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The transfer factor (diffusing capacity) as a predictor of hypoxaemia during exercise in restrictive and chronic obstructive pulmonary disease

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Summary. Thirty patients (17 with restrictive, eight with chronic obstructive pulmonary disease and five with combined pulmonary changes) were studied. Ordinary pulmonary function tests were made and in addition the transfer factor (diffusion capacity) was measured at rest and compared to the arterial oxygen tension at rest and during maximal exercise. There was a significant correlation ($r = 0{\cdot}89$) between the transfer factor at rest and the oxygen tension during maximal exercise in both the patients with restrictive and those with obstructive lung disease, but no correlation was found between the transfer factor and the resting oxygen tension. Exercise induced hypoxaemia ($P_{O_2} < 8{\cdot}-8{\cdot}5$ kPa) occurred in some patients and this could be predicted with an excellent sensitivity and specificity if a discrimination point for the transfer factor of 50 per cent of predicted or less was chosen.

Determination of the transfer factor at rest is thus a good screening test for exertional hypoxaemia and can be used to select patients for exercise testing when the purpose is to detect hypoxaemia.

Key words: diffusing capacity at rest, screening test, exertional hypoxaemia, interstitial lung disease, obstructive lung disease.

Introduction

Various pulmonary disorders can give rise to different degrees of hypoxaemia depending on the nature and severity of the disease. Resting hypoxaemia in chronic obstructive pulmonary disease is now considered a clear indication for chronic oxygen therapy, which has been proved to reduce mortality and improve quality of life (Nocturnal Oxygen Therapy Trial Group, 1980; MRC Working Party, 1981). Interstitial lung disease with resting hypoxaemia is also treated with oxygen, even though this therapy does not alter the ultimate survival (Chrystal *et al.*, 1981).

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Normoxaemia at rest but increasing hypoxaemia during exercise is also an indication for oxygen administration to guarantee proper function of vital organs such as the heart and brain in both interstitial and chronic obstructive pulmonary disease (Chrystal *et al.*, 1981; Raffestin *et al.*, 1982). Exercise oxygenation has also, to some extent, been used to stage and follow the fibrotic process in interstitial lung disease (Chrystal *et al.*, 1976).

Exercise testing may, however, be laborious for the patient and arterial cannulation is usually necessary. This test is thus not suitable for repetitive follow-ups in many patients. In contrast, measurement of the transfer factor at rest is easy and quick to perform, can be repeated many times and a value of 50–55% or less has been found to predict hypoxaemia or desaturation during exercise in both interstitial (Kelley *et al.*, 1986) and chronic obstructive lung disease (Owens *et al.*, 1984).

The aim of the present paper was to study a possible relationship between the arterial oxygen tension during exercise and the transfer factor at rest in our patients with restrictive and/or chronic obstructive pulmonary disease. The above-mentioned studies (Owens *et al.*, 1984; Kelley *et al.*, 1986) were unable to show a significant correlation, even though they could predict exercise hypoxaemia. We also especially wanted to find out in our patient material whether it was possible to demonstrate a cut-off point below which hypoxaemia during exercise was probable.

Patients and methods

PATIENTS

Thirty patients referred to the department of clinical physiology for pulmonary function testing were studied. The examination included exercise testing with measurements of arterial oxygen and carbon dioxide tensions. The diagnoses of the patients are shown in Table 1. The patients were categorized as restrictive if they had reduced lung volumes (total lung capacity and/or vital capacity) and as obstructive if they had

Table 1. Clinical diagnoses

	Patients studied (*n*)
Restrictive	
Pulmonary fibrosis + fibrosing alveolitis	6
Status post virus pneumonia or allergic alveolitis	3
Status post pulmonary tuberculosis or sarcoidosis	2
Status post pleuritis (one case also adipositas)	4
Dyspnoea + small lung volumes	2
Obstructive	
Chronic obstructive pulmonary disease	8
Obstructive and restrictive	
Chronic obstructive pulmonary disease in combination with either allergic alveolitis, asbestosis, silicosis, tuberculosis or adipositas	5

reduced FEV/VC% and/or increased residual volume (Table 2). There were twenty-one men and nine women; their ages ranged from 25–75 years (mean 52).

