The Groningen lung transplant program
Ouwens, Jan Paul

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Chapter 3

Size matching in lung transplantation using predicted Total Lung Capacity.

J.P. Ouwens, T.W. van der Mark, W. van der Bij, A. Geertsma, W. J. de Boer,
and G. H. Koëter.

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Abstract:

**Introduction:** Height is used in allocation of donor lungs as an indirect estimate of thoracic size. Total lung capacity, determined by both height and gender, could be a more accurate functional estimation of thoracic size. We retrospectively evaluated size matching criteria based on height versus predicted total lung capacity, and evaluated if a total lung capacity mismatch was related with clinical and functional complications.

**Methods:** The ratio of donor and recipient height, as well as the ratio of predicted total lung capacity of donor and recipient were calculated in 80 patients after bilateral lung transplantation. Complications evaluated were persistent atelectasis, persistent pneumothorax and increased number of days on intensive care, occurrence of bronchiolitis obliterans syndrome and limitation of exercise capacity.

**Results:** Median height donor/recipient ratio was 1.01 (0.93-1.12). Median predicted total lung capacity donor/recipient ratio was 1.01 (with a clearly broader range 0.72-1.41). Neither gender mismatch nor total lung capacity mismatch was related with clinical or functional complications.

**Conclusions:** Allocation of donor lungs based upon height alone leads to a substantial mismatch in total lung capacity caused by gender mismatch. The absence of complications suggests that a greater height donor and recipient discrepancy can be accepted for allocation than previously assumed.
Introduction:

Size matching in lung transplantation (LTx) has been performed in the past by measuring the submammary thoracic perimeter\(^1\), by matching chest X-rays\(^2\), \(^3\), anthropometry, weight\(^4\), predicted lung size\(^5\), and height. None of these methods warrant an appropriate lung size with respect to the size of the thoracic cage. The best approach to donor-recipient (D/R) size matching has not been determined so far.

In general, allocation of donor lungs is primarily based on blood group and height. Height mismatch may sometimes preclude allocation. The effect of the anatomic difference in shape of the thoracic cavity between males and females on the possible permitted height mismatch is unknown. It may be expected that size matching based upon height only will be associated with discrepancies in estimated thoracic size in case of a gender mismatch. A female recipient will receive a greater lung from a male donor although the height of donor and recipient is equal. Similarly, a male recipient will receive a smaller lung from a female donor although height of donor and recipient is equal. Total lung capacity (TLC) depends on height and gender and may thus be regarded as a more accurate, functional estimation of thoracic size.

In the present study size matching based on height versus size matching by both height and gender were retrospectively evaluated by calculating ratios of height D/R as well as ratios of predicted TLC D/R. Since an increased range of ratios of predicted TLC was expected, we investigated whether these size discrepancies have lead to clinical and functional complications.

Methods:

Patients:
Ninety-six bilateral lung transplantations (BLTX) were performed between November 1990 and September 1998 in the Groningen University Hospital. The predicted TLC of all donors and recipients was calculated using the regression equations of the European Respiratory Society\(^7\), \(^8\).

For men: TLC predicted = 7,99H - 7,08.
For women: TLC predicted = 6,60H - 5,79.

(H: standing for height (m))

These equations apply for persons of Caucasian descent, in the age range between 18 and 70 years, and a height between 1.55 - 1.95 m (men) or 1.45 - 1.80 m (women).

Size-matching:
The degree of height matching was defined as the ratio of donor and recipient height (height D/R). The degree of thoracic size matching was defined as the ratio of donor and recipient predicted TLC (TLC D/R).

Clinical and functional complications:
The range of predicted TLC is, by definition determined by gender mismatching. Three cohorts of patients were defined according to the predicted TLC ratios: a gender matched group: male (M) to male and female (F) to female (group 1), and two gender mismatched groups: M to F (group 2) and F to M (group 3). Possible clinical complications of thoracic size mismatching were separated in short-term and long-term complications. Short-term complications included an extended number of days on intensive care, persisting atelectasis and persisting pneumothorax. Atelectasis and persisting pneumothorax were defined as defects that originated directly on the first chest X-ray after LTx and still present after one
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Week. Long-term clinical complications were defined as a decreased maximum exercise capacity 6 and 12 months after LTx in a gender mismatch group and early occurrence of bronchiolitis obliterans syndrome (BOS) compared to the gender match group. BOS grade 1 was defined as a persisting decline of FEV1 <80% of the mean of the two best FEV1-values, with or without changes in histology (i.e. grade 1A or 1B according to International Society for Heart and Lung Transplantation criteria for the classification of BOS).

