Ventilation Asymmetry after Transplantation for Emphysema

Role of Chest Wall and Mediastinum

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After single-lung transplantation for emphysema, the hyperinflated native lung and the graft have different extents and rates of inflation and emptying. This requires that breathing produces asymmetrical expansion of the chest wall, displacement of the mediastinum, or both. In a first study in four seated transplant recipients, we measured the volumes of the two hemithoraces with optoelectronic plethysmography. Functional residual capacity and total lung capacity were identical on the native and transplanted sides, and changes in chest wall volume during CO_2-induced hyperpnea and FVC maneuvers were similar on both sides. Studies with computerized tomography in three of these patients and in four additional patients in supine posture indicated that the mediastinum was shifted toward the graft at functional residual capacity and total lung capacity. The mediastinum moved toward the native lung during tidal and full inspiration and toward the graft during tidal and forced expiration; additional studies with fluoroscopy showed qualitatively similar changes in upright posture. In summary, the two hemithoraces assume identical static volumes and show similar volume changes during CO_2-induced hyperpnea and FVC maneuvers in patients with single-lung transplantation for emphysema; displacement of the mediastinum accommodates part, if not all, of the unequal lung volumes and asymmetrical ventilation.

Keywords: chest wall; emphysema; mediastinum; transplantation

In the early experience with single-lung transplantation (SLT) for emphysema, the occurrence of acute native lung hyperinflation and gross ventilation-perfusion mismatch in the early postoperative period raised serious concern as to whether the procedure was safe and physiologically feasible (1). However, the more recent experience has shown that this complication is in part related to early dysfunction of the graft—due to ischemia-reperfusion injury, acute rejection, or infection, and is neither inevitable nor insurmountable (2). Yet, from the physiologic point of view, the marked imbalance between the mechanical properties of the native lung and the graft results in a complex situation. We, and others, have shown that in stable patients, hyperinflation of the native lung is associated with a shift of the mediastinum toward the graft and a reduction in the volume of the graft at full inflation (3–6). These studies, however, did not investigate how the presence of two lungs with very different mechanical properties may impact on chest wall dynamics.

Inhalation studies have shown that ventilation is predominantly distributed to the graft, which has a much lower impedance than the native lung (6); for example, in a study of 13 patients with SLT for emphysema, ventilation scans obtained during quiet breathing after inhalation of ^{133}Xe indicated that the graft received about 80% of the inhaled isotope (7). Similarly, the expiratory flow–volume curve in such patients typically shows two phases, i.e., an initial high-flow phase originating from the graft followed by a low-flow phase coming from the native lung (6, 8, 9). This biphasic pattern reflects differences in expiratory volumes and time constants between the two lungs.

Imbalances in the extent and rate of inflation or emptying between the native and transplanted lungs can theoretically be accommodated by different changes in the volume of the two hemithoraces, by displacement of the mediastinum, or by a combination of both (10). More specifically, the larger inspiratory volume of the graft may be accommodated by both a larger expansion of the chest wall on the transplanted side and displacement of the mediastinum toward the native lung; conversely, the larger expiratory volume and the shorter expiratory time constant of the graft may be accommodated by both a larger and more rapid deflation of the chest wall on the transplanted side and displacement of the mediastinum toward the graft. The contribution of these mechanisms depends on the relative impedances of the mediastinum, diaphragm–abdomen, and rib cage boundaries to displacement and deformation.

We hypothesized that asymmetrical expansion of the chest wall and displacement of the mediastinum would both be involved. To test this hypothesis, we measured changes in the volume of the two hemithoraces and motion of mediastinum during forced expiration and CO_2-induced hyperpnea in eight patients with SLT for emphysema. The volume of the two sides of the chest wall was assessed using optoelectronic plethysmography, as recently reported by Lanini and colleagues (11), and displacement of the mediastinum was assessed using dynamic computerized tomography (CT). Some of the results of these studies have been previously reported in the form of an abstract (12).

METHODS

Patients

Eight patients with SLT for emphysema were studied (Table 1). They were all informed of the nature and extent of the study, as approved by the Human Studies Committee of the institution; one patient (Number 3) accepted to participate in Study 1, but not in Study 2.

