Eur Respir J 2000; 16: 482–485
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European Respiratory Journal
ISSN 0903-1936

Effect of preoperative hyperinflation on static lung volumes after lung transplantation

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ABSTRACT: It is still not known whether persistent increases in functional residual capacity (FRC) and residual volume (RV) after lung transplantation are due to pre-existing hyperinflation. Therefore, the aim of this study was to determine the effects of chronic lung hyperinflation on static lung volumes after heart/lung (HLT) and bilateral lung transplantation (BLT).

Static lung volumes were measured in 33 patients before and at 6 month intervals for up to 3 yrs after HLT (n=25) or BLT (n=8). The preoperative diagnosis was cystic fibrosis in 25 patients and other chronic hyperinflated lung diseases in eight patients.

After surgery, total lung capacity returned to predicted normal values but FRC and RV remained greater than expected for either the recipient or the donor. At 1 yr after surgery, mean±SD FRC and RV were 130±18% and 151±34% of the predicted values for the recipient ($p<0.001$), and these figures did not change significantly over time. Similar abnormalities were found in patients with and without cystic fibrosis.

After transplantation for lung diseases producing chronic hyperinflation, there is a persistent increase in functional residual capacity and residual volume. This alteration is present in patients operated on for diseases developed in both childhood and adulthood and is not recovered over time. It may be due to irreversible changes in the structure of the ribcage.

Eur Respir J 2000; 16: 482–485.

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Keywords: Chest wall
cystic fibrosis
hyperinfiation
lung transplantation

Received: November 25 1999
Accepted after revision April 14 2000

Two previous studies have reported that patients with cystic fibrosis (CF) demonstrate a persistent increase in functional residual capacity (FRC) and residual volume (RV) after lung transplantation [1, 2]. Because this alteration was not present in patients undergoing transplant for primary pulmonary hypertension [1], a causal relationship with the preoperative hyperinflation was suggested. However, interpretation of the results was made difficult by the very small number of patients studied and the fact that many of them were investigated in the early postoperative period. In addition, it is not known whether transplantation for hyperinflated lung diseases other than CF is associated with a similar increase in FRC and RV. The aims of the present studies were, therefore, to: 1) assess static lung volumes in a group of 25 CF patients before and for up to 3 yrs after surgery; and 2) compare these results with those obtained in patients transplanted for non-CF hyperinflated lung diseases.

Material and methods

Patients

Between August 1983 and June 1999, 84 heart/lung (HLTs) and 19 bilateral lung transplantations (BLTs) were performed in 103 patients at the Erasme University Hospital. Of these, 40 HLT and 12 BLT were performed for diseases which produced chronic hyperinflation, as defined by values of FRC, RV and RV/total lung capacity (TLC) that exceeded the 90% confidence interval of normal values [3]. The HLT procedures were performed *via* a median sternotomy and the BLT procedures *via* a transverse thoracotomy (clam shell incision). Fifteen patients were excluded because either their survival was <1 yr (n=12) or evidence of bronchiolitis obliterans syndrome (BOS) [4] was found before the end of the first postoperative year (n=3). Four additional patients were excluded because of diaphragm paralysis, pulmonary lymphoma and asthma. Thus, 33 patients (25 with HLT) who had given verbal informed consent to the procedures were included in the study. Transplantation was performed for CF in 25 patients, bronchiectasis in three, emphysema in three, histiocytosis X in one, and coal miner's pneumoconiosis in one. The study population consisted of 25 males and eight females who were 29.8±10.7 yrs of age at the time of transplantation. The induction immunosuppressive therapy consisted of antithymocyte globulin, azathioprine or mycophenolate mofetil, cyclosporin, and methylprednisolone and maintenance immunosuppression included azathioprine or mycophenolate mofetil, cyclosporin or tacrolimus, and methylprednisolone.

Methods

Measurements of vital capacity (VC), FRC, RV and TLC were obtained with the patient seated in a constant-volume body plethysmograph, and measurements of forced vital capacity (FVC), forced mid-expiratory flow, and forced expiratory volume in one second (FEV_1) were made using a Sensormedics 2400 Unit (Sensormedics, Anaheim, CA, USA) following the guidelines of the

American Thoracic Society [5]. FRC was measured at a breathing frequency of <1 Hz, and the reported values are the mean of at least three measurements that agreed to within ±5%. The largest inspiratory VC was used to calculate TLC and RV. Measurements that had been obtained within 1 yr before operation and at ~6-month intervals from surgery for up to the end of the third postoperative year were selected for analysis; for postoperative data, inclusion in the analysis was restricted to measurements that had been performed when the patients did not have any respiratory symptoms, were free of pulmonary infection and rejection, and had stable FEV_1 and normal chest radiographs. In addition, patients who showed irreversible decay in FEV_1 of >20% of the largest postoperative value were considered to have BOS [4]; in these patients, only data that pertained to the period preceding the diagnosis were included in the analysis.

