

## Respiratory dysfunction in congestive heart failure: correction after heart transplantation

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**ABSTRACT:** Severe chronic congestive heart failure (CCHF) is known to induce a restrictive ventilatory defect, with a small decrease in lung transfer factor for carbon monoxide (TLCO). The aim of the present work was to assess the reversibility of this dysfunction.

We studied a group of 47 patients with CCHF, before and one year after heart transplantation. The measurements included static and dynamic lung volumes, TLCO and cardiac function.

On initial evaluation, vital capacity (VC), total lung capacity (TLC) and TLCO were reduced to 76, 79 and 64% of the predicted value (% pred), respectively. Forced expiratory volume in one second (FEV<sub>1</sub>) was decreased to 69% pred, with a FEV<sub>1</sub>/VC ratio below 0.70 in 13 out of 47 patients. One year after transplantation, cardiac function had markedly improved, as shown by a normalized left ventricular ejection fraction (from 18% preoperatively to 59% postoperatively), and mean pulmonary wedge pressure (from 26 to 12 mmHg). At this time, VC (94% pred) and TLC (98% pred) were within the normal range, whereas TLCO remained low (67% pred). The FEV<sub>1</sub>/VC ratio did not change, even in the subgroup with an initial low value. Smoking habits did contribute to the low TLCO and FEV<sub>1</sub>/VC ratio.

In conclusion, respiratory dysfunction induced by CCHF is reversible, with the exception of the reduction in TLCO, which probably reflects permanent changes in the lung vasculature. CCHF does not induce an obstructive ventilatory pattern.

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Although the effects of chronic congestive heart failure (CCHF) on respiratory function have long been debated, information on the serial changes induced by therapy has remained limited, until recently. Measuring lung volumes in 12 patients with severe CCHF at a time of exacerbation of dyspnoea and 5-15 days after increased diuretics, Pison *et al.* [1] found an increase in vital capacity (VC) from 85 to 95% predicted (pred), and in forced expiratory volume in one second (FEV<sub>1</sub>) from 70 to 78% pred. A similar improvement in lung volumes also occurred in patients with mitral stenosis [2] within one week after percutaneous transvenous mitral commissurotomy, a procedure which is able to suddenly normalize the left atrial pressure [3]. However, the carbon monoxide lung transfer factor (TLCO) decreased from 105 to 96% pred in these patients.

In patients with mitral and/or aortic valve disease [4] corrected by valve replacement, there was a decrease in VC and TLCO 10 weeks postoperatively, which, however, subsequently improved over time so that by the 25th week, VC had returned to its initial value in the aortic group and had even overpassed the preoperative value in the mitral group. Such results suggest that the beneficial haemodynamic changes obtained after surgery can be, at least transiently, counterbalanced by the surgical

procedure itself. The negative effects on lung function of sternotomy and extracorporeal circulation are, however, well established in patients undergoing coronary artery bypass grafting [5-7].

In view of the above data, it is difficult to predict to what extent heart transplantation could correct the respiratory dysfunction due to CCHF. Both CASAN *et al.* [8] and HOSENFUD *et al.* [9] reported an incomplete correction of lung volumes, whereas TLCO was found to decrease from 83 to 69% pred, 4-14 months after transplantation [8].

The present study was, therefore, performed to further assess the precise effect of heart transplantation on various indices of lung function, and to correlate the magnitude of the changes observed with the extent of haemodynamic improvement. We have, thus, retrospectively studied lung function and haemodynamic data in a large group of patients, before and one year after heart transplantation.

### Patients and methods

The population retrospectively studied included 47 patients (42 males and 5 females), who underwent heart transplantation between 1984-1988. These patients were 17-63 yrs of age (mean 49 yrs) at the time that they

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were referred to our hospital with severe congestive heart failure, graded as either class III or IV disease according to the New York Heart Association (NYHA) classification. All were receiving maximal medical therapy and were felt, by the referring cardiologist, to be in a state of compensated CCHF. Only 10 subjects had a whole clinical course lasting less than one year. Table 1 divides the patients according to the aetiology of heart disease; as can be seen, in a large majority, the initiating mechanisms were either coronary artery disease or unknown ("idiopathic"). It is worth emphasizing that only 12 of the subjects had never smoked. Thus, the majority of them were either exsmokers (n=17) or still smoked (n=18) at the time they were admitted for evaluation before transplantation. Only two, however, continued their smoking habit after transplantation.