Statistical analysis:
An increased occurrence of a persisting atelectasis in case of a M to F match (relatively larger lungs in a smaller thoracic cavity) and persisting pneumothorax in case of a F to M match (relatively smaller lungs in a larger thoracic cavity) was analysed by a chi-square test. The relation between thoracic size mismatch and increased number of days on the intensive care and decreased exercise capacity was calculated by analysis of variance (one-way ANOVA). Occurrence of BOS in the three gender (mis)match groups was analysed using Kaplan-Meier survival estimates. A possible relation between gender or TLC mismatching and early occurrence of BOS was investigated by a log rank test. P-values<0.05 were considered statistically significant.

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Diagnosis of the recipient:</th>
<th>Donors</th>
<th>Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Gender</td>
<td>M 49 / F 31</td>
<td>M 50/ F 30</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>36 (18-54)</td>
<td>45 (20-64)</td>
</tr>
<tr>
<td>Height (median, range)</td>
<td>1.75 (1.55-1.95)</td>
<td>1.74 (1.55-1.94)</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bronchiectasis</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>- Bronchiolitis obliterans syndrome</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- Chronic obstructive pulmonary disease</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>- Emphysema due to alpha-1-antitrypsin-deficiency</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>- Cystic fibrosis</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>- Idiopathic pulmonary fibrosis</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>- Eisenmenger syndrome</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Results:

Twelve patients were excluded with a donor age below 18 years, 2 patients with a height outside the ranges, and 2 patients with a combination of age and height outside the ranges applicable for the regression equations of the ERS. Thus, 80 patients were included in the study (characteristics are given in table 1). Height and gender distribution for donor and
recipients were similar. The median age of the recipient group was 9 years higher compared to the donor group caused by a relatively high percentage of patients with emphysema. The median height D/R ratio was 1.01 (range 0.93-1.12) (table 2). These ranges were centred around 1 in all four possible gender combinations. A similar observation was made for ranges based on predicted TLC for groups, which were gender matched. However, in the groups with gender mismatch, TLC D/R ratio was larger than 1 in case of a male donor and a female recipient and below 1 in case of female donor and a male recipient. The median predicted TLC D/R ratio was 1.01 (range 0.72-1.41). This difference in range between the height ratio and the TLC-ratio is therefore caused by gender mismatch.

Gender mismatch or TLC- mismatch was not accompanied with significant increased clinical or functional complications (table 3) nor differences in freedom from BOS (p=0.590)(figure 1). During transplantation, the size match seemed satisfactory in all patients. No mechanical difficulties were observed and no pneumoreduction procedures were performed during transplantation.

Table 2: Actually accepted height ratios and predicted TLC ratios for the different gender combinations. Notice the differences in predicted TLC caused by gender mismatch (D= donor, R= recipient).

<table>
<thead>
<tr>
<th>Gender combination</th>
<th>Actually accepted range in height D/R ratio</th>
<th>Calculated range in TLC D/R ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male D → Male R (n=39)</td>
<td>0.93-1.12</td>
<td>0.87-1.26</td>
</tr>
<tr>
<td>Female D → Female R (n=20)</td>
<td>0.96-1.10</td>
<td>0.92-1.23</td>
</tr>
<tr>
<td>Male D → Female R (n=10)</td>
<td>0.98-1.08</td>
<td>1.15-1.41</td>
</tr>
<tr>
<td>Female D → Male R (n=11)</td>
<td>0.93-1.03</td>
<td>0.72-0.89</td>
</tr>
</tbody>
</table>

Table 3: Comparison of clinical complications between the 3 cohorts: gender match M→M and F→F, gender mismatch M→F and gender mismatch F→M.