Pulmonary function tests

Before exercise all patients underwent pulmonary function tests under resting conditions. Vital capacity and forced expiratory volume in one second were measured with a Bernstein spirometer. A Morgan transfer test instrument (PK Morgan Ltd, Chatham, Kent, UK) was used to determine the functional residual capacity, residual volume and total lung capacity (helium re-breathing method). The transfer factor was measured by the single-breath CO method with the same instrument according to Cotes (1975). The waste and sample volumes were 900 ml (sometimes, if necessary, lowered to 700 and 600 ml, respectively), and the breath-holding time nine seconds. The inspired gas mixture contained 14% He, 0·27% CO and approximately 20% O_2 in N_2. The measurement was performed in duplicate and the mean value is presented.

The predicted normal values for lung volumes were those of Berglund *et al.* (1963) and Grimby and Söderholm (1963) and the values for transfer factor those of Cotes (1975) and Billiet *et al.* (1963).

EXERCISE TEST

The exercise test was preceded by a twelve-lead ECG in the supine position at rest. The exercise was performed in the sitting position on an electrically braked bicycle ergometer (Siemens-Elema) and the ECG was recorded every second min during exercise and at intervals for 10 min afterwards. The initial load was 50 watts for men and 30 watts for women and the load was increased every sixth min by 50 watts for men and 30 watts for women until exhaustion or severe dyspnoea. The predicted normal values for exercise capacity were those of Nordesjö and Landelius (1975).

Arterial blood gases were measured through an indwelling brachial-artery catheter before and after exercise in the supine position and at the fifth min of every exercise load and also immediately before terminating the exercise.

Statistical analyses, sensitivity and specificity values were calculated by standard methods.

Results

The majority of the patients in this study belonged to the restrictive group (17) of pulmonary diseases and only eight were of the obstructive type while even fewer (five) had both obstructive and restrictive changes (Table 1). Table 2 shows that most of the patients were not severely ill, and only one (obstructive) had a resting arterial oxygen tension below 8 kPa (7·7 kPa, Fig. 1) which, however, rose to 13 kPa at maximal exercise. The mean working capacity in the three groups ranged between 57 and 70% of predicted (Table 2). There was a significant ($P<0·01$) correlation between the

Table 2. Pulmonary function tests

	Restrictive	Obstructive	Obstructive and restrictive
	($n = 17$)	($n = 8$)	($n = 5$)
Vital capacity (litres)	3·3 ± 0·95 (72)	3·9 ± 1·15 (87)	2·9 ± 0·93 (66)
Forced expiratory vol/1 s (litres)	2·7 ± 0·87 (77)	2·7 ± 1·00 (83)	1·9 ± 0·58 (64)
FEV/VC (percent)	79 ± 9.1	69 ± 9·7	69 ± 15·9
Total lung capacity (litres)	4·7 ± 0·89 (72) ($n = 14$)	6·0 ± 1·44 (96)	5·0 ± 0·61 (79)
Functional residual capacity (litres)	2·6 ± 0·65 (81) ($n = 14$)	3·4 ± 0·61 (116)	2·7 ± 0·41 (81)
Residual volume (litres)	1·4 ± 0·56 (78) ($n = 14$)	2·3 ± 0·60 (125)	2·0 ± 0·52 (99)
Working capacity (watts)	85 ± 35·7 (57)	97 ± 35·9 (70)	84 ± 53·3 (70)
Transfer factor (ml/min and mmHg)	18·1 ± 8·27 (64)	21·3 ± 7·52 (79)	22·5 ± 6·52 (90)
Arterial oxygen tension (kPa):			
At rest	10·3 ± 1·72	9·8 ± 1·70	10·1 ± 0·91
During exercise	10·2 ± 2·15	10·6 ± 1·86	11·1 ± 1·51
Arterial carbon dioxide tension (kPa):			
At rest	4·9 ± 0·41	4·7 ± 0·53	5·0 ± 0·46
During exercise	4·6 ± 0·50	4·3 ± 0·49	4·6 ± 0·72

Values within brackets denote per cent of predicted.

transfer factor and the working capacity in percent of predicted, although the correlation coefficient was not particularly high ($r = 0·50$). No correlation could, however, be found between the arterial oxygen tension at maximal exercise and the working capacity (in percent of predicted).