Study 1

Changes in the volume of each hemithorax were measured during CO_2-induced hyperpnea and forced expiration in the four male patients in seated posture using optoelectronic plethysmography (ELITE; BTS, Milan, Italy) (11, 13–17). The 3-D coordinates of 83 markers applied to the chest wall (Figure 1A) were recorded as a function of time by two pairs of infrared charge-coupled device cameras; sampling frequency was 50 Hz. Airflow was recorded at the mouth with a Lilly

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TABLE 1. DETAILS OF TRANSPLANTED PATIENTS STUDIED

Patient No.	Sex	Age (*yr*)	Height (*cm*)	Weight (*kg*)	Side of Tx	FEV_1 (*% Pred*)	BOS Grade	Time Between Tx and Study (*yr*)
1	M	56	174	83	Right	55	1	10.2
2	M	61	176	56	Right	57	0	1.8
3	M	59	183	63	Right	55	0	1.7
4	M	60	167	65	Left	46	1	1.9
5	F	60	170	62	Left	53	0	0.5
6	F	52	151	39	Left	43	1	7.9
7	F	48	158	58	Right	55	1	7.4
8	F	57	163	57	Left	73	0	9.7

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; F = female; M = male; No. = number; Tx = transplantation.

type pneumotachograph and a Validyne differential pressure transducer (Validyne Corp., Northridge, CA), and end-tidal CO_2 partial pressure was monitored by an infrared CO_2 meter. After 15 seconds of quiet breathing, the patient inspired to total lung capacity (TLC) and performed a forced expiratory maneuver. For the CO_2-induced hyperpnea, the subject breathed through a rebreathing bag filled with 6–8 L of a mixture containing 7% of CO_2 balanced with O_2. Two FVC maneuvers and two runs of CO_2-induced hyperpnea were obtained in each patient.

The volumes of the chest wall on each side of the midsagittal plane were calculated (15). Changes in the volume of each hemithorax during the FVC maneuver and the CO_2-stimulated tidal breaths were displayed as x-axis (native)–y-axis (graft) plots. Potential differences in the magnitude of volume changes and in the rate of inflation or emptying between

