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European Journal of Cardio-thoracic Surgery 39 (2011) 115–119

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Donor predicted post-operative forced expiratory volume in one second predicts recipients' best forced expiratory volume in one second following size-reduced lung transplantation

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Received 4 February 2010; received in revised form 12 May 2010; accepted 18 May 2010; Available online 1 July 2010

Abstract

Objective: The limited number of available grafts is one of the major obstacles of lung transplantation. Size-reduced lung transplantation allows the use of oversized grafts for small recipients. Optimal lung size matching is vital to achieve best functional outcome and avoid potential problems when using oversized grafts. We hypothesise that donor-predicted postoperative forced expiratory volume in 1 s ($ppoFEV_1$) correlates with the recipient best FEV_1 after size-reduced lung transplant, being useful for the estimation of function outcome. **Methods:** All patients undergoing size-reduced or standard bilateral lung transplantation were included (1992–2007). Donor $ppoFEV_1$ was calculated and corrected with respect to size reduction and correlated with recipient measured best FEV_1 post-transplant. In addition, pre- and postoperative clinical data including surgical complications and outcome of all size-reduced lung transplant recipients were compared with standard lung transplant recipients. **Results:** A total of 61 size-reduced lung transplant recipients (lobar transplants, $n = 20$; anatomic or non-anatomic resection, $n = 41$) were included and compared to 145 standard transplants. The mean donor–recipient height difference was statistically significant between the two groups ($p = 0.0001$). The mean donor $ppoFEV_1$ was comparable with recipient best FEV_1 (2.7 ± 0.6 vs 2.6 ± 0.7 l). There was a statistically significant correlation between donor $ppoFEV_1$ and recipient best FEV_1 ($p = 0.01$, $r = 0.688$). The 30-day mortality rate and 3-month, 1- and 5-year survival rates were comparable between the two groups. **Conclusions:** In size-reduced lung transplantation, postoperative recipient best FEV_1 could be predicted from donor-calculated and corrected FEV_1 with respect to its size reduction. Compared to standard lung transplantation, equivalent morbidity, mortality and functional results could be obtained after size-reduced lung transplantation.

Keywords: Donor–recipient mismatch; Lung transplantation; Reduced-size lung transplant

1. Introduction

Lung transplantation is an established therapy for end-stage lung disease. According to the recent International Society for Heart and Lung Transplantation (ISHLT) report, more than 20 000 adults underwent lung transplantation between January 1995 and June 2007 [1]. The overall outcome is improving, with survival rates being 78% at 1 year and 51% at 5 years after lung transplant, according to the report [1]. Others and we have reported even superior outcome results for selected patients, particularly in cystic fibrosis (CF) [2,3]. Improvements in outcome are due to better donor organ preservation and operative techniques, enhanced immunosuppressant drug management and prevention of infection. However, there is an ongoing paucity of suitable donor organs as the availability of cadaveric donor lungs has failed to increase with the rise in numbers of transplant candidates. For transplant recipients requiring bilateral lung transplantation, donor-to-recipient supply and demand mismatch is even further increased [4]. Due to the increasing scarcity of donors, in particular for smaller recipients, advanced operative strategies have been developed [5–10]. Size-reduced lung transplantation is increasingly performed, often in urgent cases. Peripheral segmental resection is the most common method for downsizing, whereas lobar and split-lung transplants are the other options performed [5–10]. Whenever size-reduced lung transplants are undertaken, appropriate size matching of donor organs and the recipient is vital. Oversized lung grafts can potentially lead to atelectasis and impaired airway clearance due to bronchial anatomy distortion. Undersized grafts cause lung hyperexpansion and might limit exercise tolerance due to haemodynamic compromise. In most

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1010-7940/$ – see front matter
doi:10.1016/j.ejcts.2010.05.019

transplant centres, surgeons use estimated donor total lung capacity (TLC) for size matching; however, its predictive value for post-transplant lung function is uncertain. A recent study including 27 size-reduced lung transplant recipients concluded that postoperative TLC can be predicted by donor TLC, corrected by the number of transplanted lung segments [5]. We hypothesise that the donor-predicted postoperative forced expiratory volume in 1 s ($ppoFEV_1$) correlates with the recipient best FEV_1 after size-reduced lung transplantation, being a useful tool for the estimation of functional outcome post-transplant.

2. Material and methods

Patients undergoing primary bilateral lung transplantation at the University Hospital Zurich, Switzerland, between January 1992 and December 2007 were included in the study and subdivided into two groups: size-reduced lung transplants and standard lung transplants. Patients after single-lung, heart–lung and lung re-transplantation were excluded from the study. All patients' demographic data were collected retrospectively.