At rest (Fig. 1) there was no correlation between the arterial oxygen tension and the transfer factor in either group of patients. At maximal exercise (Fig. 2), however, the arterial oxygen tension correlated significantly ($r = 0·89$; $P < 0·01$) with the transfer factor measured at rest in both the restrictive and obstructive groups of patients. Among the relatively few patients with both obstructive and restrictive changes no such correlation could be found; in this group, however, no patient had a transfer factor below 60% of predicted.

The change in arterial oxygen tension from rest to maximal exercise also showed a significant correlation to the transfer factor at rest in both the restrictive ($P < 0·01$) and the obstructive ($P < 0·05$) patients. The correlation coefficients ($r = 0·65$ and 0·78, respectively) are, however, lower than for the correlation mentioned above between the oxygen tension at maximal exercise *per se* and the transfer factor.

If a transfer factor of 50% or less of predicted is used as a cut-off point, a very good sensitivity and specificity is reached (Table 3), with either 8·0 or 8·5 kPa as a value of hypoxaemia in exercise. At 8·0 kPa the sensitivity and at 8·5 kPa the specificity is 100%.

The decrease in arterial oxygen tension during exercise in the patients studied was not due to hypoventilation, as the carbon dioxide tension did not increase (Table 2).

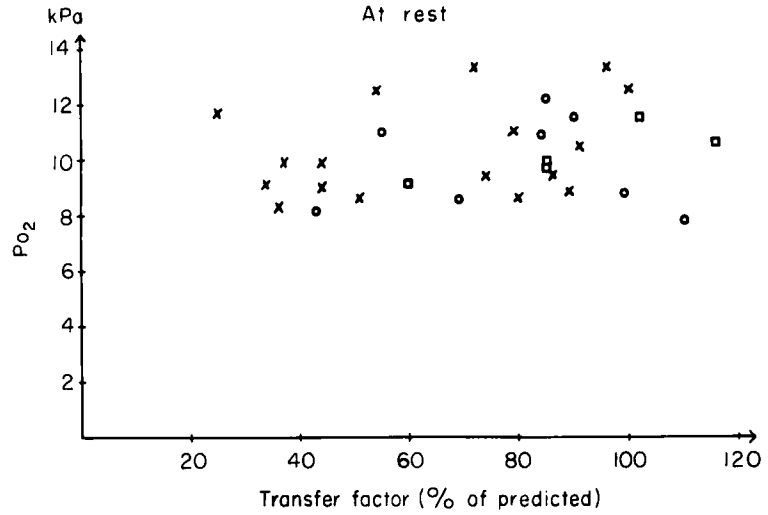

Fig. 1. The correlation between the transfer factor (percent of predicted) at rest and the arterial oxygen tension (P_{O_2} in kPa) also at rest for the restrictive (×), obstructive (○) and obstructive+restrictive (□) patients.

Discussion

The mechanism for exertional hypoxaemia, i.e., normoxaemia at rest and hypoxaemia during exercise, is not completely understood in patients with different types of lung disorders. However, in both interstitial and chronic obstructive lung disease ventilation – perfusion inhomogeneity leading to venous admixture seems to be the main cause (Wagner *et al.*, 1976; Minh *et al.*, 1979; Jernudd-Wilhelmsson *et al.*, 1986). In interstitial lung disease diffusion impairment is also thought to contribute. Hypoventilation is probably of no major importance, which could also be confirmed in the present study. Despite the fact that the mechanisms causing exertional hypoxaemia are thus at least partly different in interstitial and in chronic obstructive lung disease, it is evident that hypoxaemia or desaturation can be revealed by measurement of the transfer factor at rest (Owens *et al.*, 1984; Risk *et al.*, 1984; Coates *et al.*, 1986; Kelley *et al.*, 1986). It has been suggested that the more descriptive term 'transfer factor' is to be preferred, as it is not only diffusion that is measured (cf. Cotes, 1975) but the total transfer of gas from the alveoli to the blood.