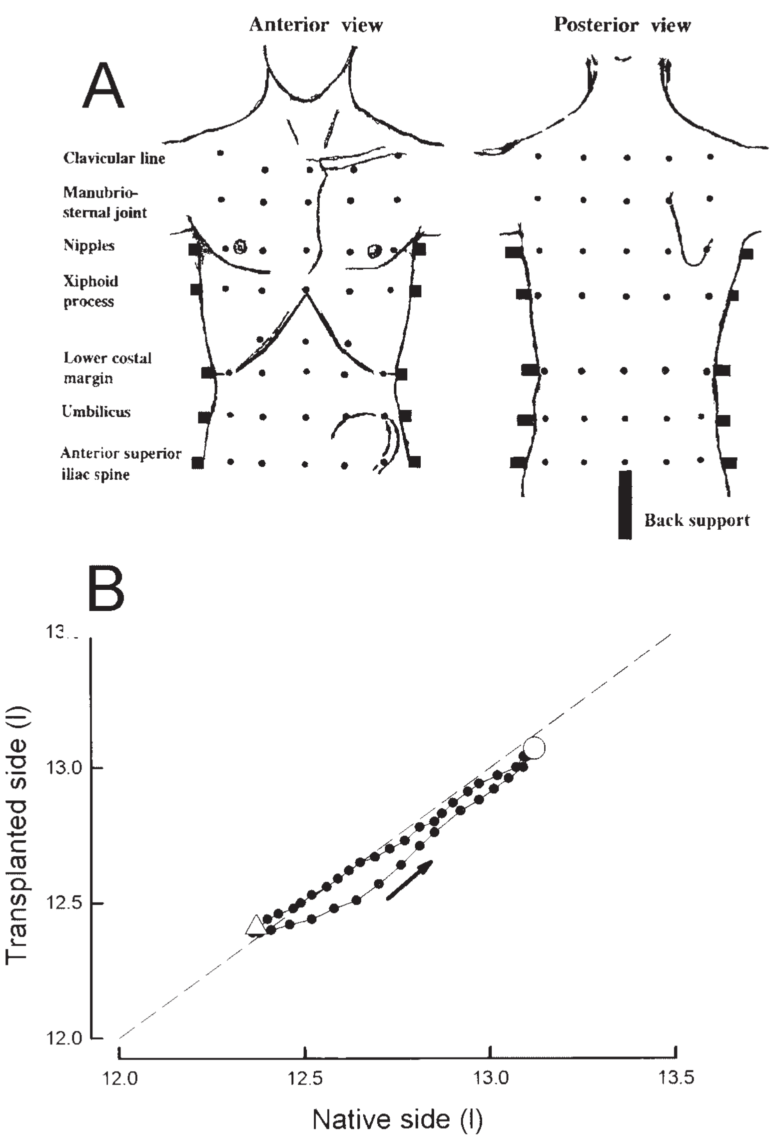

Figure 1. (*A*) Placement of reflective markers on the ventral (left) and dorsal (right) aspects of the chest wall. The markers were arranged in seven rows horizontally, five vertical rows anteriorly and posteriorly, and one vertical row bilaterally in the midaxillary line. (*B*) Changes in the volume of the hemithorax on the transplanted (*y-axis*) and the native (*x-axis*) sides during a CO_2-stimulated breath. The *open triangle* corresponds to end-expiration and the *open circle* to end-inspiration; the *arrow* indicates the inspiratory phase of the loop. The *dashed line* is the identity line. Note that the loop (*closed circles*) is almost superimposed to this line.

the native and transplanted hemithoraces were assessed by computing the slopes of the lines joining the end-expiratory and end-inspiratory points (Figure 1B) and the phase angle of the inspiratory–expiratory loop, respectively.

Study 2

Dynamic CT data were obtained using a commercially available Multidetector scanner (Somatom Plus Volume Zoom; Siemens Medical Systems, Forschheim, Germany). Dynamic real-time scans were obtained at mid-chest level during quiet breathing and during forced expiration using the C.A.R.E. Vision software (Siemens Medical Systems, Forschheim, Germany), which provides fluoroscopic scans at 6 frames/second. Four to six tidal breaths and two forced expirations were recorded. We measured the degree of mediastinal shift (Figure 2), and the transverse cross-sectional areas of the native lung and the graft on each scan (3, 5) in the seven patients, as well as in seven normal control subjects matched for age and sex.

In addition, the following studies were performed in four patients (No. 4–6, 8). First, the impact of the rate of inflation on mediastinal displacement was studied by having CT acquisitions made during a slow (~ 2.5 seconds) and a fast (~ 1 second) 1-L inspiration. Second, the effect of postoperative time on mediastinal displacement during forced expiration was assessed by repeating the CT acquisitions after a median time of 657 (range 169–711) days. Finally, the patients were studied in upright posture; displacement of the mediastinum during tidal breathing and forced expiration was assessed by fluoroscopy, and the degree of mediastinal shift between FRC and TLC was estimated on an anteroposterior chest X-ray.

RESULTS

Study 1

All four subjects performed the acquisitions satisfactorily. There was very good agreement between the volumes estimated by optoelectronic plethysmography and measured by the pneumotachograph. For the four subjects studied, values of inspiratory capacity obtained by the two techniques averaged 2.24 and 2.09 L, respectively. The slope and the intercept of the linear regressions relating values of CO_2-stimulated tidal volumes estimated by optoelectronic plethysmography and measured by the pneumotachograph averaged 0.98 and 0.026, respectively. Finally, analysis using the Bland and Altman test (18) indicated that the mean difference between tidal volumes obtained by the two techniques was 0.015 L, and limits of agreement were 0.191 and −0.161 L.

Results of the study are shown in Table 2. The volumes of the two hemithoraces were similar at both functional residual capacity and TLC. The slopes of the inspiratory–expiratory loops obtained during the FVC maneuver and CO_2-stimulated breaths were close to unity, indicating that the magnitudes of volume changes were similar on the native and transplanted sides. In addition, we found very low values of phase angle, which suggests that differences in the rate of inflation or emptying between the two hemithoraces were small.

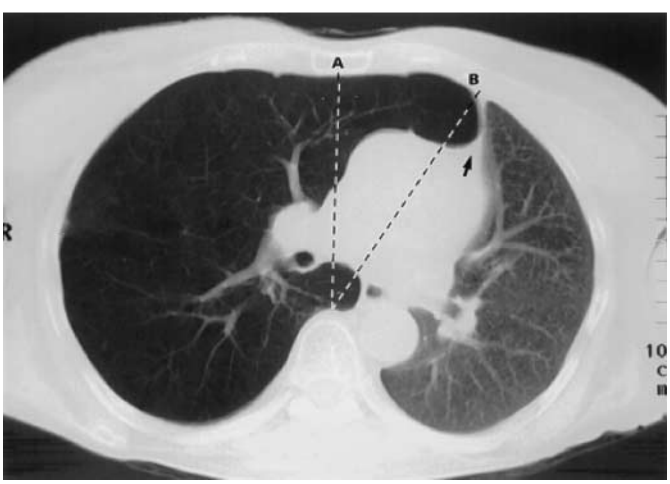

Figure 2. Representative transverse computerized tomography (CT) slice obtained during breath holding at FRC in a patient with a left transplant. *Arrow* indicates location of anterior mediastinal line. *Line A* is the midsagittal line, and *line B* was drawn from the vertebral body to the anterior mediastinal line; the degree of mediastinal shift was computed as the angle between lines A and B. Note the shift of the mediastinum toward the graft.

Study 2

The angle of mediastinal shift toward the graft in the seven patients in supine posture averaged 33.0 ± 12.4° at residual volume (RV) and 19.9 ± 8.9° at TLC ($p < 0.001$). In contrast, the mediastinum was very close to the midsagittal plane in the control subjects, and only four of these showed a slight (≤ 8°) shift toward the left lung; the angle of mediastinal shift averaged 3.2 ± 3.5° at RV and TLC. In the four patients with a left SLT who were studied upright, the aortic knob was 8.3 ± 3.8 mm closer to the midsagittal line at TLC than at FRC (*see* Figure E1 in the online supplement).

The in-room monitor invariably showed obvious motion of the mediastinum toward the native lung during quiet inspiration and back again toward the graft during expiration, both in the supine and upright postures. Typical examples are shown in Figure 3, where the angle of mediastinal shift toward the graft is on the *y*-axis, and changes in rib cage cross-sectional area are on the *x*-axis. The rate of inflation did not modify the direction of mediastinal displacement, which was invariably toward the native lung; in the four subjects studied, the decrease in mediastinal angle during the slow (mean = 2.4 seconds) and fast (mean = 1.2 seconds) inspirations averaged 11.8 ± 5.0° and 14.8 ± 6.8°, respectively.

Figure 4 shows changes in mediastinal angle and in the transverse cross-sectional areas of the native and transplanted lung (expressed as percent of values at TLC) as a function of time during a forced expiratory maneuver in the seven patients studied in supine posture. In each patient, forced expiration produced a shift of the mediastinum toward the graft (*see* also Figure E2 and Table E1 in the online supplement). The shift generally began abruptly at, or immediately after (as in Patient No. 7), the start of the maneuver and then gradually increased in magnitude, and it was associated with a more rapid decrease in the cross-sectional area of the graft than of the native lung, reflecting differences in time constants. The pattern of mediastinal displacement was very reproducible in the four patients who were studied on two separate occasions (*see* Figure E3 in the online supplement). In addition, in the four patients who were studied upright, the mediastinum also moved toward the graft during forced expiration (data not shown). On the other hand, no significant displacement of the mediastinum was observed during forced expiration in the control subjects.

DISCUSSION

The present studies have shown that the two hemithoraces assume identical volumes at FRC and TLC, and show similar volume changes during both CO_2-induced hyperpnea and FVC maneuvers in patients with SLT for emphysema; the unequal lung volumes of the native lung and the graft, and their asymmetrical ventilation are accommodated by displacement of the mediastinum rather than by volume distortion between the native and transplanted sides of the chest wall.

TABLE 2. RESULTS OF THE OPTOELECTRONIC PLETHYSMOGRAPHY (ELITE) STUDY

Static Volumes

	Volume of Hemithorax at FRC (*L*)		Volume of Hemithorax at TLC (*L*)	
Patient No.	Native	Tx	Native	Tx
1	10.0	10.6	10.9	11.6
2	9.4	9.1	10.4	10.2
3	14.8	15.5	15.8	16.5
4	12.1	11.5	13.3	13.0
Mean ± SD	11.56 ± 2.44	11.68 ± 2.70	12.61 ± 2.50	12.87 ± 2.81

Dynamic Volumes

	FVC		CO_2 Rebreathing		
Patient No.	Slope	Phase Angle (°)	Number of Breaths	Slope	Phase Angle (°)
1	1.06	−1.7	78	1.21	5.9
2	0.98	5.7	93	0.81	−0.7
3	0.98	0.1	86	0.70	−4.5
4	1.33	−2.1	51	1.01	−6.5
Mean ± SD	1.09 ± 0.16	0.5 ± 9.5		0.94 ± 0.13	−1.4 ± 5.2

Definition of abbreviations: FRC = functional residual capacity; TLC = total lung capacity; Tx = transplantation.