<table>
<thead>
<tr>
<th>Clinical or functional complication</th>
<th>Significance (p=)</th>
<th>M→M and F→F (n=59)</th>
<th>M→F (n=10)</th>
<th>F→M (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with persisting atelectasis &gt;1 week (n, %)</td>
<td>0.373</td>
<td>5 8.5%</td>
<td>0 0%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Cases with persisting pneumothorax &gt;1 week (n, %)</td>
<td>0.592</td>
<td>4 6.8%</td>
<td>1 10%</td>
<td>0 0%</td>
</tr>
<tr>
<td>Number of postoperative days on intensive care unit</td>
<td>0.088</td>
<td>11</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Mean exercise capacity 6 months after LTx (Watt)</td>
<td>0.264</td>
<td>71</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>Mean exercise capacity 12 months after LTx (Watt)</td>
<td>0.183</td>
<td>85</td>
<td>71</td>
<td>61</td>
</tr>
</tbody>
</table>
Figure 1: Gender (mis) match and freedom from bronchiolitis obliterans syndrome (BOS) after lung transplantation (LTx).

Discussion:

This study showed that allocation of donor lungs based upon height leads to substantial mismatch in Total Lung Capacity, which is mainly caused by gender mismatch. This mismatch in TLC does not lead to early and late clinical and functional complications. The study showed that for precise size matching, allocation on height alone is not sufficient in case of gender mismatch, but the absence of complications also suggest that a wider range of height matching could be possible in the gender matched and gender mismatched groups. An accurate estimate of possible permitted height mismatch for the different gender combinations without occurrence of clinical and functional complications cannot be given. A study to explore possible permitted size mismatching more quantitatively would require more observations of complications. Such a study is clearly not possible. In clinical practice, mismatch in TLC is often avoided by using smaller male donors for female recipients and by using larger female donors for male recipients. However, our data suggest that more leniency in height mismatching is possible, predominantly in the case of gender matching. In case of a male to female match, a lower donor height and in case of a female to male match a higher donor height may be possible. On the other hand, in case of a male to female match, prudence is called for lower recipient (or higher donor) heights and for higher recipient (or lower donor) heights in case of a female to male match.

Early experience suggested that donor lungs too large for the recipient’s thoracic cavity resulted in atelectasis and impaired ventilation, resulting in frequent infections. Size matching is therefore limited and sometimes pneumoreduction by a surgical stapler is necessary in case of excess volume.
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Outcome measures of size mismatching are hard to define. The early and late complications mentioned like pneumothorax, atelectasis, an increased number of ICU days and exercise capacity are determined by many factors. These parameters however are a reasonable choice to define size mismatch as outcome measures.

One of the investigated long-term functional complications was the possible relationship between the occurrence of BOS and TLC-mismatching or gender mismatch. This syndrome is believed to be an immunologic process and not related with size matching. In a recent study however, a relationship between gender mismatch and graft survival after LTx has been suggested. Especially male donors and female recipients had a poor prognosis with respect to graft function possibly caused by the difference in thoracic size between male donors and female recipients.

The fact that no differences in clinical complications were found between the three gender (mis) matched groups must be interpreted with caution. In descriptive studies, as presented here, it is not always possible to choose the optimum group sizes for avoiding a type II error. However, with the given group size, a difference of 30% in occurrence of complications would have been detected.

Allocation using the predicted TLC D/R was studied as a concept in patients after bilateral lung transplantation. The value of this method and the possible range in TLC for single lung transplantation recipients must be studied in the future. Exceptions for using the predicted TLC are recipients with a restrictive lung disease. In these patients, donor lungs should be selected with great caution because of the small thoracic cavity of the recipient due to their underlying disease. In practice, this means that height of the donor should not exceed height of the recipient. Parenchymal injury, obstruction, repeated infections and even pneumoreduction could be a consequence.

The regression equations we used apply for a certain range in height, age and Caucasian race. Predicted values for the TLC for children above age of 5 years can be calculated with special regression equations developed for children based on TLC-He measurements. Conversion factors for calculation predicted values of people of other ethnic groups for adjusting European reference values are applicable. Predicted lung size of a person of other or mixed racial origin is intermediate between that of the parents.

Due to donor organ shortage, most lung transplantation centres have long waiting lists. Therefore, donor lungs can usually be allocated. However, in case of a special blood group, special height or in case of seriously ill patients on a special urgency waiting list, height mismatch may preclude proper allocation. This study suggests that increased ranges in height for allocation of donor lungs are permitted which may have impact for allocation of donor lungs for patients with special blood group, special height or urgent patients.

References: