPD a significant improvement in the resting degree of Va/Q mismatch is observed during submaximal exercise. Thus, evidence accumulated to date suggests that exercise never worsens Va/Q inequality in COPD; on the contrary, the degree of Va/Q mismatch present at rest either improves or remains unaltered, probably depending on the severity of airflow limitation. Patients with moderate airflow limitation may improve the distribution of alveolar ventilation during exercise (thus, Va/Q mismatch), while the ventilatory reserve in patients with severe COPD may be so reduced that it cannot improve sufficiently during exercise to enhance Va/Q inhomogeneity.

Despite the observation that Va/Q relations do not deteriorate during exercise in COPD, some patients, particularly those with more severe disease, often have a fall in arterial Po2 while exercising. The decrease in PaO2 is multifactorial: (1) the ventilatory limitation of these patients (airflow obstruction) results in a relatively reduced minute ventilation during exercise. The increase in alveolar ventilation is lower than that of carbon dioxide production. As a consequence, both alveolar and arterial PCO2 rise. Other things being equal, this should be accompanied by a fall in PaO2; (2) patients with advanced COPD generally develop pulmonary hypertension, particularly during exercise. A higher right ventricular afterload results in a lower mixed venous Po2 during exercise than that expected for the same degree of workload. Again, everything else being equal (basically Va/Q mismatch), the lower the input Po2 to the lung (PvO2) the lower the Po2 leaving the lung (PaO2); (3) the ventilatory limitation of these patients also precludes the shift of the mean Va/Q ratio towards a higher value that occurs during exercise in healthy subjects. This shift normally compensates for the impact of the lower PvO2 that develops with exercise on the end capillary Po2 of lung units with low Va/Q and shunt. This effect is minimal or absent in COPD; and (4) different studies have demonstrated a good agreement, both at rest and during exercise, between the PaO2 value predicted from the degree of Va/Q mismatching, as measured by the MIGET, and that directly measured in the arterial blood (fig 3). This observation suggests that there is no significant limitation in the diffusion of oxygen from the alveoli to the capillary blood in COPD; yet, there is one report suggesting that during exercise patients with COPD can simultaneously improve their baseline Va/Q mismatch and present some degree of alveolar-capillary diffusion limitation. This single observation requires confirmation in future studies and, even if it is reproduced, in absolute terms its relevance seems to be very small in comparison with patients with idiopathic pulmonary fibrosis (see below).

**EFFECTS OF OXYGEN BREATHING**

Theoretically the administration of high concentrations of inspired oxygen has two potential effects on the Va/Q distribution: (1) to increase the basal amount of shunt; and (2) to release hypoxic pulmonary vasoconstriction. Clinical studies in patients with COPD using the MIGET have shown that, as a result of an effective collateral alveolar ventilation, the increase in shunt is minimal during oxygen breathing. Releasing hypoxic pulmonary vasoconstriction significantly worsens Va/Q relations, however, as evidenced by more blood flow being diverted towards lung units with low Va/Q ratios. The latter effect has been observed in different studies. Torres and associates reported significant deterioration of Va/Q mismatch during 100% oxygen breathing in a group of patients with COPD who were being weaned from mechanical ventilation. We have found a similar increase in Va/Q mismatch in patients with advanced disease recovering from an acute exacerbation and in patients with mild airflow obstruction. Moreover, Castaing and associates reported a significant increase in the amount of blood flow perfusing areas with low Va/Q ratios while patients with COPD were breathing an oxygen concentration of just 26%. In COPD, therefore, oxygen breathing produces a significant worsening of the basal distribution of Va/Q ratios resulting from the release of hypoxic vasoconstriction. This finding enhances the relevance of hypoxic vasoconstriction as an efficient mechanism contributing to maintain adequate Va/Q matching. However, the capability of the pulmonary vasculature to react when faced with alveolar hypoxia may be influenced by structural abnormalities of the pulmonary vessels themselves. We have found less hypoxic vasoconstriction in patients who displayed more pronounced abnormalities in pulmonary muscular arteries compared with patients with less structural derangement.