Values of volumes for each hemithorax and values of slope and phase angle for FVC maneuver are means of two measurements per patient; values of slope and phase angle for CO_2 rebreathing are means computed on number of breaths shown for each patient.

Critique of Methods

We used 38 anterior markers, 35 posterior markers, and 10 lateral markers, which is nine markers less than Gorini and colleagues (17) and Lanini and colleagues (11), and three markers less than Cala and colleagues (15). In addition to the 7 horizontal and 12 vertical rows used in the present study, these authors placed a few extra markers on the pulmonary rib cage. Yet, our data indicate a very good agreement between the volumes estimated by optoelectronic plethysmography and measured by the pneumotachograph. This suggests, in agreement with the sensitivity analysis made by Cala and colleagues (15), that removing a small number of markers does not impact significantly on the accuracy of the technique.

With the dynamic CT technology currently available, acquisitions could only be obtained at a single-chest level for a period of 3 seconds; we selected the mid-chest level, where the angle of mediastinal shift can be easily measured (Figure 2). So, these acquisitions did not allow us to compute either the changes in the volume of each lung over time (data shown in Figure 4 refer to the transverse cross-sectional area, as opposed to the volume, of each lung), the volume swept by displacement of the mediastinum, or the displacement of the hemidiaphragm on the native versus the transplanted side. Therefore, we cannot determine whether displacement of the mediastinum accounted fully for the asymmetrical ventilation or whether there was a contribution of asymmetrical diaphragm motion.

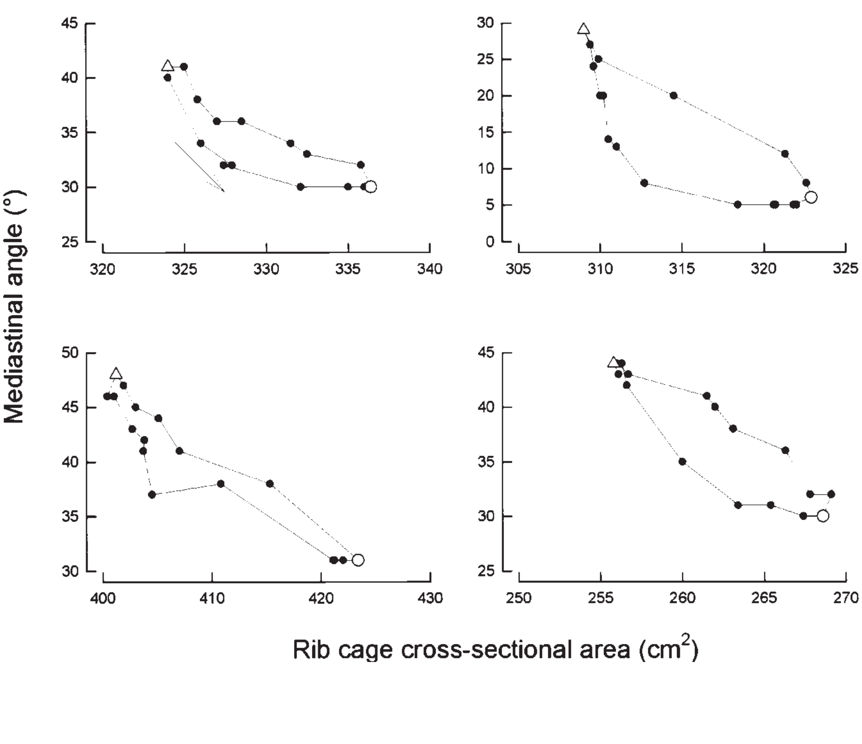

Figure 3. Changes in the angle of mediastinal shift toward the graft (*y-axis*) and in rib cage cross-sectional area (*x-axis*) during a tidal breath in four representative patients. Same conventions as in Figure 1B. Note that inspiration is accompanied by a reduction in mediastinal angle, that is, by displacement of the mediastinum toward the native lung.