Predicted values for lung volumes were derived from the European Coal and Steel Community Working Party [3] on the basis of the recipients′ anthropometric characteristics. Because these were (on average) similar to those of the donors, the predicted values for the recipients and donors were not significantly different. Statistical analysis was performed using analysis of variance for repeated measurements (lung volumes over time), a paired t-test for paired comparisons (age and height of recipients *versus* donors), and the Mann-Whitney U-test for unpaired comparisons (HLT *versus* BLT patients and CF *versus* non-CF patients). Correlation analysis using linear regression was performed between post- and preoperative lung volumes, and predicted volumes for the donor and recipient. A p-value of <0.05 was considered statistically significant. All data are reported as mean±SD.

Results

The median time of follow-up was 24 months and a total of 142 functional tests were analysed. Follow-up was available at 12 months in all 33 patients, at 24 months in 21, and at 36 months in 17. All patients demonstrated a favourable short-term outcome after transplantation and achieved normal FEV_1 (*i.e.* at the time of the last test included in the analysis, mean FEV_1 was 94.8±12.4% of the predicted value). However, two patients developed BOS and one died during the course of the study; data inclusion was limited to 12 months for the two patients with BOS and to 24 months for the latter patient. Finally, 10 patients had not reached the second anniversary of their transplant at the end of this study and three the third anniversary.

Figure 1 shows the mean TLC, FRC, RV and RV/TLC before and for up to 3 yrs after surgery in the 33 patients in the study. Before transplantation, there was a marked increase in FRC and RV and a moderate increase in TLC.