Table 1. - Initiating mechanism of congestive heart failure

	n
Ischaemic cardiomyopathy	25
Idiopathic cardiomyopathy	17
Valvular disease	2
Alcoholic cardiomyopathy	1
Toxic cardiomyopathy	1
Post-partum cardiomyopathy	1

Heart transplantation was performed 0-322 days (mean 45 days) after acceptance into the transplantation programme. As part of the initial evaluation before transplantation, all patients underwent conventional pulmonary function tests and right heart catheterization. Lung function measurements were repeated as part of the standard follow-up protocol one year after the surgical procedure in the whole group, whereas catheterization was repeated in only 33 of the 47 patients.

Haemodynamic data were obtained conventionally, including measurements of pulmonary artery pressure (Ppa), wedge pressure (Ppw), and cardiac output (CO) by thermodilution. In addition, left ventricular ejection fraction (LVEF) was also measured by radionuclide angiography, following intravenous injection of technetium-99m.

All lung volume measurements were carried out with the patients seated in a constant volume body plethysmograph (Jaeger, Würzburg, Germany). Each measurement of the functional residual capacity was followed by a complete expiration to the residual volume (RV) level, a maximal inspiration (VC) to the total lung capacity (TLC) level, and a forced expiration during which (FEV<sub>1</sub>) was determined. During these manoeuvres, flow was measured at the mouth with a Lilly type pneumotachograph. At least three series of measurements were performed. Results were expressed as absolute volumes and as percentage of predicted, calculated from the reference values given by QUANER [10]. The lung transfer factor for carbon monoxide (TLCO) was determined by single-breath method, using a Jaeger® diffusion test, the effective alveolar volume (VA) being calculated from the helium dilution observed during the manoeuvre. Since there was considerable

variation in the haemoglobin concentration between patients and over time, TLCO was normalized to a standard haemoglobin value [11].

It is important to stress that, both at the initial evaluation and one year after transplantation, the haemodynamic and lung function measurements were performed within a short period of time. Indeed, the mean time between the two assessments never exceeded a few days.

### Statistics

We used paired Student's t-test to assess whether heart transplantation was associated with changes in lung function tests and haemodynamic measurements, and unpaired t-test to compare subgroups of patients. The Kruskal-Wallis analysis was used to correlate smoking status (nonsmoker, ex-smoker, current smoker) with the pre-transplantation pulmonary function results. Unless otherwise stated, data are presented as mean±SD, and the criterion for statistical significance was taken as p<0.05.

### Results

#### Haemodynamic and lung function characteristics before transplantation

In most patients, haemodynamic measurements clearly indicated severe congestive heart failure, Ppw exceeding 20 mmHg in 39 out of 47 subjects (table 2). Ppa and

Table 2. - Changes in haemodynamic measurements and pulmonary function with heart transplantation

	Preoperatively	1 year postoperatively	
Ppa mmHg	36±8	20±7	**
Ppw mmHg	26±8	12±6	**
CI l·min <sup>-1</sup> ·m <sup>-2</sup>	2.23±0.64	2.87±0.55	**
PVR mmHg·l <sup>-1</sup> ·min	2.97±1.56	1.65±0.74	**
LVEF %	18±9	59±13	**
VC l	3.15±0.86	3.99±0.87	**
% pred	75±18	94±14	
TLC l	5.19±1.15	6.43±1.97	**
% pred	79±16	98±14	
FEV <sub>1</sub> l	2.37±0.81	2.90±0.84	**
% pred	69±20	83±18	
FEV <sub>1</sub> /VC %	75±12	72±11	**
% pred	95±15	92±13	
TLCO mmol·min <sup>-1</sup> ·kPa <sup>-1</sup>	6.57±2.01	7.00±2.01	NS
% pred	64±16	67±18	
Kco mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> ·l <sup>-1</sup>	1.27±0.27	1.19±0.21	*
% pred	65±13	58±9	

Data are presented as mean±SD. \*\*: p<0.001; \*: p<0.05; NS: nonsignificant. Ppa: mean pulmonary artery pressure; Ppw: mean wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance; LVEF: left ventricular ejection fraction; VC: vital capacity; TLC: total lung capacity; FEV<sub>1</sub>: forced expiratory volume in one second; TLCO: transfer factor of the lungs for carbon monoxide; Kco: carbon monoxide transfer coefficient.



pulmonary vascular resistance (PVR) were also substantially increased (however, no patient had severe irreversible pulmonary hypertension), and cardiac index was considerably lowered. Left ventricular ejection fraction, as assessed by technetium ventriculography, averaged only 18% before transplantation.

