Eur Respir J
1988, 1, 98–101

The transfer factor and its subdivisions in patients with pulmonary emboli

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ABSTRACT: The carbon monoxide transfer factor and its subdivisions, the pulmonary membrane diffusing capacity and the pulmonary capillary volume were measured in fourteen subjects following submassive pulmonary emboli, as demonstrated by a ventilation-perfusion scan, and in fourteen matched controls. Transfer factor and alveolar volume were significantly lower in patients with pulmonary emboli ($p < 0.02$). Patients were given six weeks anticoagulant therapy and the measurements repeated three months later. There was a significant increase in the transfer factor and the alveolar volume ($p < 0.01$) and the membrane diffusing capacity ($p < 0.05$). It has previously been assumed that the reduction in the transfer factor following a pulmonary embolus is due to a reduction in the pulmonary capillary volume. Results of this study however, suggest that it is more likely to be due to a loss of alveolar volume, at least in subjects with submassive emboli.
Eur Respir J. 1988, 1, 98–101.

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Keywords: Alveolar volume; pulmonary embolus; transfer factor.

Received: August 27, 1986; accepted after revision September 9, 1987.

Studies have shown that the carbon monoxide transfer factor (TLCO) may be reduced following a pulmonary embolus [2, 7, 13]. The TLCO may be divided into two components, the pulmonary membrane diffusing capacity (Dm) and the pulmonary capillary volume (Vc), related by the formula:

$$\frac{1}{TLCO} = \frac{1}{Dm} + \frac{1}{\theta Vc} \qquad [14]$$

It is generally assumed that the reduction in the TLCO is due to obliteration of part of the pulmonary capillary bed with a resulting fall in Vc [7, 10, 15]. The aim of this study was to assess the effect of pulmonary emboli on the TLCO and its subdivisions and the effect of treatment on these measurements.

Patients and methods

Fourteen patients and fourteen control subjects were studied. The diagnosis of pulmonary embolus was made on the basis of a ventilation-perfusion isotope scan. None of the patients were ever in a state of clinical shock and all had sustained submassive emboli, *i.e.*, less than 60% of the pulmonary vasculature obstructed by emboli. Patients had previously been fit, with no underlying respiratory disorder and no evidence of airways obstruction on spirometry. Initial measurements were made within twelve days of the diagnosis (median 7, range 2–12 days) and repeated three months later after a six week period of anticoagulation. Measurements were also made, on one occasion only, in fourteen fit control subjects, matched for age, sex, height and smoking history.

The TLCO was measured using a single-breath technique, as standardized by OGILVIE *et al.* [11] while breathing a mixture of air, 0.3% carbon monoxide and 14% helium and again after breathing oxygen for five minutes using a mixture of 0.3% carbon monoxide, 14% helium, remainder oxygen. Measurements were made in duplicate and the mean value used. Dm and Vc were calculated according to the formula of COTES [3]. Alveolar volume (VA) was measured using single-breath helium dilution and carbon monoxide (CO) diffusion time was measured as the effective breath-holding time. Haemoglobin concentration was estimated prior to each measurement.

All patients were able to perform the tests satisfactorily and none had pleuritic chest pain at the time of testing. Smoking was not permitted for one hour prior to testing. Statistical analysis was performed using a two tailed students' paired t-test and linear least square analysis. All reference values were taken from COTES [3].

Results

Fourteen patients were studied, for details see table I. Seven were female, mean ± SD age was 40 ± 13 yr, height 1.59 ± 0.05 m and seven were male age 52 ± 7 yr, height 1.69 ± 0.06 m, number of cigarettes per smoker 20 ± 5. Of the fourteen control subjects, table II, matched for sex, mean age for females was 40 ± 12 yr, for males 53 ± 9 yr, mean height for females 1.59 ± 0.02 m and for males 1.69 ± 0.09 m and number of cigarettes per smoker per day was 15 ± 7.

Measurements for TLCO, Dm, Vc and VA in controls and patients, at the time of diagnosis and

Table I. - Patients details

Subject	Sex	Age	Height m	Time between PE and first measurement (days)	Hb at diagnosis	Hb at 3 months
1	M	55	1.76	6	13.1	13.6
2	F	24	1.56	10	11.3	11.5
3	F	34	1.64	4	12.8	14.1
4	M	50	1.70	6	15.9	14.2
5	M	42	1.75	4	15.9	16.0
6	F	38	1.50	7	13.2	13.6
7	F	66	1.62	9	14.9	14.4
8	F	52	1.52	2	13.1	13.8
9	M	46	1.75	7	15.4	16.9
10	F	51	1.58	8	14.1	14.6
11	F	32	1.63	7	12.0	12.4
12	M	61	1.65	7	13.5	13.2
13	M	59	1.68	12	14.7	13.9
14	M	64	1.73	6	15.6	15.0
Mean±SD		48±13	1.64±0.09	7±2	14.0±1.4	14.1±1.3

PE: pulmonary embolus

Table II. - Control details and values

Subject	Sex	Age	Height m	TLCO % Predicted	VA *l*	Dm $l \cdot min^{-1} \cdot mmHg^{-1}$	Vc ml
1	M	52	1.68	90	5.25	36.1	62.9
2	F	24	1.56	100	4.87	50.7	58.9
3	F	34	1.58	104	4.16	42.1	70.1
4	M	52	1.76	87	4.97	54.6	39.4
5	M	43	1.77	81	5.50	47.5	47.2
6	F	42	1.57	69	4.10	23.4	49.9
7	F	60	1.58	66	3.29	22.0	31.5
8	F	59	1.52	70	2.44	22.7	30.4
9	M	40	1.76	86	5.79	50.4	56.3
10	F	52	1.60	104	3.84	44.6	48.8
11	F	29	1.63	75	2.99	40.1	46.2
12	M	62	1.66	111	4.13	46.6	51.5
13	M	63	1.70	115	5.31	58.7	46.9
14	M	59	1.74	105	4.84	46.2	71.7
Mean±SD		48±12	1.65±0.08	90.0±16.5*	4.39±1.00*	41.8±11.8	50.8±12.4

Patients at diagnosis *vs* controls. *p<0.02

three months later are given in tables II and III. At the time of diagnosis patients had a significantly lower TLCO compared with control subjects: 69.2±19.1% of predicted value compared with 90.2±16.5% ($p<0.02$) and a significantly lower alveolar volume: 3.58±0.92 *l*, compared with 4.39±1.0 *l* ($p<0.02$).

Repeat measurements in the fourteen patients three months later demonstrated a significant rise in TLCO: 78.8±16% compared with 69.2±19% ($p<0.01$), in VA: 4.16±0.82 *l* compared with 3.58±0.92 *l* ($p<0.01$) and in Dm 38.5±13.5 $ml \cdot min^{-1} \cdot mmHg^{-1}$ compared with 32.3±19 $ml \cdot min^{-1} \cdot mmHg^{-1}$ ($p<0.05$). There was no significant difference in the Vc between controls and patients at the time of diagnosis or in patients between the first and second measurements.

The coefficient of variation based on duplicate measurements for TLCO and its subdivisions were all less than 10%.

There was a significant correlation between Dm and VA: $r=0.72$ ($p<0.001$). There was no significant difference in the mean transfer coefficient (KCO) between patients and controls, 104±24% of predicted value compared with 107±21%, and no significant change in the patient group after three months, mean KCO 103±19%.

Table III. - Patient values

	Patients at diagnosis				Patients at 3 months			
Subject	TLCO % predicted	VA *l*	Dm ml·min^{-1}·mmHg^{-1}	Vc ml	TLCO % predicted	VA *l*	Dm ml·min^{-1}·mmHg^{-1}	Vc ml
1	87	3.83	47.9	55.3	95	4.44	57.7	51.1
2	60	3.38	30.1	47.3	66	4.32	36.9	43.8
3	40	2.33	15.8	40.5	68	3.87	31.9	41.9
4	72	4.00	26.6	71.0	71	3.47	28.8	46.7
5	104	6.27	87.8	48.7	113	6.40	71.6	59.6
6	75	3.65	29.6	44.6	94	3.52	40.3	52.1
7	83	3.54	28.7	40.7	89	3.58	31.1	35.6
8	63	3.24	20.5	47.3	57	3.34	22.7	26.4
9	81	3.15	37.5	58.4	94	4.70	47.5	48.2
10	95	4.01	44.8	43.6	89	3.55	33.6	42.4
11	49	2.23	19.6	40.0	67	3.49	45.6	33.7
12	61	4.13	32.0	26.5	70	4.30	39.1	22.6
13	48	3.22	15.1	46.6	62	4.49	28.0	36.1
14	52	3.20	16.7	49.1	68	4.78	24.3	47.0
Mean±SD	69.2±19.1**	3.58±0.92	32.3±19.0	47.1±10.2	78±16***	4.16±0.82***	38.5±13.5*	41.4±10.1

Patient at diagnosis *vs* 3 months .*p<0.05; **p<0.02; ***p<0.01

Discussion

This study confirms the results of previous workers, in demonstrating a reduction in TLCO following a pulmonary embolus [2, 7, 13] and has shown that the underlying defect is reversible following treatment with anticoagulants. It is generally assumed that the reduction in TLCO is the result of obliteration of the capillary bed by emboli with a reduction in Vc [7, 10, 15]. There was no difference in Vc between patients and controls in this study however, with no improvement following treatment in patients, and it is probable that the observed reduction in TLCO was due to a reduction in alveolar volume. The large capillary reserve of the lung, with recruitment of capillaries and the possible formation of collaterals with bronchial arteries may explain why Vc is maintained in patients following minor pulmonary emboli [8, 12, 16]. A recent study looking at the aetiology of hypoxia in pulmonary emboli demonstrated ventilation-perfusion mismatch, with relative overperfusion of areas distant from the site of the emboli [1]. Only one study has shown a reduction in Vc following pulmonary embolism [15], which subsequently improved following treatment with streptokinase. Half the patients, however, had suffered a massive pulmonary embolus, *i.e.* greater than 60% of the pulmonary vasculature occluded by clot. In cases of minor emboli, cardiac output is presumably maintained by redistribution of the circulation, whereas, in the case of massive emboli this may not be possible, resulting in a fall in output and in the measured Vc.