At our centre, we follow the recently published ISHLT guidelines regarding referral and selection of lung transplant candidates [11]. Organ preservation was performed with Euro-Collins solution (until 2000), thereafter with Perfadex® (Vitrolife, Gothenburg, Sweden). Before antegrade flush, 500 μg prostaglandin E_1 (Prostin VR, Upjohn, Puurs, Belgium) was injected into the pulmonary artery in all cases. Harvesting of the donor lungs were undertaken *en bloc* after perfusion. Since 2000, we also use retrograde flush with Perfadex® at the time of the back-table preparation. The decision to perform size-reduced lung transplantation was made in the operating theatre during implantation. Peripheral segmental wedge resections were undertaken with a commercially available stapler device. For lobar transplants, lobectomy was done on the back table. For bilateral sequential lung transplants, bilateral trans-sternal anterior thoracotomy (clamshell incision) or two separate anterolateral thoracotomies (since 2000) were performed. First, the bronchial anastomosis was done followed by venous (atrial cuff) and pulmonary artery anastomosis. The recipient's main bronchus was divided one ring proximal to the upper lobe bronchus branch. Bronchial arteries were ligated off the peribronchial tissue without electrocoagulation. All dissection on the bronchus was performed using 'minimal' or 'no touch' technique to keep the peri-bronchial tissue intact. The donor bronchus was cut back as close as possible to the origin of the upper lobe bronchus with special attention to the peribronchial tissue. Absorbable suture material polydioxanone (PDS, Ethicon Inc., NJ, USA) was used. A continuous suture to the membranous wall (PDS, 4/0) and end-to-end anastomosis with interrupted single stitches (PDS, 3/0) to the cartilaginous part was performed. According to our standard protocol, patients received induction therapy (anti-thymocyte globulin or basiliximab) and triple immunosuppressive therapy including cyclosporine, azathioprine or mycophenolate mofetil (since 1997) and prednisone. Anti-infective prophylaxis was used according to our centre's protocol described elsewhere [12]. Post-transplant management at our centre includes routine surveillance bronchoscopies with trans-bronchial biopsies and broncho–alveolar lavage during the first 6 months after transplant, serial laboratory lung function tests and regular outpatient clinic follow-up visits.

Donor FEV_1 (donor FEV_1 (male) = 4.3 × height − 0.029 × age; donor FEV_1 (female) = 3.95 × height − 0.025 × age) was calculated and corrected for $ppoFEV_1$ with respect to size reduction [13]. We estimated $ppoFEV_1$ by using the following equation: $ppoFEV_1$ = donor $FEV_1 \times (1 - S \times 0.0526)$, with S = number of resected segments [14]. The calculated value was correlated with the recipient's best FEV_1 value measured following transplantation. Donor TLC (male) = 7.99 × height − 7.08 and donor TLC (female) = 6.6 × height − 5.79 were calculated and corrected for predicted postoperative TLC (ppoTLC) with respect to size reduction [13,14].

Pre- and peri-operative variables, outcome and complications of all patients who underwent size-reduced lung transplantation were retrospectively analysed and compared with the patients undergoing standard lung transplantation.

2.1. Statistical analysis

Descriptive statistics was used, and data are expressed as mean ± standard deviation. The statistical analysis was performed with SPSS 15.0 for Windows. Actuarial survival rates were calculated by the Kaplan–Meier method and compared with the log-rank test. To test for univariate differences in categorical variables, we used Pearson's chi-square test. For correlation analysis, Pearson's correlation test was used. The Mann–Whitney *U*-test was used to compare continuous variables between the groups. $p < 0.05$ was considered significant.

The University Hospital Zurich's Research Ethics Committee granted approval for this study.

3. Results

During the study period, we performed lung transplant operations in 235 patients. Size-reduced lung transplantation was performed in 65 patients (27.6%). Three patients who underwent single-lung transplantation and one heart–lung transplant patient in the size-reduced group and 25 patients who underwent single-lung transplantation in the standard group were excluded. Therefore, 61 recipients in the size-reduced group and 145 recipients in the standard group were included in the study. Indications for size-reduced and standard lung transplantation are displayed in detail in Fig. 1. In both groups, CF was the most common indication. The underlying diagnoses were not different between the two groups ($p = 0.1$). Demographic data of both patient groups are displayed in Table 1.