For the group as a whole, TLC and VC averaged  $79 \pm 16$  and  $76 \pm 18\%$  of the predicted value, respectively (table 2). On the average,  $FEV_1$  was also diminished to  $69 \pm 20\%$  of predicted. Even if the  $FEV_1$  decrease was somewhat larger than the average reduction in VC, the  $FEV_1/VC$  ratio remained largely within normal limits. In 13 (28%) of the patients, however, the  $FEV_1/VC$  ratio was below 0.70 (mean  $FEV_1/VC$   $58 \pm 8\%$ ; range 41–67%).

Tlco was frequently altered, with a mean corrected value of  $6.57 \pm 2.01$  mmol·min<sup>-1</sup>·kPa<sup>-1</sup>. Transfer coefficient (Kco) was similarly reduced; being lower than 75% of predicted in two thirds of the patients and, for the whole group, it amounted to 64% predicted.

#### Factors influencing pretransplant lung function tests

**Severity and duration of heart disease.** There was no relationship between the degree of transfer factor impairment and the severity of heart failure, whether the latter was assessed by the decrease in cardiac index and left ventricular ejection fraction or by the increase in Ppa and Ppw.

When the same indices of heart failure were analysed to assess their potential relationship to alterations in TLC, VC,  $FEV_1$ , or  $FEV_1/VC$  ratio, the only significant relationship was found between the reduction in VC and decreased cardiac index ( $r=0.40$ ;  $p<0.05$ ).

The effect of heart disease duration on the extent of the ventilatory restrictive defect was also analysed in the group of 34 patients who did not show an obstructive type of defect. Among them, the 10 patients with a short clinical history (less than 1 yr) had a mean predicted VC of  $82 \pm 14\%$ , whereas the corresponding value for the 24 subjects with a long-lasting heart disease was  $70 \pm 17\%$ . This difference, however, failed to reach the level of significance ( $p=0.06$ ).

**Smoking status.** No relationship was found between the smoking habits and TLC or VC. In contrast, smoking was

Table 3. — Effect of smoking status on preoperative pulmonary lung function

	Smoking status			
	Current	Former	Lifetime non	
Patients n	18	17	12	
Age yrs	$50 \pm 8$	$53 \pm 7$	$42 \pm 14$	NS
$FEV_1/VC$ %	$69 \pm 15$	$77 \pm 7$	$80 \pm 12$	*
Tlco mmol·min <sup>-1</sup> ·kPa <sup>-1</sup>	$6.16 \pm 2.18$	$6.53 \pm 1.67$	$6.57 \pm 2.35$	NS
Kco mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> ·l <sup>-1</sup>	$1.17 \pm 0.17$	$1.27 \pm 0.23$	$1.57 \pm 0.34$	**

Data are presented as mean  $\pm$  SD. \*:  $p<0.05$ ; \*\*:  $p<0.005$ ; NS: nonsignificant. For abbreviations see legend to table 2.

significantly related to the degree of airflow obstruction ( $p<0.05$ ), and to the extent of transfer factor impairment ( $p<0.005$ ) (table 3). Indeed, whereas the mean  $FEV_1/VC$  ratio and Kco of the 12 patients who never smoked were 99 and 72% predicted, respectively, the corresponding values in current smokers only amounted to 88 and 60% predicted, respectively.

**Effect of heart transplantation.** On assessment one year after transplantation, cardiac function had greatly improved (table 2).

The lung function data in the group as a whole are given in table 2, whereas figure 1 gives the results for each of the subgroups of patients categorized according to smoking status. As can be seen, heart transplantation was associated with a marked increase in lung volumes. Indeed, the rise in TLC and VC with transplantation was significant in each of the three subgroups of patients ( $p<0.001$ ) and, for the group as a whole, both the increments in predicted VC and TLC amounted to 19% ( $p<0.001$  for both); as a result, the restrictive type of ventilatory defect which was observed before the surgical procedure was no longer present. In each of the subgroups, there was also a significant increase in  $FEV_1$  after transplantation ( $p<0.001$ ). For the group of 47 patients, the rise in  $FEV_1$ , expressed as predicted value, amounted to 14% ( $p<0.001$ ).

