Single-breath test in lateral decubitus reflects function of single lungs grafted for emphysema

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Van Muylem, Alain, Pietro Scillia, Christiane Knoop, Manuel Paiva, and Marc Estenne. Single-breath test in lateral decubitus reflects function of single lungs grafted for emphysema. J Appl Physiol 100: 834-838, 2006. First published November 23, 2005; doi:10.1152/japplphysiol.01307.2005.—The slope of the alveolar plateau for nitrogen derived from the single-breath test is useful to assess the function of bilateral lung grafts, but this technique is not applicable to patients with single-lung grafts due to the confounding influence of the native lung. We tested the hypothesis that the nitrogen slope measured in lateral decubitus with the graft in nondependent position may primarily reflect the distribution of ventilation in this lung. Fifteen patients with single-lung transplantation for emphysema, 10 healthy controls, and 7 patients with advanced emphysema performed single-breath washouts in right and left lateral decubitus; nitrogen slope was measured between 75 and 100% of expired volume. In 10 transplant recipients, the volume of each lung was measured in the two postures by computerized tomography. Nitrogen slope was unaffected by posture in normal controls and emphysema patients. On the other hand, nitrogen slope in transplant recipients was invariably smaller, with the graft in nondependent vs. in dependent position. Values of nitrogen slope with the graft in nondependent position were similar to those obtained in normal controls but significantly smaller than those obtained in emphysema patients. Computerized tomography studies in this position indicated that the volume expired below functional residual capacity was exclusively contributed by the graft. We conclude that, in patients with single-lung transplantation for emphysema, the terminal portion of the nitrogen slope obtained in lateral decubitus with the graft in nondependent position could reflect primarily the distribution of ventilation in this lung. To test this hypothesis, we performed a feasibility study in which single-breath washout tests were obtained in right and left lateral decubitus in 15 patients with single-lung transplantation for emphysema, 10 normal controls, and 7 patients with advanced emphysema. In addition, we measured the volumes of the graft and the native lung at different levels over the vital capacity range using computerized tomography (CT) in 10 transplant recipients. Some of the results of these studies have been previously reported in abstract form (27).

METHODS

Patients. Between January 1990 and the end of the study in July 2005, 28 single-lung transplantations for emphysema were performed at our institution. Nine patients were alive at the start of the study in January 2004, and seven patients were transplanted during the study period. One patient who had undergone an upper lobe lobectomy of the native lung for posttransplant lymphoma and was not in a clinically stable state was excluded. Fifteen patients thus participated in the study after written informed consent to the protocol was received, which was approved by the Human Studies Committee of the institution. Data obtained in the transplant recipients were compared with data obtained in 10 normal subjects matched for age and sex with the donors and 7 patients with advanced emphysema. At the time of studies, all transplant recipients were clinically stable and free of acute infection and rejection.

Techniques. Single-breath tests were performed in right and then in left lateral decubitus. The subjects were connected to a double bag-in-box system through a nonbreathing valve with a 20-ml instrumental dead space. They inhaled a gas mixture containing 100% O2 from functional residual capacity (FRC) to 1 liter above FRC and then expired at a constant flow of ~0.20 l/s (24). To account for differences in dilution and expired volume in the two postures, N2 concentration was expressed as a percentage of mean expired concentration, and volume was expressed as a percentage of total expired volume (Fig. 1), yielding slope values that are without units. The slope of the alveolar plateau was calculated over two different volume ranges by a linear regression analysis performed between 50 and 75% and between 75 and 100% of the expired volume. Single-breath tests were always performed in duplicate by the same investigator who was blinded to the side of the transplantation, and slope values were calculated as the average of two measurements.

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expiratory volume in 1 s (FEV1) averaged 58.5 of 107–4,706 days). For the group as a whole, the forced interval between transplantation and study was 710 days (range with eight right and seven left transplants; the median time are given in Table 1. There were eight men and seven women of the alveolar plateau for N2 (SN2) (between 75 and 100% of expired volume).

