

# The alveolar-capillary membrane diffusing capacity and the pulmonary capillary blood volume in heart transplant candidates

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## Abstract

**Objectives**—To determine the mechanism of impairment of pulmonary transfer factor for carbon monoxide ( $TL_{CO}$ ) in heart transplant candidates, as this is the most common lung function abnormality.

**Setting**—Regional cardiopulmonary transplant centre.

**Methods**— $TL_{CO}$  and its components (the diffusing capacity of the alveolar-capillary membrane ( $D_M$ ) and the pulmonary capillary blood volume ( $V_C$ )) were measured using the Roughton and Forster method and the single breath technique in 38 patients with severe chronic heart failure awaiting heart transplantation (mean age 51 years, range 19 to 61; mean left ventricular ejection fraction 12.8%). Results were compared with data from 26 normal subjects (mean age 47 years, range 27 to 62).

**Results**—Mean per cent predicted  $TL_{CO}$ ,  $D_M$ , and  $V_C$  were significantly reduced in patients (69.9%, 81.4%, and 80.2% of predicted, respectively) compared with controls (97.7%, 100.1%, and 102.3% of predicted, respectively,  $p < 0.001$ ). The relative contribution of the two components of  $TL_{CO}$  in patients was similar to that of normal subjects, with each component accounting for approximately 50% of the total resistance to diffusion ( $1/TL_{CO}$ ).

**Conclusions**— $TL_{CO}$  impairment in patients with severe chronic heart failure awaiting heart transplantation results from a proportionate reduction in both  $D_M$  and  $V_C$ , suggesting a significant disturbance of the pulmonary vascular bed.

(Heart 2000;83:156–160)

Keywords: heart failure; diffusing capacity; pulmonary transfer factor; pulmonary capillary blood volume

Heart failure is associated with a variety of pulmonary function abnormalities including reduced lung volumes, airway obstruction, and reduced pulmonary transfer factor for carbon monoxide ( $TL_{CO}$ ).<sup>1,2</sup> Studies in patients who are not candidates for heart transplantation (that is, those with less severe heart failure) have shown that  $TL_{CO}$  is usually normal or only slightly reduced even during episodes of acute heart failure.<sup>1,3–5</sup> It was suggested that the increased pulmonary capillary blood volume in acute congestive heart failure probably compensates for the effects of pulmonary oedema which would be expected to reduce  $TL_{CO}$ .<sup>1</sup> Puri and associates<sup>6</sup> provided the first report on the changes of  $TL_{CO}$  and its components in stable patients with mild to moderately severe chronic heart failure (New York Heart Association (NYHA) functional classes II and III). In the entire group (38 patients), mean  $TL_{CO}$  was reduced compared with controls and this was primarily due to a reduction in the diffusing capacity of the alveolar-capillary membrane ( $D_M$ ).  $TL_{CO}$  and  $D_M$  were both lower in patients in NYHA functional class III than in those in class II. In contrast, there was no significant difference in mean pulmonary capillary blood volume ( $V_C$ ) between NYHA class II patients and normal controls, though  $V_C$  was greater in class III patients than in the controls. It was suggested that  $D_M$  might be a useful marker for the alveolar-capillary membrane damage caused by pulmonary hypertension.

In patients with severe chronic congestive heart failure awaiting heart transplantation,  $TL_{CO}$  impairment is more frequent.<sup>7–12</sup> However, the  $TL_{CO}$  components  $D_M$  and  $V_C$  have not been determined in these patients.

Our aim in this study was to determine the mechanism of  $TL_{CO}$  impairment in patients with severe chronic heart failure awaiting heart transplantation in terms of the relative contribution of each of its components.

## Methods

### STUDY POPULATION

$TL_{CO}$  and its components were determined in 38 patients with severe chronic heart failure awaiting heart transplantation (candidates) and 26 normal subjects recruited as volunteers from the general population, in whom there was no evidence of cardiopulmonary disease. All heart transplant candidates were stable at the time of assessment. Antifailure treatment consisted of diuretics (all patients), angiotensin converting enzyme inhibitors (30 patients), digoxin (19 patients), and other vasodilators (13 patients). The exclusion criteria of the study were: current smoking or smoking cessation for less than one year before assessment; treatment with amiodarone or  $\beta$  blockers; history of primary lung disease; and abnormal spirometric or lung volume results.