Size reduction was achieved by lobar transplantation ($n = 20$) and anatomic or non-anatomic resections ($n = 41$). On the right side, the middle lobe was the most commonly resected lobe ($n = 37$), followed by lingula resection ($n = 27$) on the left side. Otherwise, downsizing was achieved by right upper lobectomy ($n = 12$), right lower lobectomy ($n = 1$), left upper lobectomy ($n = 14$), left lower lobectomy ($n = 4$) and non-anatomic wedge resections ($n = 19$), respectively (more

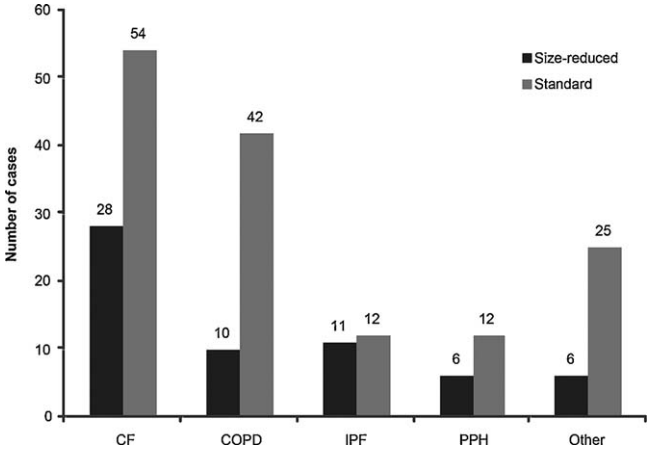

Fig. 1. Indications for lung transplantation for recipients who underwent size-reduced and standard lung transplantation. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; PPH, primary pulmonary hypertension.

than one size reductions might have been performed in one recipient). The mean donor–recipient height difference was statistically significant between the groups; the mean donor–recipient weight difference, however, was comparable (Table 1). Right ischaemia time in the size-reduced group was longer than the standard group but comparable for the left side (Table 1). Total operation time was statistically longer in the size-reduced group compared with the standard group (435.9 ± 85.1 vs 385.9 ± 97.4 min, $p = 0.0001$). Intubation time and intensive care unit stay, however, were comparable between the two groups.

One patient in the standard group required surgical revision due to a small bronchial leak on the 5th postoperative day. Bronchial narrowing without any clinical implications occurred in two patients in the size-reduced group and in eight patients in the standard group ($p = 0.09$). The other surgical complications such as prolonged air leak, pleural effusion and haemorrhage requiring thoracotomy were comparable between the two groups. The 30-day

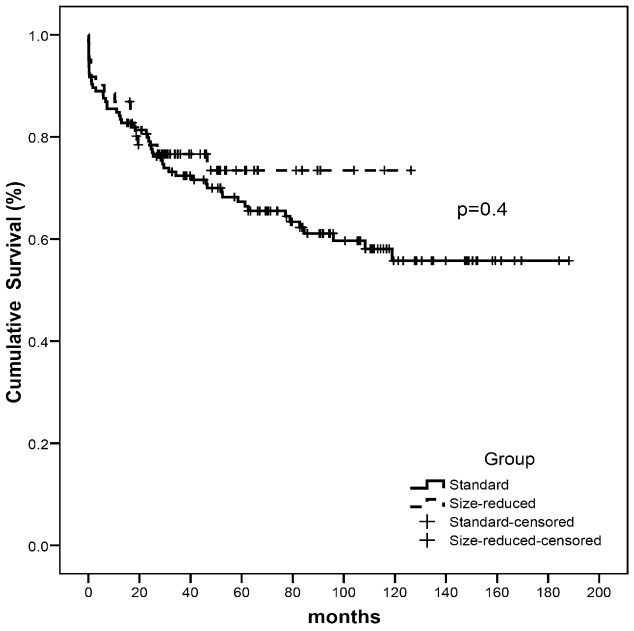

Fig. 2. Cumulative post-transplant survival according to Kaplan–Meier survival estimates of the size-reduced ($n = 61$) and standard groups ($n = 145$).

mortality rate was comparable between size reduced and standard groups (4.9 vs 8.3%), $p = 0.6$. The 3-month, and 1- and 5-year survival rates were comparable between the two groups (90 ± 3%, 86 ± 4% and 74 ± 6% after size-reduced and 89 ± 2%, 85 ± 3% and 68 ± 4% after standard lung transplantation, respectively) (Fig. 2).