Thin-section CT scans were performed in 10 patients on the same day as the single-breath tests. Acquisitions were made with the patients in right and left lateral decubitus on a Sensation 64 scanner (Siemens, Medical Solution, Forchheim, Germany) using the multidetector spiral mode (5-mm slice thickness, acquisition 64 x 0.6 mm, pitch 1.4, 120 kV, 124 effective mA-s, 0.37-s rotation time). Acquisitions were performed from the lung apex to the lung base at total lung capacity (TLC), at 1 liter above FRC, at FRC, and at residual volume (RV); when the patient was on the side with the graft in nondependent position, one additional acquisition was made between FRC and RV. To attain this volume and the volume corresponding to FRC + 1 liter, the patient was connected to a spirometer. At each volume, acquisitions were obtained from the lung apex to the lung base, and images were reconstructed every 5 mm. The Pulmo CT option from Siemens (14) was used to trace the lung contours on each scan and measure lung area; lung volume was then calculated using values of lung area and slice interval (6).

Comparisons were made using paired and unpaired t-tests, and two-way ANOVAs for repeated measurements, when appropriate. The level of statistical significance was taken as P < 0.05. Data are presented as means ± SD throughout, unless otherwise stated.

RESULTS

All subjects performed the single-breath tests satisfactorily, within ~15 min. Details of the 15 transplant recipients studied are given in Table 1. There were eight men and seven women with eight right and seven left transplants; the median time interval between transplantation and study was 710 days (range of 107–4,706 days). For the group as a whole, the forced expiratory volume in 1 s (FEV1) averaged 58.5 ± 9.6% of predicted and 87.2 ± 11.4% of the best postoperative value; 12 patients were in bronchiolitis obliterans syndrome (BOS) stage 0 (FEV1 between 100 and 81% of the best postoperative value), and 3 patients (patients 2, 5, 10) were in BOS stage 1 (FEV1 between 80 and 66% of the best postoperative value) (8, 9). One patient (patient 7) who had a malacia treated by a stent placed in the middle and lower bronchus on the side of the transplant could not be classified using the BOS scoring system (9). The other patients had patent anastomoses and no malacia at endoscopy. The group of healthy controls consisted of five men and five women who were 37.4 ± 14.3 y of age; the group of emphysema patients included four men and three women who were 55 ± 8 y of age and had a mean FEV1 of 19.8 ± 4.3% of predicted.

Figure 1 shows typical single-breath washout curves obtained in right and left lateral decubitus in a patient with emphysema, a patient with a left transplant, and a control subject. As expected, the two washout curves were superimposed in the emphysema patient and the control subject. On the other hand, in the transplant recipient, the slope of the alveolar plateau for N2 (SN2) measured between 75 and 100% of the expired volume was much steeper when the test was performed with the graft in dependent vs. in nondependent position. Figure 2 shows that this difference was observed in all of the subjects studied. The values found with the graft in dependent position (0.67 ± 0.26) were similar to those found in the emphysema patients (0.55 ± 0.24; P = 0.36), but they were significantly greater than those found with the graft in nonde-
Table 2. Contributions of graft and native lung to expired volume

<table>
<thead>
<tr>
<th>Graft Dependent</th>
<th>Native Dependent</th>
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<tbody>
<tr>
<td></td>
<td>Native lung</td>
</tr>
<tr>
<td>TLC – FRC + 1 liter</td>
<td>0.13±0.013</td>
</tr>
<tr>
<td>FRC + 1 liter – FRC</td>
<td>0.43±0.22</td>
</tr>
<tr>
<td>FRC – RV</td>
<td>0.22±0.22</td>
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Volumes were derived from computerized tomography studies, and are all expressed in liters ± SD. TLC, total lung volume; FRC, functional residual capacity; RV, residual volume. P values refer to the comparison between the volume contributed by the graft vs. the native lung in each position.
A graft (Tx) measured by computerized tomography in 10 single-lung transplant recipients for emphysema who were in lateral decubitus with the graft in dependent position. The 4 volumes measured correspond to total lung capacity, functional residual capacity (FRC) + 1 liter, FRC, and residual volume. For the sake of clarity, error bars are not shown (x-axis) when they are twice as great as those shown for individual lung volumes (y-axis). B: same as above, but data were obtained with the graft in nondependent position. One additional acquisition was made between FRC and residual volume.