The lower panel of figure 1 illustrates the effect of transplantation on the  $FEV_1/VC$  data for each of the three

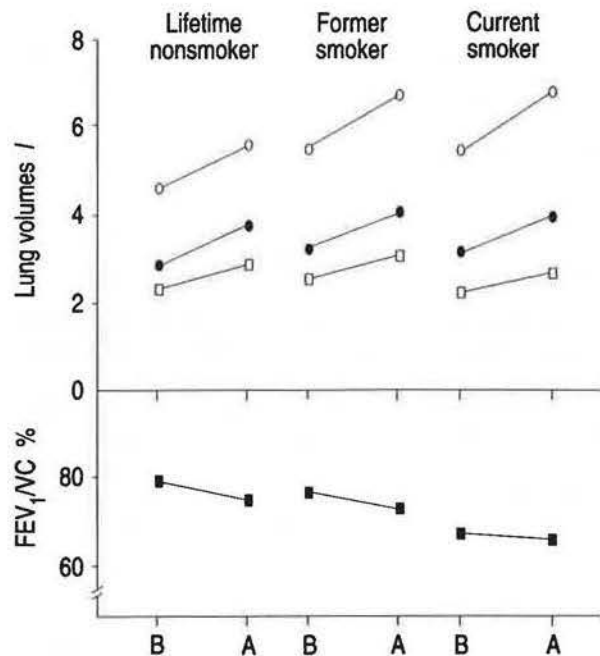


Fig. 1. — Effect of heart transplantation on TLC, VC and  $FEV_1$  (upper panel); and  $FEV_1/VC$  ratio (lower panel), in each of the subgroups of patients categorized according to smoking status lifetime non, former or current smokers). Mean absolute values are shown. —○—: total lung capacity (TLC); —●—: vital capacity (VC); —□—: forced expiratory volume in one second ( $FEV_1$ ); —■—:  $FEV_1/VC$  ratio; B: before; A: after.



subgroups. As already stated, smoking status significantly affected the pretransplant  $FEV_1/VC$  ratio, with the lowest value measured in the group of current smokers. With transplantation, there was a trend toward a decrease in this ratio in each subgroup, which reached the level of significance only in the group of patients who had never smoked ( $p < 0.05$ ). For the group of 47 patients as a whole, the  $FEV_1/VC$  ratio was slightly reduced, even though it remained largely within normal limits (table 2). Figure 2 shows the effect of transplantation on the obstructive ventilatory defect ( $FEV_1/VC$  ratio  $< 0.70$ ) that was initially present in 13 of the patients and persisted in 10 patients after treatment.

As shown in table 2, for the whole group, there was a slight but nonsignificant improvement ( $p = 0.14$ ) in  $TLCO$  with transplantation, whereas  $KCO$  decreased slightly.

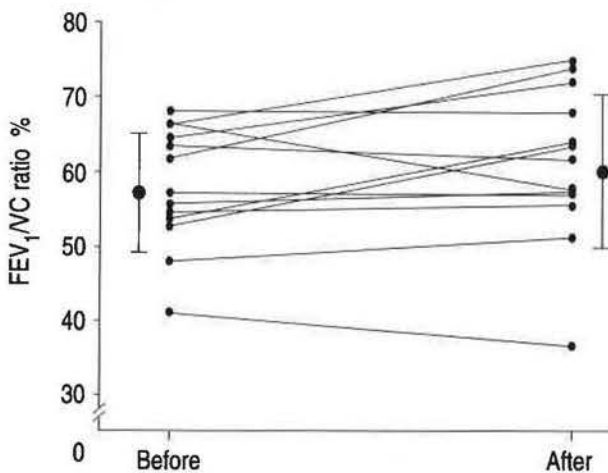


Fig. 2. —  $FEV_1/VC$  ratio before and one year after transplantation in the 13 patients who, on initial evaluation, showed an  $FEV_1/VC$  ratio below 0.7. Individual data are illustrated as well as mean  $\pm$  SD values. For abbreviations see legend to figure 1.