In the size-reduced patient group, the mean calculated and corrected donor ppoFEV_1 was comparable with recipients' mean best post-transplant FEV_1 (2.7 ± 0.6 vs 2.6 ± 0.7 l, $p = 0.1$). Moreover, the correlation between donor ppoFEV_1 and recipient best FEV_1 post-transplant was statistically significant ($p = 0.01$, $r = 0.688$) (Fig. 3). In the size-reduced patient group, the mean calculated and corrected donor TLC was comparable with recipients' mean best post-transplant

Table 1. Patients' pre-, peri-, and postoperative demographic data.

	Size-reduced group	Standard group	*p*
N	61	145	
Age (years)	40.5 ± 17.7	40.9 ± 14.7	0.9
Female	38	61	0.01
Waiting list time (days)	211.1 ± 217.9	134.01 ± 131.5	0.008
D–R height difference (cm)	11.9 ± 11.5	4.1 ± 7.7	0.0001
D-R weight difference (kg)	16.6 ± 20.1	11.2 ± 18.1	0.08
Ischaemia time; right (min)	257.13 ± 88.9	228.9 ± 81.1	0.03
Ischaemia time; left (min)	323.5 ± 78.4	298.4 ± 85.4	0.09
Total operation time (min)	435.8 ± 85.1	385.9 ± 97.4	0.0001
Intubation time (days)	3.12 ± 5.8	4.36 ± 19.8	0.6
ICU stay (days)	9.75 ± 11.4	10.04 ± 20.8	0.6
Bronchial narrowing (*N*)	2	8	0.09
Donor ppoFEV_1 (l)	2.7 ± 0.6		0.09[a]
Best FEV_1 (l)	2.6 ± 0.7		
30-day mortality (%)	4.9	8.3	0.6
5-year survival (%)	74	68	0.4

All values are given as mean ± standard deviation. D–R, donor–recipient; FEV_1, forced expiratory volume in 1 s; ICU, intensive care unit; ppoFEV_1, predicted postoperative forced expiratory volume in 1 s.

[a] Between donor ppoFEV_1 and recipient best FEV_1.

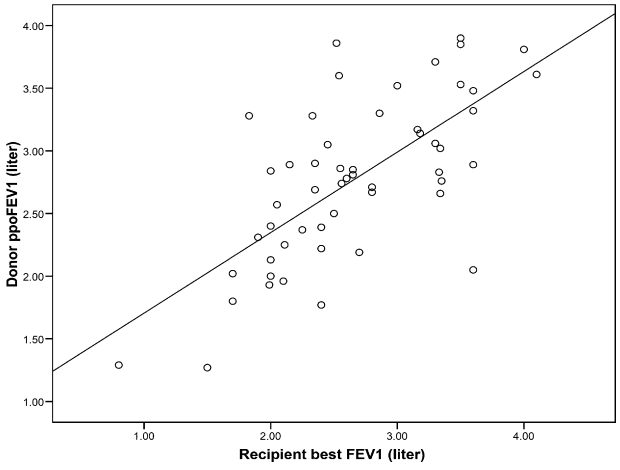

Fig. 3. Scatter graph showing the correlation between donor ppoFEV_1 and recipient best FEV_1. The correlation was statistically significant ($r = 0.688$, $p = 0.01$). FEV_1, forced expiratory volume in 1 s; ppoFEV_1, predicted postoperative forced expiratory volume in 1 s.

TLC (4.2 ± 1.1 vs 4.9 ± 0.9 l). Further, the correlation between donor ppoTLC and recipient best TLC post-transplant was statistically significant ($p = 0.002$, $r = 0.617$).

4. Discussion

Our study shows that, in size-reduced lung transplantation, the postoperative recipient best FEV_1 could be predicted from the donor's calculated and corrected FEV_1, adjusted for the number of transplanted segments. Moreover, our data demonstrate that size-reduced lung transplantation can be performed safely with peri- and postoperative complications and post-transplant outcome is very well comparable to standard lung transplantation.