![Graph showing comparison of measured arterial Po2 at rest and during exercise](http://thorax.bmj.com/)
EFFECTS OF BRONCHODILATORS

Bronchodilator agents are commonly used in COPD. A possible undesirable effect of these drugs is that they can further worsen the basal degree of VA/Q mismatch, an effect that has been attributed to their interaction with hypoxic pulmonary vasoconstriction. Ringsted and coworkers\(^1\) studied how the intravenous administration of the β agonist agent terbutaline interacted with VA/Q relations in COPD. Terbutaline caused a significant increase in cardiac output and had different effects on VA/Q distributions depending on the severity of COPD. In those patients with higher PaO\(_2\) (68 (8) mm Hg) and less airflow limitation (FEV\(_1\) 28 (13)% of predicted), terbutaline increased VA/Q mismatch. By contrast, terbutaline had no effect upon the VA/Q distributions of patients who were more severely ill (FEV\(_1\) 16 (4)% of predicted; PaO\(_2\) 50 (10) mm Hg). This different response to terbutaline could be attributed to the loss of hypoxic pulmonary vascular tone in those patients with more severe airflow limitation and, presumably, greater morphological alterations of the pulmonary vessels. A worsening of VA/Q distributions in patients with severe COPD (FEV\(_1\) 32 (19)% of predicted) after nebulated fenoterol was also reported by Ferrer and associates\(^8\). Interestingly, a different response to β adrenergic agents was reported by Ballester and coworkers\(^9\) in a group of patients with severe chronic asthma (FEV\(_1\) 39 (10)% of predicted). These authors found that 300 µg salbutamol administered through a metered dose inhaler had no effect on VA/Q distributions. Since the degree of airflow obstruction was similar in the two latter series\(^8,9\), the different effects of the β adrenergic agents on VA/Q relations may be attributed to a higher effective dose of drug when it is delivered through a nebuliser. Other possibilities include a low specificity of fenoterol for the β receptor (compared with salbutamol), or that classical COPD and chronic asthma do not share precisely the same pathophysiological mechanisms, or both. The effect of other bronchodilating agents on VA/Q relations in COPD has also been tested. Ferrer and associates\(^8\) reported that the administration of nebulated ipratropium bromide had no effect on VA/Q distributions. We also assessed the effect of intravenous aminophylline in a group of patients recovering from an acute exacerbation and found no changes in VA/Q distributions.\(^1\) This lack of response to aminophylline occurred despite this group of patients showing a significant worsening in VA/Q relations during 100% oxygen breathing, thus suggesting that hypoxic pulmonary vasoconstriction was enhancing a certain degree of VA/Q matching. In summary, β adrenergic agents may have undesirable effects on VA/Q relations in patients with COPD. These effects seem to be related to the severity of the structural impairment, the β selectivity of the drug, and the dose administered. Other drugs, such as ipratropium bromide or the methylxanthines, seem to have less effect on VA/Q relations in COPD.

EFFECTS OF VASODILATORS

It is commonly believed that severe pulmonary hypertension worsens the prognosis of patients with COPD. Based on this assumption, attempts have been made to lower the pulmonary hypertension by means of continuous oxygen therapy, or pulmonary vasodilator treatment, or both. The major effect of vasodilators upon the pulmonary circulation is to inhibit vasoconstriction. As discussed above, however, inhibition of hypoxic pulmonary vasoconstriction has a negative impact on VA/Q relations in COPD. Studies where VA/Q distributions and pulmonary haemodynamics have been recorded simultaneously after the administration of pulmonary vasodilators have substantiated such deleterious effects. Mélot et al\(^10\) showed that the administration of 20 mg nifedipine, a calcium channel blocker, decreased pulmonary vascular resistance by 28% of baseline. This vasodilator effect was accompanied by a significant fall in PaO\(_2\) (from 52 (4) to 47 (3) mm Hg), due to the increase in perfusion of areas with a low VA/Q ratio. This suggests that nifedipine had suppressed the beneficial effect of hypoxic vasoconstriction on VA/Q relations.