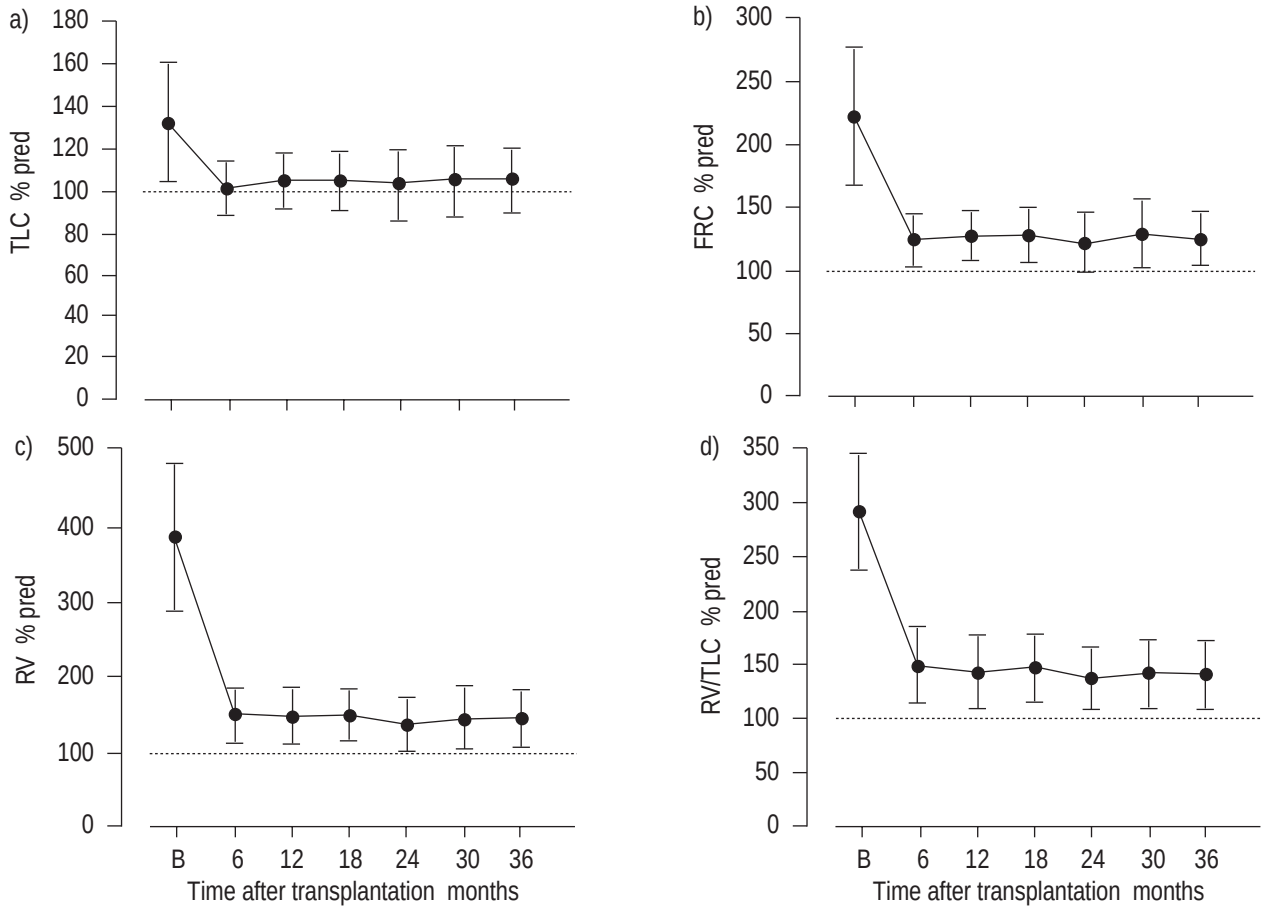

Fig. 1. – a) total lung capacity (TLC); b) functional residual capacity (FRC); c) residual volume (RV); and d) RV/TLC before (B) and at 6-month intervals after heart/lung or bilateral lung transplantation. Data are presented as mean±SD (n=33 at B and 6 and 12 months, n=21 at 18 and 24 months, and n=17 at 30 and 36 months). Predicted values are those of the recipient. Note that FRC, RV and RV/TLC remain greater than predicted after surgery.

Mean FRC, RV and TLC were 229±58, 399±105 and 135±29% pred, respectively, and the RV/TLC ratio was 292±42% pred. The degree of preoperative hyperinflation was not significantly different in patients with and without CF. Surgery caused a dramatic decrease in TLC (mean 103±11% pred) at the end of the first postoperative year. Conversely, although FRC and RV were also decreased after transplantation, these volumes remained significantly greater than predicted; at 1 yr after surgery, mean FRC and RV were 130±18 and 151±34% pred ($p<0.001$), respectively, and these values did not change significantly over time (figs. 1 and 2). Because TLC was within normal limits, the RV/TLC ratio increased to 147±31% pred at 1 yr after surgery ($p<0.001$). The degree of postoperative hyperinflation did not differ significantly according to either the preoperative diagnosis (CF *versus* non-CF diseases) or type of surgery (HLT *versus* BLT). TLC at 1 yr after surgery positively correlated with predicted values for the recipient ($r=0.80$, $p<0.001$) and donor ($r=0.74$, $p<0.001$), and with preoperative values ($r=0.54$, $p<0.01$). Corresponding values of r for FRC were 0.69 ($p<0.001$), 0.49 ($p<0.01$) and 0.45 ($p=0.01$), and for RV were 0.48 ($p<0.01$), 0.23 (NS) and 0.32 (NS).

Discussion

The present study confirms and expands the previous observation [1, 2] that patients with CF show a persistent increase in FRC and RV after lung transplantation throughout the three yrs after lung transplantation. Furthermore, the present data indicate that FRC and RV are similarly increased in patients operated on for hyperinflated lung diseases other than CF. Because the patients studied here were clinically stable and showed no functional evidence of airflow obstruction, the postoperative hyperinflation cannot be ascribed to chronic allograft rejection. Abnormalities in the elastic behaviour of the transplanted lung and weakness of the expiratory muscles are also unlikely to be involved [1, 2]. Finally, an effect of the median sternotomy [6] is excluded since patients undergoing HLT for primary pulmonary hypertension have normal postoperative lung volumes [1].

In a previous study, it was suggested that the persistent increase in FRC and RV originated in the chest wall [1]. This was supported by measurements of chest wall dimensions which showed that, compared to a group of matched normal subjects, CF patients who had received