### Discussion

The main results of the present study can be summarized as follows: 1) patients with CCHF exhibit a restrictive ventilatory defect which is corrected after successful heart transplantation; 2) the obstructive ventilatory pattern found in some patients does persist after transplantation; in fact, it is more closely linked to smoking habits than to heart failure; and 3) the CO transfer defect observed in our population does not improve after transplantation, despite the increase in lung volumes.

The finding of a slight restrictive ventilatory defect (decrease in VC and TLC) before transplantation is in agreement with several recently published shorter series of patients, with a similar degree of chronic congestive heart failure not due to valvular heart disease [1, 8, 9, 12–19]. Our postoperative results confirm that static lung volumes return to the normal range after post-transplantation correction of the haemodynamic status at rest [8, 9, 16, 19].

In the present study, there is no close relationship between the haemodynamic data and the lung volume

changes. Previous workers [20, 21] reported a weak correlation between the increase in pulmonary pressure and the decrease in vital capacity. However, they included patients with normal pulmonary pressures; if we exclude these patients, the correlation disappears. On the other hand, HOSENPUD *et al.* [9] found that the post-transplantation increase in forced vital capacity was closely related to the reduction in heart volume. Unfortunately, in the present retrospective study, we were not able to analyse enough preoperative chest X-rays to confirm their data. Patients with chronic heart disease also suffer from respiratory muscle weakness [18, 22, 23], as part of a generalized skeletal muscle dysfunction, which can be corrected after adequate therapy of heart failure and physical training [24]. An improvement in respiratory muscles might contribute to the observed normalization of lung volumes.

Airway obstruction is also supposed to occur in patients with CCHF. In a recently published "State of the Art" paper, SNASHALL and CHUNG [25] write that: "Chronic heart failure is also associated with airway narrowing". However, if present, this airway narrowing is not reflected in a decrease in the  $FEV_1/VC$  ratio, which usually remains within the normal range in patients with CCHF [8, 9, 13–19]. Moreover, after transplantation and normalization of the haemodynamic status, our data and those of others [9, 16, 19] do not show any increase in the  $FEV_1/VC$  ratio. The obstructive ventilatory defect observed in a few patients with CCHF is best explained by a high prevalence of smoking habits, both in the present and in previous series [8, 9, 14, 16, 19]. It must be emphasized that none of the recent studies on patients with CCHF included tests supposed to be sensitive to peripheral airways dysfunction.

Whereas, for the changes in lung volumes measurements, a very consistent pattern is found in all of the published series, such is not the case for the single-breath CO lung transfer factor. Preoperatively, in agreement with others [14, 17, 26], we found a consistent decrease in  $TLCO$  and  $TLCO/VA$ . SIEGEL *et al.* [26] even showed a more severe decrease in  $TLCO$  in patients with crackles audible at the lung bases, than in those without. In other series, the decrease in absolute  $TLCO$  is less evident, so that the  $TLCO/VA$  ratio is normal [8, 16, 19]. The reason for these discrepancies is not evident. A difference in smoking habits between populations is possible; WRIGHT *et al.* [14] and ourselves found higher  $TLCO$  in lifetime non-smokers, compared to current or former smokers. Selection criteria also differ between studies: both GROEN *et al.* [16] and RAVENS-CRAFT *et al.* [19] obtained  $TLCO$  measurements in only a third of their heart transplant recipients. The results of postoperative measurements are, however, similar: there is a decrease in the  $TLCO/VA$  ratio [8, 16, 19, present study], with no consistent change [16, 19, present study], or even a decrease [8] in absolute  $TLCO$ . These rather negative postoperative changes in the lung diffusing properties are in contrast with the positive changes in the lung volumes described previously. Some authors hypothesize that continuous administration of cyclosporin could be responsible for subclinical alterations in pulmonary interstitium or pulmonary vessels [7,



16]. If it were so, we expect that this toxic effect would become more pronounced over time, which is not the case [16]. An alternative, more attractive, explanation is persistence of pulmonary vessel abnormalities after transplantation, a fact which is well-established after surgical correction of valvular heart disease [4].

In conclusion, lung dysfunction observed in patients with severe chronic congestive heart failure is largely corrected after heart transplantation. However the CO lung transfer factor remains altered, which probably indicates persistence of lung vessel abnormalities.

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