### LUNG FUNCTION TESTS

#### *Spirometry and lung volumes*

Standard spirometry and lung volumes were measured using a body plethysmograph.

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Accepted 23 August 1999

Measured variables included vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>), and total lung capacity (TLC). Predicted normal values were determined using the European Community for Steel and Coal equations for all variables.<sup>13</sup> The lower limit of normality for each variables was defined as the predicted value minus 1.64 standard deviations of the reference regression equation according to the guideline of the European Respiratory Society.<sup>13</sup>

#### *TL<sub>CO</sub> and its components*

Roughton and Forster showed that the measurement of TL<sub>CO</sub> at different alveolar oxygen tensions allows the estimation of the diffusing capacity of the alveolar-capillary membrane (D<sub>M</sub>) and the instantaneous pulmonary capillary blood volume available for gas transfer (V<sub>C</sub>).<sup>14</sup> According to Roughton and Forster, the relation between TL<sub>CO</sub> and its components is described by the following equation:

$$1/TL_{CO} = 1/D_M + 1/\theta V_C \quad (1)$$

where  $1/TL_{CO}$  is reciprocal of the transfer factor for the entire lung and represents the total resistance of the lung to CO transfer. By analogy,  $1/D_M$  represents the resistance of the alveolar-capillary membrane and  $1/\theta V_C$  represents the resistance of the total mass of erythrocytes in the capillary blood (intracapillary resistance). Theta ( $\theta$ ) is the standard rate at which 1 ml of whole blood takes up CO and this is dependent on the prevailing alveolar oxygen tension and haemoglobin concentration. In the conventional calculation of TL<sub>CO</sub>, haemoglobin concentration is assumed to be normal (146 g/l).<sup>15</sup> The effect of haemoglobin on TL<sub>CO</sub> values can be determined using a modified version of the classic Roughton and Forster equation described by Cotes<sup>16</sup> and recommended by both the European Respiratory Society and the American Thoracic Society<sup>15 17</sup>:

$$1/TL_{CO} = 1/D_M + 1/([Hb] \times \theta V_C) \quad (2)$$

where [Hb] is the haemoglobin concentration as a fraction of normal (that is, actual haemoglobin divided by 14.6). Thus the application of the Roughton and Forster model permits the determination of the relative contribution of D<sub>M</sub>, V<sub>C</sub> and blood haemoglobin to TL<sub>CO</sub> changes.

The steps and details of estimating TL<sub>CO</sub> and its components (D<sub>M</sub> and V<sub>C</sub>) were identical to a protocol we have previously validated.<sup>18</sup> In brief, TL<sub>CO</sub> was measured using the single breath method (Transflow; PK Morgan, Rainham, Kent, UK) according to the recommendations of the European Respiratory Society (ERS).<sup>15</sup> The standard oxygen gas consisted of CO (0.28%), helium (He) (14%), O<sub>2</sub> (18%) with the remainder nitrogen whereas high oxygen gas mixture consisted of CO (0.28%), He (14%) with the remainder O<sub>2</sub> (85.72%). The sequence of measurements was in the following order: TL<sub>CO</sub> at standard oxygen concentration was measured first and the mean of two technically acceptable TL<sub>CO</sub> values was re-

ported as the subject's TL<sub>CO</sub>. The subject was then allowed five minutes breathing room air followed by another five minutes breathing pure oxygen while wearing a nose clip. The single breath TL<sub>CO</sub> at high oxygen concentration was then measured using the same steps of standard TL<sub>CO</sub> measurement, except for the use of the high oxygen mixture in the inspired gas mixture. The steps of room air breathing and pure oxygen breathing were repeated, a second high oxygen TL<sub>CO</sub> measurement was made, and the mean of two technically acceptable values was reported as the subject's TL<sub>CO</sub> at high oxygen concentration. The interval between the sets of standard and high oxygen measurements and between each of the high oxygen measurements was 10 minutes.