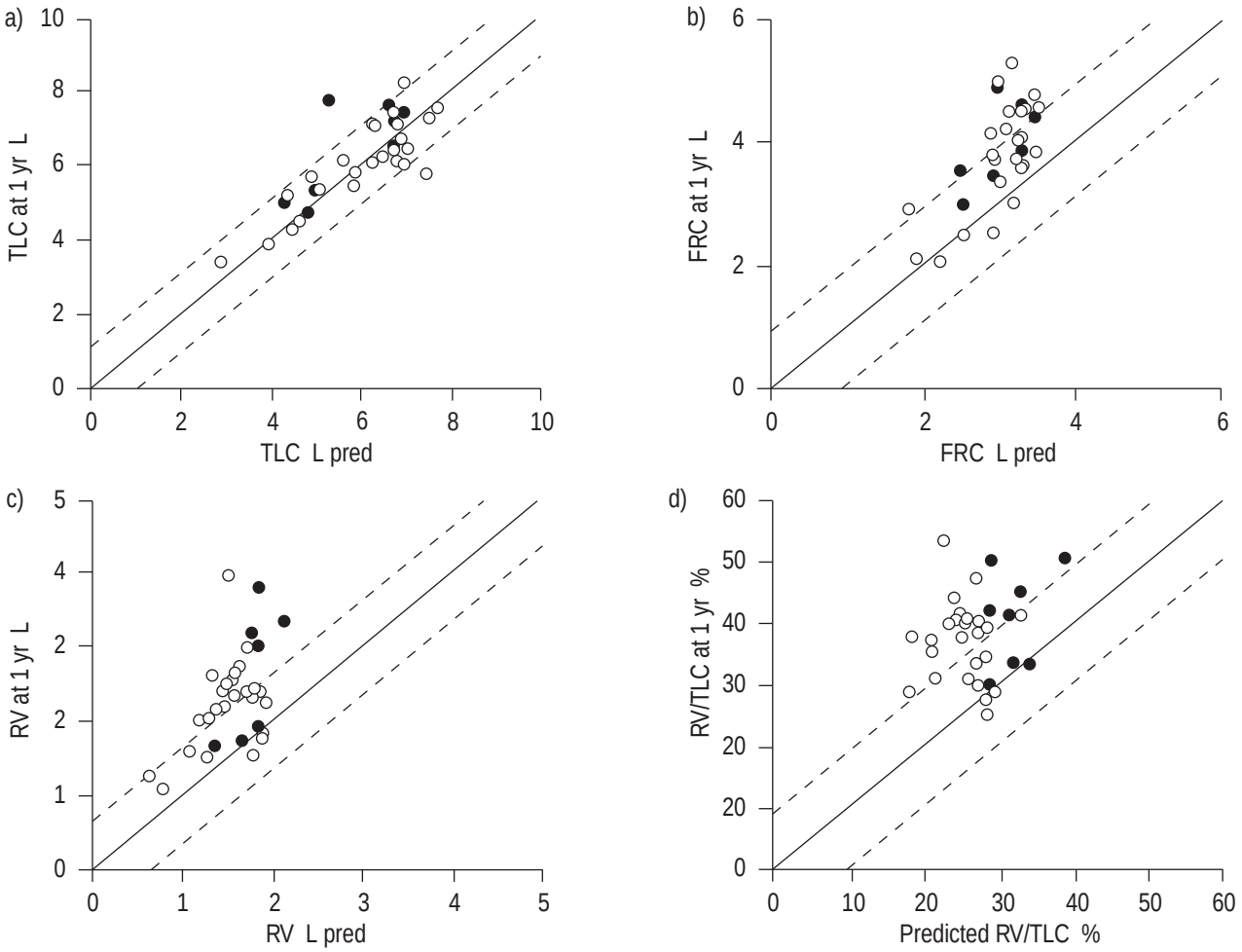

Fig. 2. – Individual values of: a) total lung capacity (TLC); b) functional residual capacity (FRC); c) residual volume (RV); and d) RV/TLC at 1 yrs after heart/lung or bilateral lung transplantation *versus* predicted values of recipients (n=33). ○: cystic fibrosis patients; ●: non-cystic fibrosis hyperinflated lung diseases patients. —— : line of identity; - - - - : 90% confidence interval of normal values [3]. L pred: predicted value in litres.

transplants demonstrated an increase in the anteroposterior diameter of the ribcage at FRC. A similar distortion of the ribcage towards a more circular shape is also present in patients with severe chronic obstructive pulmonary disease [7], and is associated with displacement of the static pressure/volume (PV) curve of the chest wall towards higher lung volumes [8]. Thus, an attractive hypothesis would be that chronic hyperinflation produces structural changes in the ribcage that persist, at least in part, after transplantation and displace the chest wall PV curve upwards. This displacement, in turn, would result in resetting of the balance between the unchanged inward recoil of the lungs and increased outward recoil of the chest wall with consequent increases in FRC and RV. The current observation that postoperative hyperinflation is found in both CF patients, who generally showed altered lung function in childhood, and patients with hyperinflated lung diseases which develop in adulthood indicates that remodelling of the ribcage does not have to occur during growth to be partly irreversible.

It was observed that, in contrast to FRC and RV, TLC was within normal limits after surgery in the present study, which is in agreement with the findings of TAMM *et al.* [9] and CHACON *et al.* [2]. This may suggest that the preoperative alterations in chest wall shape at TLC [7] did not persist after transplantation, or, more probably, that these alterations did not significantly affect the volume of the system at full inflation after surgery. This volume is set by the balance between the force generated by the inspiratory muscles and the inward recoil of the respiratory system. Since, at full inflation, this recoil originates primarily in the lungs, the increased outward chest wall recoil described above would not be expected to have a substantial effect on TLC. On this basis, the finding of postoperative values of TLC within normal limits can be understood.

In summary, functional residual capacity and residual volume show a persistent increase after lung transplantation for diseases which produce chronic hyperinflation. The authors postulate that this alteration is due to irreversible changes in the structure of the ribcage.

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