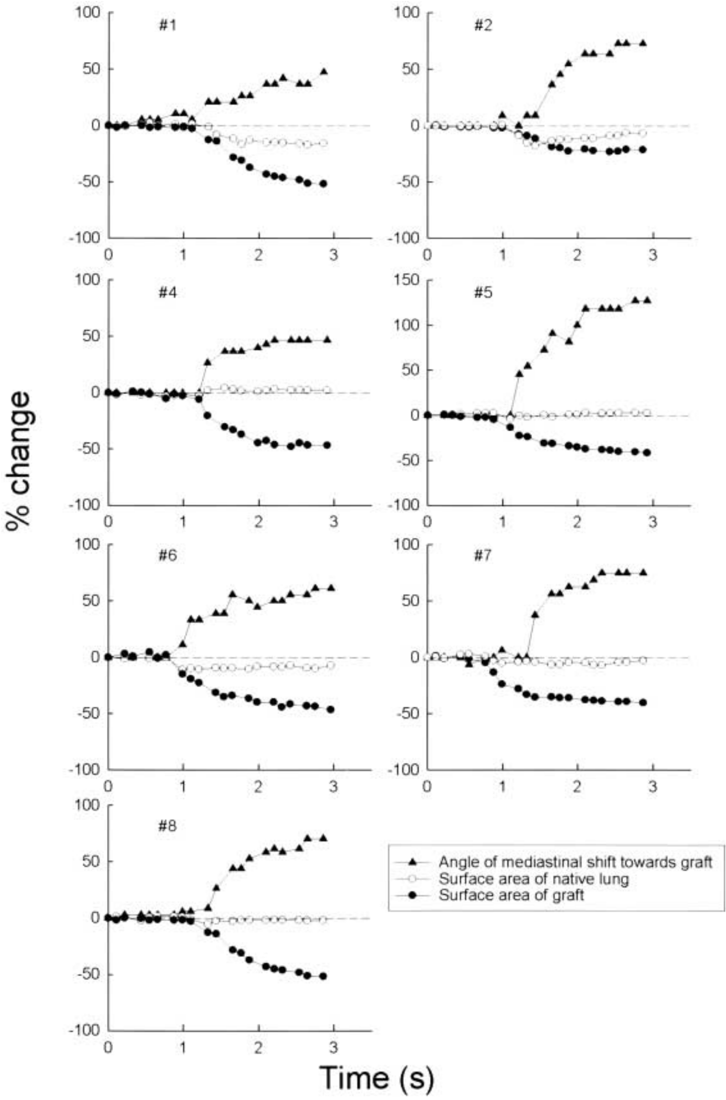

Figure 4. Changes in the angle of mediastinal shift toward the graft (*see* Figure 2) and in the transverse cross-sectional area of the native lung and of the graft during forced expiration in the seven patients studied in supine posture. Data are expressed as percent changes relative to values obtained at total lung capacity; so, an increase in mediastinal angle above 100% indicates that the angle more than doubled during the maneuver. During breath holding at total lung capacity, the angle of mediastinal shift and the cross-sectional areas of each lung were kept almost constant; once expiration started, the cross-sectional area of the graft decreased and the mediastinum was shifted toward the transplanted side. Note that the cross-sectional area of the native lung decreased much less than that of the graft and barely changed in four of the seven patients.

We did not assess regional distortions or phase lags between the hemithorax on the native and transplanted side. The aim of this study was to look for the presence of volume distortion between the two hemithoraces, i.e., to compare the pattern of volume changes on each side, and assess whether asymmetrical changes in volume contributed to the unequal ventilation. So, the observation that volume changes were similar in the two hemithoraces (*see below*) does not imply the absence of regional distortions or phase lags.

For obvious technical reasons, acquisitions with the optical reflectance system and with the CT were made in different body postures. Because the compliance of the chest wall and the mediastinum may be different seated and supine (19), supine CT findings may not apply upright. We therefore restudied four patients in the standing posture using fluoroscopy and chest radiographs; changes were qualitatively similar to those observed in supine posture, i.e., the mediastinum was moving toward the native lung during quiet and full inspiration, and back again toward the graft during quiet and forced expiration.