In this study both the patients with restrictive and those with chronic obstructive lung disease showed a significant correlation between the transfer factor measured at rest and the arterial oxygen tension at maximal exercise. To our knowledge a significant correlation has not been shown earlier. In most studies (Owens *et al.*, 1984; Coates *et al.*, 1986; Kelley *et al.*, 1986) arterial oxygen saturation has been measured or calculated instead. As small changes in the oxygen saturation are less easily detected in the upper flat oxy-haemoglobin dissociation curve than the corresponding

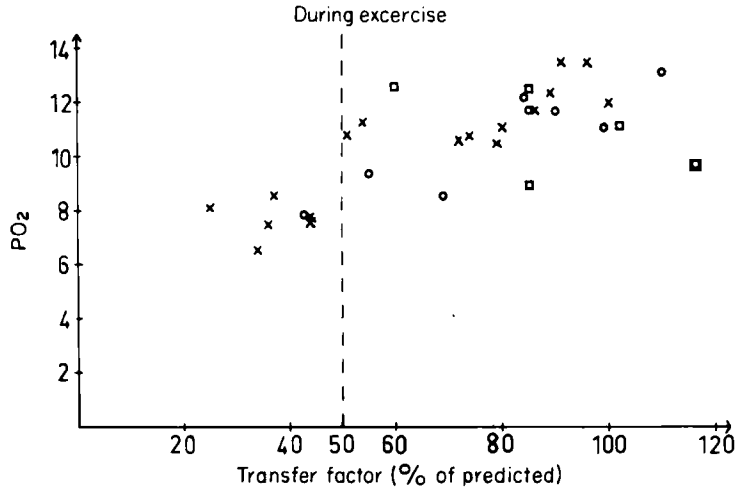

Fig. 2. The correlation between the transfer factor (percent of predicted) at rest and the arterial oxygen tension (Po_2 in kPa) during maximal exercise for the restrictive (×), obstructive (○) and obstructive+restrictive (□) patients. The correlation coefficient $r=0{\cdot}89$ ($P<0{\cdot}01$) for both the restrictive and the obstructive patients.

Table 3. Sensitivity and specificity at 50 percent of predicted transfer factor for different levels of hypoxaemia

PO_2 kPa	Sensitivity percent	Specificity percent
≤8·5	88	100
≤8·0	100	93

larger changes in the oxygen tension, a correlation between the transfer factor and the saturation is therefore more difficult to reveal.

We found, however, no correlation between the transfer factor and the resting oxygen tension. The transfer factor thus seems to be more closely related to exercise-induced hypoxaemia than is the oxygen tension at rest (Kelley *et al.*, 1986). Some of our patients with exertional hypoxaemia had a completely normal arterial oxygen tension at rest (about 10–12 kPa).

The main interest of the present study was to find out if also in this patient material a discrimination or cut-off point could be demonstrated below which exertional hypoxaemia could be expected. This has been shown in earlier studies. Owen *et al.* (1984) found e.g., in obstructive patients that if the transfer factor was 55% of predicted or less, arterial desaturation occurred with a strikingly high frequency (sensitivity 100% and specificity 67%). Kelley *et al.* (1986) reported likewise in a mixed material that a transfer factor below 50% of predicted is strongly suggestive of exercise-induced arterial desaturation of at least 4% (sensitivity 89% and specificity

93%). We could also confirm in the present study that a transfer factor of 50% of predicted or less is an excellent cut-off point which gives a high degree of sensitivity or specificity, if an arterial oxygen tension of either 8·0 or 8·5 kPa is used as a measure of exertional hypoxaemia. As our patients consisted mainly of those with restrictive or interstitial disease, and only one with chronic obstructive lung disease had a transfer factor below 50%, some caution must of course be observed in the interpretation of our results in the obstructive group.

The transfer test at rest seems, however, less suitable as a predictor of a reduced arterial oxygen tension above hypoxaemia during exercise.

It is, thus, our belief that both in interstitial and chronic obstructive pulmonary disease measurement of the transfer factor at rest can be used as a screening test to predict exercise-induced hypoxaemia. This could be of great help in selecting those patients who should undergo exercise testing in order to better assess the severity of the disease.

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