After three months and presumed resolution of the emboli, there was a significant increase in TLCO, VA and Dm. Both atelectasis and bronchoconstriction [9] occur in areas of lung involved by an embolus, and subsequent loss of lung volume has been held responsible for the occurrence of shunting found in some studies [5, 17]. Local reduction in ventilation, demonstrable by ventilation scanning does occur, since between 30 and 37% of matched ventilation-perfusion defects in patients suspected of having an embolus can subsequently be shown to have suffered an embolus on angiography [6]. Shunting occurs only after 48 h from presentation [5] which may account for the fact that the ventilation scans in our patients were normal, scans usually being performed within 48 h of presentation. For technical reasons, some subjects were not tested for up to twelve days after the diagnosis was established. Shunting has been shown to occur for a number of weeks after the initial incident [17], however, and thus abnormalities were still detectable in our study.

The TLCO is dependent on lung volume as is Dm [4], confirmed by the significant correlation between Dm and VA. The rise in VA thus accounts for both the rise in TLCO and Dm after treatment. There was a tendency for the patient group as a whole to have a lower Dm than controls at the time of presentation but this failed to achieve statistical significance.

There was an overall fall in Vc observed in patients after three months, although this did not achieve statistical significance. COTES *et al.* [4], measuring TLCO at different lung volumes, found that Dm fell as VA was reduced, while Vc increased. The mechanism of this phenomenon remains to be explained, but the apparent fall in Vc may in part be the result of the rise in VA rather than reflecting any damage to the

pulmonary vasculature. Further embolisation, despite a course of anticoagulants, may explain why VA fell in a few patients after three months, while reduction in Vc may have occurred because of failure of the compensatory mechanisms to redistribute blood flow following recurrent emboli. The reduction in TLCO seen in two subjects may be secondary to a fall in VA or Vc. None of the patients suffered a clinical recurrence of their pulmonary embolus however, and any explanation for the apparent fall in Vc must be tentative.

There was no correlation between the size of the perfusion defect and the reduction in TLCO. Only a crude estimate of the perfusion defect could be made however, and it was of a similar size, one or two segmental defects only, in most patients.

As this was an acute study it was not always possible to tightly control the period between the last cigarette and the measurement of TLCO. A recent study has shown that alveolar CO falls by 50% in a mean of 13.5 min after a cigarette, with a much slower fall thereafter [18]. After one hour, which in our study was the minimum time elapsed between smoking a cigarette and the measurement of TLCO, whilst the expired CO would not have returned to baseline levels, it is likely that the difference would be relatively small and would have a minimal effect on the measured TLCO. More importantly, perhaps, is the fact that patients are likely to have smoked more cigarettes at home than they did in hospital, resulting in a higher baseline carboxyhaemoglobin level at three months. This could result in a relative underestimate of TLCO at three months but we were still able to demonstrate a significant increase in this measurement. Performing the TLCO measurement on air before oxygen results in a higher CO back pressure for the second measurement than if the tests had been performed the other way round, the net result being that in this study we have overestimated Dm and underestimated Vc. Since the measurements were performed in the same order throughout the study, however, our overall conclusions remain valid.

In summary, we confirm that a reduction in TLCO does occur following a pulmonary embolus. This is not due to a reduction in Vc, at least in submassive emboli, but rather to a loss in alveolar volume, presumably due to atelectasis and/or bronchoconstriction. These abnormalities are reversible following treatment with anticoagulants.

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RÉSUMÉ: Le facteur de transfert pulmonaire pour le monoxyde de carbone et ses subdivisions, la capacité de diffusion de la memebrane et le volume capillaire pulmonaire ont été mesurés chez 14 sujets après une embolie pulmonaire non massive démontrée par une scintigraphie pulmonaire de perfusion et de ventilation, ainsi que chez 14 sujets témoins appariés. Le facteur de transfert et le volume alvéolaire étaient abaissés chez les malades ($p < 0.02$). Les mesures furent répétées trois mois plus tard, après un traitement anticoagulant de six semaines. On note alors une augmentation significative du facteur de transfert et du volume alvéolaire ($p < 0.01$) ainsi que de la capacité de diffusion de la membrane ($p < 0.05$). Il était généralement admis que la réduction de la capacité de transfert après embolie pulmonaire résultait d'une diminution du volume capillaire pulmonaire. Les résultats de cette étude suggèrent qu'elle est plutôt, en cas d'embolie pulmonaire non massive, secondaire à une diminution du volume alvéolaire.