By contrast, when hypoxic vasoconstriction is enhanced – as when administering almitrine bimesylate, a peripheral chemoreceptor agonist with an effect on the pulmonary circulation – an improvement in VA/Q relations takes place paralleling the increase in pulmonary vascular tone.\(^11,12\)

Patients with moderate COPD may not develop pulmonary hypertension at rest; however, most of them will demonstrate it during exercise. We assessed the effects of nifedipine on VA/Q distributions and pulmonary haemodynamics during exercise in a group of patients with COPD and mild pulmonary hypertension at rest.\(^5\) Nifedipine reduced the increase in pulmonary vascular resistance observed during exercise without the drug but also significantly worsened VA/Q matching. These data suggest that the deleterious effect of vasodilators on VA/Q relations is also apparent during exercise and that hypoxic pulmonary vasoconstriction is an important mechanism in enhancing VA/Q matching also while exercising.\(^3\)

Idiopathic pulmonary fibrosis

Patients with idiopathic pulmonary fibrosis (IPF) characteristically present with dyspnoea on exertion, loss of lung volume, reduced transfer factor for carbon monoxide (TLCO), and mild arterial hypoxaemia at rest that worsens during exercise.\(^23\) The latter had been considered almost a hallmark of the disease. Despite this well known clinical picture, before the MIGET became available several questions remained poorly understood. Most prominent among them were: (1) what is the precise mechanism of abnormal gas exchange in lung fibrosis—that is, VA/Q inequality or oxygen diffusion limitation – particularly during exercise? (2) how does the pulmonary vasculature interact with the mechanisms of abnormal pulmonary gas exchange? and (3) what is the relationship of TLCO (a measurement frequently carried out
in the clinical arena) to the mechanisms of abnormal gas exchange in fibrosis?

MECHANISM OF ABNORMAL GAS EXCHANGE (VA/Q INEQUALITY VERSUS OXYGEN DIFFUSION LIMITATION)

The alveolar interstitium is markedly thickened in patients with IPF.\(^{23}\) In 1951 Austrian and coworkers coined the term “alveolar-capillary block syndrome” and suggested that arterial oxygen desaturation during exercise in lung fibrosis was caused by impairment in diffusion of oxygen molecules between the alveolar gas and the capillary blood.\(^{24}\) This notion was extensively incorporated into the medical literature until 1976 when Wagner et al\(^{25}\) first used the MIGET in a group of patients with various interstitial diseases (IPF, asbestosis, sarcoïdosis). These authors were not able to find any evidence for limitation of oxygen diffusion; instead they reported that the main cause of arterial hypoxaemia in these patients was VA/Q inequality.\(^{25}\) A study by Jermudd-Wilmelsm\(_{26}\) et al,\(^{26}\) also in patients with a wide range of interstitial lung diseases, reported similar results. Based on these observations a significant role for oxygen diffusion limitation as the cause of arterial hypoxaemia in lung fibrosis was refuted by most authors. However, an important point was being missed. Several authors had shown that different interstitial diseases respond differently to exercise in terms of gas exchange.\(^ {27-29}\) The mechanisms leading to oxygen desaturation during exercise may therefore differ. In 1988, for example, we compared two groups of patients (IPF versus asbestosis) matched for gender, age, and degree of mechanical derangement, and showed that PaO\(_2\) fell almost constantly during exercise in IPF but could decrease, increase, or remain unchanged in asbestosis (fig 4).\(^ {29}\)

Stimulated by these observations, in 1991 Agusti et al\(^ {30}\) used the MIGET to separate the role of VA/Q inequality from that of oxygen diffusion limitation in a selected group of patients with “lone” IPF, as the paradigm of the vast group of lung interstitial disorders.\(^ {25}\) Figure 5 presents the VA/Q distribution obtained in two of those patients. At rest, breathing room air, both patients showed relatively well preserved VA/Q distributions with a very small amount of shunt and/or blood flow perfusing units with low VA/Q ratios. The observation of minimal abnormalities in the VA/Q distribution of these patients is consistent with the fact that they usually have minimal hypoxaemia at rest.\(^ {31}\)

The MIGET can predict the arterial Po\(_2\) value that should result from the measured VA/Q distribution, taking into account all the factors that may influence gas exchange in humans (FiO\(_2\), minute ventilation, cardiac output), on the explicit assumption that there is no oxygen diffusion limitation.\(^ {10,11}\) The comparison of this predicted Po\(_2\) value with that actually measured in the arterial blood thus provides information on any hypothetical “alveolar-capillary block for oxygen”. Figure 6 shows that, in patients with IPF, both at rest and (more) during exercise, the predicted Po\(_2\) value was systematically higher than the measured PaO\(_2\).\(^ {30}\) In absolute terms, at rest, the difference between the predicted and measured Po\(_2\) values averaged 6 mm Hg, representing 19% of the actual alveolar–arterial oxygen gradient.\(^ {30}\) In other words, in patients with IPF studied at rest, 80% of arterial hypoxaemia was due to VA/Q mismatch and almost 20% to a limitation in the diffusion of oxygen.\(^ {30}\) This observation has been also substantiated in patients with sarcoïdosis.\(^ {31}\)

During exercise most patients showed significant arterial desaturation but the baseline degree of VA/Q inequality either did not change or improved (fig 5).\(^ {10}\) Under these circumstances the fall in arterial Po\(_2\) was due to a significant increase in oxygen diffusion limitation and a low mixed venous Po\(_2\) during exercise that amplified the net result of any gas exchange impairment present at rest.\(^ {10,11}\)

*Increased oxygen diffusion limitation*

During exercise the difference between the predicted and measured Po\(_2\) values increased from 6 to 19 mm Hg (fig 6), expressed as per-

![Graph](http://example.com/graph.png)

*Figure 4* Arterial P\(_{O2}\) values measured at rest and during exercise in two groups of patients (IPF v asbestosis) matched for gender, age, and degree of mechanical impairment.\(^{25}\) It is evident that while patients with IPF showed a homogeneous fall in arterial oxygenation during exercise, patients with asbestosis had a much more heterogeneous response. For more explanation see text.
MIGET in chronic pulmonary diseases

Figure 5 Ventilation-perfusion distribution obtained in two representative patients with idiopathic pulmonary fibrosis studied at rest breathing room air, at rest breathing 100% oxygen, and during exercise (breathing room air). For more explanation see text. Reproduced with permission of Am Rev Respir Dis.

Low mixed venous PO_2

It is well established that, for any given amount of V̇A/Q inequality, arterial PO_2 will increase or decrease in parallel to mixed venous PO_2. Further, when there is some degree of oxygen diffusion limitation (as is the case in patients with IPF) the lower the mixed venous PO_2 the more pronounced the defect becomes and the more prominent the degree of arterial hypoxaemia.

It can therefore be concluded that: (1) when analysing pulmonary gas exchange in patients with interstitial lung disease it is important not to mix patients with different interstitial diseases into a single group; (2) in IPF (and also in sarcoidosis) the basic mechanism of arterial hypoxaemia at rest is V̇A/Q inequality, but some oxygen diffusion limitation is also apparent (even at rest). During exercise both mechanisms share similar pathophysiological relevance; and (3) during exercise the increase in oxygen diffusion limitation is probably due both to the shorter capillary transit time and to the lower mixed venous PO_2.

Figure 6 Plot of measured PO_2 in the arterial blood of the patient versus the PO_2 value predicted from the MIGET. The line of identity is also shown. For more explanation see text. Reproduced with permission of Am Rev Respir Dis.
area. Some have suggested, however, that hypoxic pulmonary vasoconstriction may also play a part in its development. To investigate the relation of gas exchange to the functional status of the pulmonary circulation in IPF we studied the effects of 100% oxygen breathing in these patients and observed two patterns of gas exchange response to oxygen breathing which are exemplified in the two patients presented in fig 5. The patient depicted on the top of fig 5 (labelled JSS) did not show any noticeable change with 100% oxygen. In contrast, in the patient on the bottom of fig 5 (labelled MRG) the breathing of oxygen significantly increased the amount of blood flow perfusing poorly ventilated areas. These observations suggest that the pulmonary vasculature may respond to oxygen only in some patients with IPF, probably those with less...
anatomical vascular derangement. Interestsingly, those patients who exhibited more pulmonary vascular reactivity improved the VA/Q distributions during exercise (breathing room air), while those showing no evidence of hypoxic pulmonary vasoconstriction being released by oxygen (at rest) did not show such improvement of the VA/Q distributions during exercise (fig 5).

The increase in perfusion of poorly ventilated lung units while breathing pure oxygen represents release of hypoxic pulmonary vasoconstriction. Such an increase can be calculated using the MITG as the percentage change from baseline in the dispersion of the perfusion distribution while breathing 100% oxygen (ΔLogSD Q). This variable may be more sensitive to small changes of the pulmonary vascular tone than the standard pressure-flow measurements. Figure 7 shows AlogSD Q plotted against (A) the exercise values of mean pulmonary artery pressure, (B) DISP R-E* (an overall index of VA/Q mismatch), and (C) arterial Po2 measured in patients with IPF. It is of the greatest interest to observe that the higher the pulmonary vascular response to oxygen at rest (higher AlogSD Q), the less is the severity of the pulmonary hypertension developed during exercise (panel A); also, those patients with more vascular reactivity at rest associate less VA/Q mismatch (panel B) and a higher arterial Po2 (panel C) during exercise.

In summary, these data indicate that those patients with IPF and with fixed changes of the pulmonary vasculature (probably because they also have a more advanced clinical disease) did not show any (or minimal) evidence of hypoxic vasoconstriction being released by oxygen at rest and, at the same time, these patients were those who showed more severe pulmonary hypertension, more VA/Q mismatch, and lower arterial Po2 during exercise (fig 7).

RELATION OF TLCO TO THE MECHANISMS OF ABNORMAL GAS EXCHANGE

A low diffusing capacity for carbon monoxide (TLCO) is characteristic of IPF and, as such, is frequently used in clinical management. However, whether or not it reflects an impairment in the diffusion of oxygen from the alveolar air to the capillary blood was a matter of debate before the MITG; in fact, as stated above, even the presence of a limitation in the diffusion of oxygen in IPF was not at all clear. A low TLCO in IPF can also reflect a diminished capillary surface area, as it does in emphysema or in primary pulmonary hypertension.

Figure 8 shows that Kco (that is, TLCO normalised for the measured alveolar volume) expressed as a percentage of the reference value was significantly related to the overall degree of pulmonary gas exchange impairment during exercise (expressed as the alveolar-arterial oxygen gradient, panel A) and also to the two basic mechanisms of gas exchange impairment during exercise in IPF (see above): a limitation in the diffusion of oxygen (panel B) and the degree of VA/Q inequality (panel C). It was also observed (graph not shown) that the lower the Kco (% reference) the greater the increase in pulmonary vascular resistance during exercise which, as an index of pulmonary vascular compliance, is an estimate of the surface available for capillary perfusion. The degree of statistical significance of all these correlations was considerably lower when TLCO was considered.

Taken all together, these data indicate that the measurement of the diffusing capacity of carbon monoxide in IPF is an indicator of (1) the overall degree of gas exchange impairment to be expected during exercise and, as a corollary, of the two basic mechanisms of exertional hypoxaemia in these patients (VA/Q mismatch and oxygen diffusion limitation); and (2) the amount of pulmonary vascular derangement present and, possibly, also of the degree of vascular reactivity. From the clinical standpoint, and given that the statistical strength of the observed relations was much higher for Kco than for TLCO, we would recommend the use of the former in the clinical evaluation of these patients.

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