Fig. 3. A: average values (±SE) for the volumes of the native lung and the graft (Tx) measured by computerized tomography in 10 single-lung transplant recipients for emphysema who were in lateral decubitus with the graft in dependent position. The 4 volumes measured correspond to total lung capacity, functional residual capacity (FRC) + 1 liter, FRC, and residual volume. For the sake of clarity, error bars are not shown (x-axis) when they are twice as great as those shown for individual lung volumes (y-axis). B: same as above, but data were obtained with the graft in nondependent position. One additional acquisition was made between FRC and residual volume.

Because the current technology does not allow to measure dynamic changes in volume (5), the volumes of each lung were measured in static conditions at four or five different levels over the vital capacity range, rather than during a continuous expiration similar to the one used during the washout test. It should be stressed, however, that this expiration was performed at very low flow rates, which could be considered as approximating quasi-static conditions. In theory, the static conditions used for the CT acquisitions may increase the magnitude of the pendelluft phenomenon between the graft and the native lung. By decreasing the volume of the former and increasing the volume of the latter, this phenomenon could make the volumes of the two lungs (as assessed by CT) more different from those in dynamic conditions. This difference might translate into an overestimation of the vertical distance between the curves shown in Fig. 3, A and B, but it is not expected to change the slope of these curves, that is, the relative contribution of each lung to the expired volume (Table 2).

Present studies. SN2 values measured between 75 and 100% of the expired volume in the transplant recipients with the graft in dependent position were greater than those found in the emphysema patients, which suggests that they reflected the very heterogeneous ventilation of the emphysema native lung. This is supported by the CT studies, which showed that this lung contributed to the expiratory reserve volume when it was in nondependent position. A key observation of this study was that shifting the patient to the side with
the graft in nondependent position significantly decreased SN2. This finding was observed in each patient, irrespective of the side of the transplant and of the time elapsed since surgery (which varied widely from 3.5 mo to more than 12 yr). We suggest that this effect of posture was related to the preferential emptying of the graft at low lung volumes when it was in nondependent position. The best explanation to account for both the normal SN2 values (Fig. 2) and the CT data (Fig. 3) obtained in this position is that the native lung contributed only a small fraction (if any) and that the graft contributed most (if not all) of the volume expired in the last 25% of the expired volume, which corresponded to the volume range where SN2 was measured. Therefore, when the graft was in nondependent position, SN2 measured between 75 and 100% of the expired volume likely reflected primarily the distribution of ventilation in this lung.

Values of SN2 in the three patients who were in BOS stage 1 were in the same range as those measured in the patients who were in BOS stage 0. It is possible that the slope of the alveolar plateau for helium, which is a better predictor of BOS than SN2 in patients with bilateral grafts (7), would have been increased in these three patients. Alternatively, the decline in lung function seen in these patients might be due to hyperinflation of the native lung (17) or to another cause unrelated to obliteration of the small airways (the diagnosis of bronchiolitis obliterans was not confirmed by histology); otherwise stated, the normal SN2 in the three patients might be explained by the fact that the decline in lung function was due to complications that did not make ventilation distribution more heterogeneous in the graft.

In conclusion, the present studies showed that, in patients with single-lung transplantation for emphysema, the function of the graft may be assessed by measuring the slope of the terminal portion of the single-breath washout obtained with this lung in nondependent position. Further studies are now required to 1) investigate whether this test can be applied to patients with native lung diseases other than emphysema and 2) assess the sensitivity and specificity of this test as a predictor of BOS.

GRANTS

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REFERENCES