Previous Studies

Motivated by the introduction of SLT into clinical practice (20), Hubmayr and colleagues developed two experimental models in the early nineties to study static lung–lung interactions: a model based on single-lung inflation in nonemphysematous dogs and baboons (21), and a model based on papain-induced unilateral emphysema in dogs (20). In the first model, they found that the resistance of mediastinal and chest wall structures to displacement and deformation allowed lungs of unequal size and mechanical properties to be exposed to different surface pressures. On the other hand, in the model of emphysema, the loss of elastic recoil and more positive pleural pressure on the emphysematous side caused a shift of the mediastinum toward the untreated side; as a result, the two hemithoraces assumed a new uniform pleural pressure despite side-to-side differences in lung volume. More recently, Lin and colleagues (10) studied the mechanical effects of asymmetrical lung inflation in patients undergoing thoracic surgery and requiring endobronchial intubation; they fitted values of right and left airway pressures measured during asymmetrical inflations into a four-element mathematical model and calculated a variable that reflected limitation to unequal lung expansion. Their results suggested that the mediastinum is the most compliant pathway determining the extent of asymmetrical lung inflation in humans, but they did not have data on mediastinal motion to support this possibility directly.

Current Studies

In the present investigation, we measured the volumes of the two hemithoraces and motion of the mediastinum during respiratory maneuvers in recipients of SLT for emphysema. We found that hyperinflation of the native lung displaced the mediastinum toward the graft, but did not produce any detectable differences in the static volumes of the two hemithoraces. Similarly, differences in the extent and rate of inflation or deflation between the native and transplanted lungs did not translate into volume distortion between the two sides of the chest wall, which showed similar volume changes during both CO_2-induced hyperpnea and FVC maneuvers. This absence of volume distortion is similar to what has been recently reported by Lanini and colleagues in normal subjects (11), and is attributable, at least in part, to the coordinated activation of the respiratory muscles; when this coordination is impaired, as in patients with acute hemiplegia, changes in the volume of the healthy versus the paretic side of the chest wall become asymmetrical during voluntary and CO_2-induced hyperventilation (11).

The CT studies showed that the mediastinum was invariably displaced toward the native lung during (tidal and full) inspiration and back again toward the graft during (tidal and forced) expiration, indicating that the predominant contribution of the graft to ventilation was accounted for, at least in part, by motion of the mediastinum. This motion, which was absent in the normal control subjects, was a robust finding: it was present in the seven patients studied, and its direction was independent of the size of the breath, of the rate of inspiration, of body posture, and of the time elapsed since surgery. These results are consistent with a much greater resistance of the external boundaries of the chest wall as compared with that of the mediastinum to displacement and/or deformation (10). Part of the asymmetry in ventilation might also result from asymmetrical motion of the diaphragm on the native versus the transplanted side; however, we cannot comment on the role played by this mechanism because the CT scanner used here did not allow us to assess dynamic motion of the diaphragm dome (*see above*).

The displacement of the mediastinum toward the native side during inspiration must result, at least in part, from a greater fall in pleural pressure, reflecting the decreased dynamic compliance of the emphysematous lung. This, however, may not be the only mechanism involved. Because the mediastinum is attached to the sternum ventrally, the thoracic outlet cranially, and the diaphragm caudally (via the pericardium), its displacement during inspiration may be related, at least in part, to stretching caused by descent of the diaphragm dome and/or ventral motion of the sternum. This phenomenon was not seen in the normal subjects whose mediastinum was in the midsagittal plane; however, when it is shifted laterally, as in SLT recipients for emphysema, the tension caused by expansion of the chest wall may contribute to the mediastinum's movement toward the midsagittal plane, i.e., toward the native lung, during inspiration. Conversely, the mediastinum was abruptly shifted toward the transplanted side at the very beginning of forced expiration; we suggest that by decreasing tension in the mediastinum, deflation of the chest wall allowed this structure to be attracted by the much greater elastic recoil of the graft.

In conclusion, the present studies have shown that in patients with SLT for emphysema (*1*) the two hemithoraces assume identical volumes at both FRC and TLC; (*2*) the two hemithoraces have similar extents and rates of inflation and deflation during CO_2-induced hyperpnea and FVC maneuvers; and (*3*) displacement of the mediastinum accommodates part, if not all, of the unequal lung volumes and asymmetrical ventilation.

***Conflict of Interest Statement*:** A.D.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; A.V.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; P.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; G.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; G.V. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; M.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this article; M.E. does not have a financial relationship with a commercial entity that has an interest in the subject of this article.

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