Downsizing of lung grafts either by non-anatomical resection or by lobectomy is one of the methods to increase the donor pool, especially for small recipients in case of donor—recipient size mismatch. Nonetheless, it is not routinely performed in many transplant centres, probably due to the lack of data on preoperative values to predicting the functional outcome in size-reduced lung transplant recipients. In any case, best functional outcome should have the highest priority when downsizing of lung grafts is performed. Optimal size matching is also very important to avoid potential problems, which might occur following the use of oversized grafts [5—7]. Previous experimental studies have shown the adverse effects of oversized grafts on chest mechanics, atelectasis of the graft and pulmonary haemodynamics [15]. In a canine model of bilateral living donor lobar lung transplantation, both pulmonary vascular resistance and peak airway pressure were significantly increased after the chest closure due to overcrowding phenomena in animals that did not undergo size reduction, whereas little change was observed in those that underwent size reduction [15]. An oversized graft might lead to perpetual atelectasis or bronchial distortion with retention of secretions and increased risk for secondary infection. An oversized graft might lead to a higher incidence of short-term clinical complications with reduced improvement in pulmonary function. Shigemura and co-workers reported the impact of size reduction for oversized grafts on outcome in recipients with end-stage restrictive pulmonary disease [7]. Nine of 25 patients who received oversized grafts underwent size reduction, whereas 16 recipients did not, showing better lung function improvement after 6 months in size-matched recipients, although long-term survival was not different between groups. The short-term complication rate was higher in recipients who did receive standard grafts compared with size-reduced ones [7]. On the other hand, undersized grafts might lead to persistent pneumothoraces, hyperexpansion of the lung followed by increased breathing efforts, and, in extreme cases, even haemodynamic compromise [5—9]. Optimal size matching is therefore vital. For optimal size matching, different methods have been proposed, such as donor—recipient difference or ratio in body weight and height [5—7]. In addition, chest circumference and chest X-ray vertical and transverse dimensions have been used [5]. Others have used donor and recipient TLC [5—8]. Small differences in the lung graft size can be managed by stapler resection or peripheral non-anatomic wedge resection. In general, the right-side middle lobe and the lingula on the left side are resected. This technique of size reduction has been reported to lead to an approximate 10—15% downsize not only in height but also in anterior—posterior diameter as the upper lobe rotates towards the lower lobe [6]. In case of a large size difference, lobar transplantation should be considered. As previously shown by others, we also perform donor lung lobectomy on the back table, immediately before the engraftment. Other than its technical feasibility of upper lobectomy, the remaining lower lobe gives a configuration that is similar to the whole lung [6].

Preoperatively, it is important to be able to estimate the best lung function parameter that can be potentially achieved in the individual recipient [5]. To avoid functional impairment, the amount of resected lung tissue has to be taken into account when size-reduced lung transplantation is performed [16]. Different opinions exist in the published literature as to whether postoperative lung function can be determined by donor or recipient factors [5,17—19]. It has been shown that postoperative recipient TLC in size-reduced lung transplantation could be predicted by donor TLC with an excellent correlation between TLC and FEV_1 [5]. In addition, recipient's forced vital capacity (FVC) after living lobar lung transplantation can be predicted by measuring the donor's FVC before surgery, regardless of sex, height, weight or diagnosis of the recipient [15]. These conclusions support our data that, in size-reduced lung transplantation, donor-predicted postoperative lung function is important for the prediction of postoperative recipient lung function. Our data showed a significant correlation between donor $ppoFEV_1$ and recipient best FEV_1, following size-reduced lung transplantation. In our study, no significant differences between size-reduced and standard lung transplant groups were observed regarding peri- and postoperative complications and survival. The 30-day mortality was comparable between the groups. Postoperative intensive care stay and intubation time were not different; however, the differences in total ischaemic time, operation time and waiting list time were statistically significant, in contrast to previous reports [6]. The mean donor—recipient height difference was also different between the two groups, supporting the notion that donor-related parameters are important in predicting postoperative lung function rather than recipient's parameters.

Interestingly, a recent US study showed that overall post-transplant survival or lung function after standard lung transplantation was unaffected by donor-to-recipient predicted TLC ratio and actual TLC ratio [20]. The group concludes that a wider degree of lung size mismatch could be accepted without adverse effect, which may improve a patient's odds of undergoing lung transplantation [20].

In our study, post-transplant survival of the size-reduced group was 86% at 1 year and 74% at 5 years compared with 85% 1-year and 68% 5-year survival of the standard group, respectively. All our results are superior compared with ISHLT Registry overall 1- and 5-year survival rates of 78% and 51%, respectively, and are comparable to outcome after size-reduced lung transplantation reported by other centres [5,6,12].

Our analysis has limitations that are inherent in retrospective, single-centre designs. During the 15-year study period, all transplanted patients were treated with a

cyclosporine-based immunosuppressant regime. However, changes occurred regarding induction therapy and the antiproliferative agent used, which might have influenced outcome after transplant.

Thus, we conclude that, in size-reduced lung transplantation, the postoperative recipient best FEV_1 could be predicted from the donor's calculated and corrected FEV_1 with respect to its size reduction. We believe the methods used in our study are an additional tool to guiding surgeons with regard to the optimal reduction of oversized donor lungs, ensuring that the recipient gets a lung or a pair of lungs that functions optimally and avoids complications of oversizing or undersizing.

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