The values of TL<sub>CO</sub> at standard and high oxygen concentrations, with their corresponding  $\theta$  values were used to determine D<sub>M</sub> and V<sub>C</sub> by solving the Roughton and Forster equation graphically (fig 1); the intersect of the plotted line (AB) with  $1/TL_{CO}$  equals  $1/D_M$ , and its slope (BC/AB) equals  $1/V_C$ . The values of  $\theta$  were derived from the original data of Roughton and Forster obtained from in vitro CO uptake in a suspension of human erythrocytes at 37°C.<sup>14</sup> The effect of haemoglobin variability on TL<sub>CO</sub> values was determined using the modified Roughton and Forster equation as described by Cotes (equation 2).<sup>16</sup> Haemoglobin concentration in patients was determined on the same day of TL<sub>CO</sub> measurement using venous blood samples. Normal subjects were assumed to have normal haemoglobin concentration (that is, 146 g/l).<sup>15</sup>

#### DATA PRESENTATION AND ANALYSIS

TL<sub>CO</sub> and its components were expressed as percentages of predicted using the European Community for Steel and Coal equations for TL<sub>CO</sub><sup>15</sup> and the reference values of Cotes for D<sub>M</sub> and V<sub>C</sub>.<sup>19</sup> The total resistance to CO transfer ( $1/TL_{CO}$ ) and its components ( $1/D_M$  and  $1/\theta V_C$ ) were expressed in absolute values (Pa.min<sup>-1</sup>.mmol<sup>-1</sup>). Unless stated otherwise, values were presented as mean with standard error of the mean (SEM). Comparisons between the two groups (heart transplant candidates and normal controls) and between the

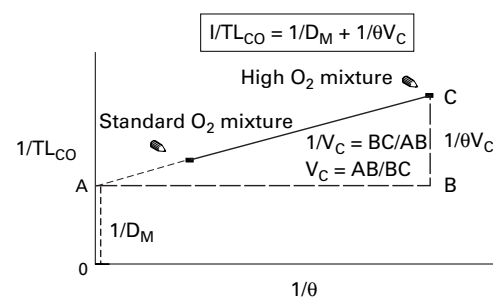


Figure 1 The graphical derivation of TL<sub>CO</sub> components (D<sub>M</sub> and V<sub>C</sub>) using the Roughton and Forster equation: a plot of  $1/TL_{CO}$  against  $1/\theta$  yields a straight line which intersects the ordinate  $1/TL_{CO}$  at point A. At this point, the value of  $1/\theta$  equals zero and therefore the value of  $1/TL_{CO}$  at point A equals  $1/D_M$ . The triangular area above the intersection represents a plot of  $1/\theta V_C$  against  $1/\theta$ .  $V_C$  can therefore be obtained by dividing  $1/\theta V_C$  by  $1/\theta$  (that is,  $1/V_C = BC/AB$ ), which is the slope of the line AC.

Table 1 Clinical characteristics of heart transplant candidates compared with normal controls

	Candidates	Normal
Number of subjects	38	26
Age; mean in years (range)	50.6 (34 to 61)	47.3 (27 to 62)
Sex		
Male	30 (79%)	20 (77%)
Female	8 (21%)	6 (23%)
Smoking status		
Non-smokers	10 (26%)	21 (81%)
Ex-smokers (for more than one year)	28 (74%)	5 (19%)
Diagnosis		
Ischaemic heart disease	25 (66%)	
Dilated cardiomyopathy	10 (26%)	
Valvar heart disease	3 (8%)	
Haemoglobin (g/l) (mean (range))	140 (119 to 173)	
LVEF (mean (range))	12.8 (6% to 26%)	
Lung function (mean % predicted (SEM))		
FVC	91.6 (2.3)	102.9 (2.1)*
FEV <sub>1</sub>	90.1 (2.2)	105.2 (3.9)*
FEV <sub>1</sub> /FVC	93.1 (1.4)	98.6 (1.8)*
TLC	91.4 (1.9)	100.2 (3.3)*

\*Denotes significant difference between the two groups;  $p < 0.05$ .

LVEF, left ventricular ejection fraction; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in the first second; TLC, total lung capacity.

subgroups of heart candidates (non-smokers and ex-smokers) were performed using the non-paired samples Student *t* test. Comparison between TL<sub>CO</sub> results before and after correction for haemoglobin in heart transplant candidates was performed using the paired samples Student *t* test.

## Results

### SUBJECTS' CHARACTERISTICS

Table 1 shows the clinical characteristics of the study groups, including lung function results. Both heart transplant candidates and normal controls had similar age and sex distribution, but they had different smoking status with significantly more ex-smokers among candidates. Because of the selection criteria, the duration between smoking cessation and assessment was at least one year in all ex-smokers (mean 3.6, range 1 to 24 years). All heart transplant candidates had severe chronic heart failure (mean left ventricular ejection fraction 12.8, range 6% to 26%). Although lung function variables (FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and TLC) were within normal limits for all subjects (a selection criterion), the mean values were slightly reduced in heart transplant candidates compared with normal controls ( $p < 0.05$ ).

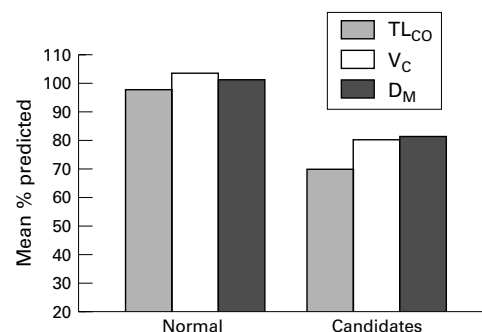


Figure 2 Pulmonary transfer factor for carbon monoxide (TL<sub>CO</sub>) and its components in heart transplant candidates compared with normal controls.

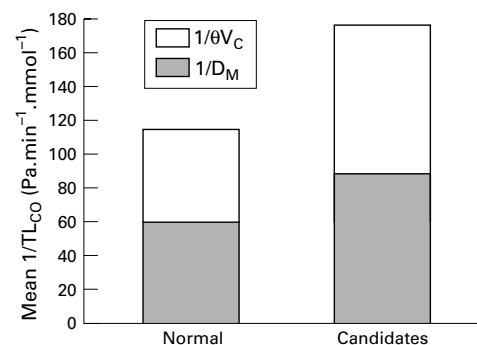


Figure 3 The total resistance to CO transfer (1/TL<sub>CO</sub>) and its components (1/D<sub>M</sub> and 1/θV<sub>C</sub>) in heart transplant candidates compared with normal controls

### TL<sub>CO</sub> AND ITS COMPONENTS IN HEART TRANSPLANT CANDIDATES COMPARED WITH NORMAL CONTROLS

Figure 2 shows TL<sub>CO</sub> and its components in heart transplant candidates compared with normal controls. Mean TL<sub>CO</sub> was significantly reduced in the heart transplant candidates (69.9 (2.0)% and 97.7 (1.6)% of predicted in candidates and controls, respectively,  $p < 0.001$ ). Similarly, D<sub>M</sub> and V<sub>C</sub> were significantly reduced in candidates (80.2 (4.2)% and 81.4 (5.4)% of predicted, respectively) compared with controls (100.0 (1.3)% and 102 (1.1)% of predicted, respectively;  $p < 0.001$ ).

Figure 3 displays the diffusion parameters in terms of their reciprocals (that is, resistance to diffusion) in the two study groups. Mean (SEM) total resistance to CO transfer (1/TL<sub>CO</sub>) was higher in heart transplant candidates than in normal controls (176.1 (8.6) v (113.9 (3.8) Pa.min<sup>-1</sup>.mmol<sup>-1</sup>,  $p < 0.001$ ). The increase in 1/TL<sub>CO</sub> in heart transplant candidates was due to a proportionate increase in both the alveolar-capillary membrane resistance (1/D<sub>M</sub>) and the intracapillary resistance (1/θV<sub>C</sub>), being 88.4 (6.3) and 87.7 (5.0) Pa.min<sup>-1</sup>.mmol<sup>-1</sup>, respectively, compared with 59.0 (1.0) and 54.9 (3.8) Pa.min<sup>-1</sup>.mmol<sup>-1</sup>, in normal subjects. 1/D<sub>M</sub> and 1/θV<sub>C</sub> contributed equally to 1/TL<sub>CO</sub> (approximately 50% each) in both normal subjects and heart transplant candidates.

Figure 4 shows scatter plots of per cent predicted TL<sub>CO</sub> against haemoglobin concentration in heart transplant candidates. Mean haemoglobin concentration in candidates was 140 g/l, and there was no correlation between per cent predicted TL<sub>CO</sub> and haemoglobin

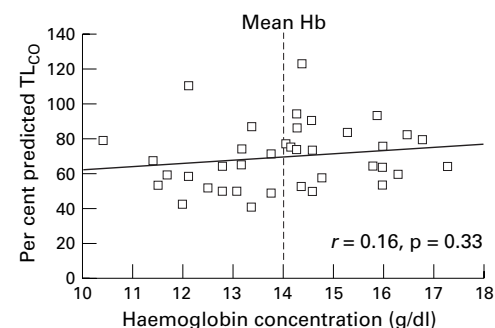


Figure 4 Scatter plots of per cent predicted pulmonary transfer factor for carbon monoxide (TL<sub>CO</sub>) against haemoglobin concentration in heart transplant candidates.

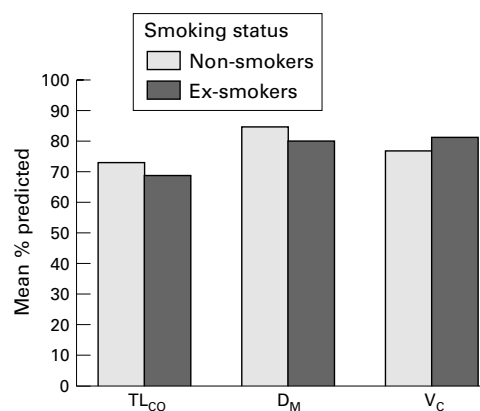


Figure 5 Pulmonary transfer factor for carbon monoxide (TL<sub>CO</sub>) and its components in heart transplant candidates subdivided in non-smokers (10 patients) and ex-smokers (28 patients). Differences between non-smokers and ex-smokers were not significant.

concentration in candidates ( $r = 0.16$ ,  $p = 0.33$ ). Correction for haemoglobin in heart transplant candidates produced no significant effect (69.9 (3.0)% *v* 71.1 (3.1)% of predicted,  $p = 0.09$ ).

The potential influence of previous history of smoking on TL<sub>CO</sub> and its components was assessed by dividing heart transplant candidates into two subgroups (non-smokers and ex-smokers). Figure 5 shows that there was no significant difference between the two subgroups in any of the diffusion parameters (mean TL<sub>CO</sub>, D<sub>M</sub>, and V<sub>C</sub> values were, respectively, 72.1 (4.1)%, 83.7 (8.7)%, and 78.5 (5.3)% in non-smokers and 69.2 (3.8)%, 80.7 (8.0)%, and 80.2 (5.4)% in ex-smokers (per cent of predicted)).

## Discussion

### TL<sub>CO</sub> AND ITS COMPONENTS IN HEART TRANSPLANT CANDIDATES

The results of this study represent the first report on the changes in TL<sub>CO</sub> components in heart transplant candidates. In addition to confirming TL<sub>CO</sub> impairment in these patients, it was shown that this impairment was due to a proportionate reduction in both of its components (D<sub>M</sub> and V<sub>C</sub>). The lack of any effect for haemoglobin concentrations on TL<sub>CO</sub> values is a reflection of their relatively normal haemoglobin concentration.<sup>16</sup>

In the only study of TL<sub>CO</sub> components in patients with chronic congestive heart failure, Puri and associates<sup>6</sup> reported that impairment of TL<sub>CO</sub> was common in patients with chronic heart failure and was primarily caused by a reduction in D<sub>M</sub>, V<sub>C</sub> being normal. The apparent discrepancy between those results and ours probably reflects the difference in the severity of heart failure. In the study of Puri *et al*, patients had mild to moderately severe chronic heart failure (NYHA classes II and III) and a mean left ventricular ejection fraction (LVEF) of 33%, whereas our patients, who were awaiting heart transplantation, had severe long standing heart failure (mean LVEF = 12.8%). In patients with mitral stenosis, D<sub>M</sub> has been shown to decline progressively with increasing severity of the disease.<sup>20</sup> In contrast, V<sub>C</sub> has a

biphasic relation with disease severity.<sup>20</sup> In mild to moderately severe mitral stenosis, V<sub>C</sub> is usually normal and may even be increased, whereas in severe cases it is reduced.<sup>21 22</sup>

### MECHANISMS OF PULMONARY CAPILLARY BLOOD REDUCTION IN HEART TRANSPLANT CANDIDATES

The volume of the pulmonary capillary blood at any instant (V<sub>C</sub>) depends on the number and dimensions of functioning pulmonary capillaries.<sup>21</sup> The mechanisms by which the size of the pulmonary capillary bed is increased are not fully understood, but experimental and clinical studies suggest that this is caused by increases in pulmonary blood flow or pulmonary capillary transmural pressure, the transmural capillary pressure appearing to be more important than the pulmonary blood flow.<sup>23</sup> These haemodynamic factors are believed to increase the size and uniformity of the pulmonary capillary bed by vascular recruitment and distension.<sup>23</sup> Therefore in any condition in which pulmonary capillary transmural pressure or the pulmonary blood flow is increased (for example, exercise, congenital heart disease with left to right shunts, and the early stages of mitral stenosis and congestive heart failure), V<sub>C</sub> would be expected to be higher than normal.<sup>21</sup> Under these circumstances, a normal or reduced V<sub>C</sub> would suggest derangement of the pulmonary vascular bed.<sup>21</sup> The present study did not investigate the direct relation between TL<sub>CO</sub> components and pulmonary haemodynamics. However, previous reports on the relation of TL<sub>CO</sub> in general and V<sub>C</sub> in particular to pulmonary haemodynamics in patients with congenital and valvar heart diseases suggest an important role for the changes in pulmonary haemodynamics in heart transplant candidates. Congenital heart diseases which result in pulmonary vascular congestion and increased pulmonary blood flow without significant pulmonary arterial hypertension are associated with increased values of TL<sub>CO</sub> and its components, with V<sub>C</sub> increasing relatively more than D<sub>M</sub>.<sup>24 25</sup> However, if pulmonary arterial hypertension or pulmonary vascular resistance is severe, these variables are usually normal or reduced.<sup>24</sup> Surgical correction of the congenital defects results in restoration of the pulmonary haemodynamics towards normal and this is associated with reduction in TL<sub>CO</sub> and its components.<sup>25</sup> TL<sub>CO</sub> in mitral valve disease has also been shown to be related to severity of pulmonary vascular resistance and pressures.<sup>22</sup> In moderately severe mitral stenosis, the increase in pulmonary venous pressure would be expected to increase V<sub>C</sub> by expanding and increasing the uniformity of the pulmonary vascular bed. However, V<sub>C</sub> is usually normal or even reduced in these cases.<sup>20</sup> This had been explained by an opposite force which counterbalances the augmenting effect of pulmonary congestion; namely, the obliteration of the pulmonary vascular bed by progressive fibrosis and repeated pulmonary emboli which are common in severe long standing mitral stenosis.<sup>22 26</sup>

Like patients with mitral valve disease, V<sub>C</sub> in patients with severe chronic heart failure

awaiting heart transplantation is determined by two factors acting in opposite directions, the increased pulmonary venous pressure tending to increase it and the pulmonary oedema and pulmonary hypertension and fibrosis tending to decrease it. Pulmonary hypertension, oedema and fibrosis will also lead to progressive decline in  $D_M$ . The finding of equally reduced  $D_M$  and  $V_C$  in our heart transplant candidates is similar to the findings in patients with severe mitral stenosis, suggesting that these patients have significant pulmonary parenchymal and vascular abnormalities which may not be completely reversible after transplantation.

Cigarette smoking can reduce  $TL_{CO}$  and its components by two mechanisms, the first methodological and the second by causing lung damage.<sup>27</sup> With respect to methodology, the effective driving pressure for gas transfer across the alveolar-capillary membrane is the difference between the alveolar partial pressure of the gas and its partial pressure in the pulmonary capillaries.<sup>16</sup> In the measurement of  $TL_{CO}$  and its components, the pulmonary capillary partial pressure of carbon monoxide is assumed to be zero.<sup>16</sup> In heavy smokers, the pulmonary capillary partial pressure for carbon monoxide and the carboxyhaemoglobin are increased, and this can lead to underestimation of  $TL_{CO}$ .<sup>15 16</sup> Smoking related lung damage is exemplified by chronic obstructive pulmonary disease, which is often associated with  $TL_{CO}$  reduction. Smoking has also been shown to reduce  $TL_{CO}$  in asymptomatic subjects who had normal airway function, but this reduction was reversible within one year of smoking cessation.<sup>27</sup> In our study, all subjects had normal airway function and all ex-smokers had stopped smoking for at least one year before assessment. In addition, there was no difference between candidates with a previous history of smoking and those without in any of the diffusion parameters. The history of previous smoking in our patients is therefore unlikely to have been a significant factor in the observed reduction in  $TL_{CO}$  and its components.

In conclusion,  $TL_{CO}$  reduction in patients with severe chronic heart failure awaiting heart transplantation is caused by a proportionate reduction in both its components ( $D_M$  and  $V_C$ ), suggesting a significant disturbance of the pulmonary vascular bed.

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