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Lung transplantation from donors outside standard acceptability criteria – are they really marginal?

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Summary

Lung transplantation (LTx) from "extended donor criteria" donors may reduce significantly organ shortage. However, its influence on results remains unclear. In this study, we evaluate retrospectively the results of LTx from donors outside standard criteria: PaO2/FiO2 ratio < 300 mmHg, age over 55 years, and history of smoking > 20 pack-years. Two hundred and forty-eight patients underwent first time LTx in our institution between January 2007 and January 2013. Seventy-nine patients (Group I) received organs from "extended donor criteria" and 169 patients (Group II) from "standard donor criteria." Recipients' and donors' demographics, perioperative variables, and outcome were compared. Donors from Group I were significantly older [median (interquartile range)]: 52.5 (44;58) vs. 42 (28.5;48.5) years ($P < 0.001$) with lower PaO2/FiO2 ratio: 366 ± 116.1 455 ± 80.5 mmHg ($P < 0.001$), higher incidence of smoking history: 57.7% vs. 41.8% ($P = 0.013$), and more extensive smoking history: 24(15;30) vs. 10 (3.75;14) pack-years ($P < 0.001$). Other parameters were comparable. Recipients' gender, diagnosis, percentage of patients operated on pump and receiving double LTx were also comparable. Recipients from Group I were significantly older: 50 (42;57) vs. 44 (29.5;53.5) years ($P = 001$). There were no differences observed in recipients' prevalence of primary graft dysfunction (PGD) grade 3 over first three postoperative days, duration of mechanical ventilation, intensive care and hospital length of stay, prevalence of rejection, and bronchiolitis obliterans syndrome (BOS). 90-day, 1-year, and 5-year survival (Group I vs. II) were also similar: 88.6% vs. 91.7%, 83.2% vs. 84.6%, and 59% vs. 68.2% (log rank $P = 0.367$). Carefully selected donor lungs from outside the standard acceptability criteria may expand existing donor pool with no detrimental effect on LTx outcome.

Introduction

LTx is a standard treatment of the end-stage respiratory failure of various origin. The number of this procedure performed per year was doubled over the last decade according to International Society for Heart and Lung Transplantation (ISHLT) registry [1]. Despite that there is still a substantial discrepancy between the number of patients awaiting transplantation and donor organ availability observed. This situation results in deaths on the transplant waiting lists. The most current data from United Sates indicate 15.7% wait-list years mortality rate and it is rising [2]. Standard criteria for donor lung acceptability – donor: age ≤ 55 years, ABO compatibility, clear chest radiogram, partial pressure of oxygen in arterial blood – $PaO_2 \geq 300$ mmHg on fraction of inspired oxygen – FIO_2 of 1.0 and positive end-expiratory pressure – PEEP of 5 cm H_2O, absence of chest trauma, no evidence of aspiration/

sepsis, no prior cardiopulmonary surgery, sputum gram stain – absence of organisms, absence of purulent secretions at bronchoscopy were proposed in 1993 by Sundaresan *et al.* and reviewed by Pulmonary Council of ISHLT in 2003 [3,4]. Very conservative selection of an "ideal donor lungs" was implemented to choose the organs potentially the most resistant to post-transplant injury in early era of LTx and based on knowledge of pulmonary physiology rather than the data driven [5,6]. Over the years, many centers were gradually relaxing these criteria accommodating the lungs obtained from an "extended criteria" donors (ECD) to standard clinical practice. Numerous institutional reports evaluated the influence of this strategy on outcomes after LTx. Unfortunately, the conflicting nature of published results renders any conclusion to no clinical value. Interestingly, results of extensive analysis of the United Network for Organ Sharing (UNOS) database published by Reyes *et al.* revealed that 56% of Ltx were performed using the lungs noncompliant with at least one of the standard acceptability criteria. Of these, only donor smoking history of more than 20 pack-year (including recent 6 months) was found to have a small but significant negative influence on survival after LTx. Surprisingly, increase in the number of standard acceptability criteria not fulfilled by the donor did not have a detrimental effect on outcomes as well [5]. In this study, we retrospectively evaluate early and mid-term results of Ltx performed in Harefield Hospital using lungs from donors older than 55 years, with history of smoking over 20 pack-year, and those with PaO_2/FiO_2 ratio below 300 mmHg in the last measurement before retrieval.

Methods

Study population

Recipients

From January 2007 to January 2013, 248 patients underwent first time lung transplantations in Harefield Hospital: 226 double-lung transplantations (DLTx) and 22 single-lung transplantations (SLTx). Two recipients who underwent early redo transplantation – DLTx and lobar SLTx – over analyzed period were excluded from the study. Recipients were divided into two groups: Group I ($n = 79$) – receiving the lungs from ECD – defined as fulfilling at least one of the three criteria: donor age > 55 years, donor history of smoking > 20 pack-year, and donor last preretrieval PaO_2/FiO_2 ratio < 300 mmHg, and Group II ($n = 168$) – remaining transplant population. Recipients demographics and preoperative characteristics are presented in Table 1.

Donors

Lungs for transplantation were obtained from 247 donors: deceased brain-dead donors (DBD) – 201 (81.3%) and Maastricht category III and IV donation after circulatory death donors (DCD) – 47 (18.7%). Donor characteristics are presented in Table 2.

Seventy-eight donors were considered as an ECD. Of those, 64 (82%) did not fulfill one criterion listed in previous chapter, and 14 (18%) did not fulfill two criteria. The distribution of criteria not fulfilled by ECD is presented in Table 3.

Table 1. Recipient demographics and perioperative characteristics.

	Group I ($N = 79$)	Group II ($N = 169$)	*P*
Age (years)	50 (42;57)	44 (29.5;53.5)	0.001
Gender (%)			
Male	57	46.2	0.11
Female	43	53.8	
Diagnosis (%)			
CF	29.1	40.1	0.19
Emphysema	35.4	29	
α1-Antitrypsin deficiency	19.0	10.1	
PF	6.3	7.1	
PH	5.1	4.1	
LAM	1.3	3.6	
Sarcoidosis	3.9	1.8	
OB	0	2.4	
Bronchiectasis	0	1.8	
In-hospital (%)	9.5	10.1	0.88
Mechanical ventilation (%)	5.6	3.2	0.47
Sat O_2 (%)	95 (91;96)	94 (92;96)	0.62
O_2 (l/min)	2 (0;2)	1 (0;2)	0.62
ECMO/iLA (%)	2.5	4.1	0.72
Double-lung transplantation (%)	88.6	92.3	0.34
Cardio-pulmonary bypass use (%)	77.2	78.1	0.87
Total ischemic time (min.)	311.50 (248.75;411.50)	328 (268;464)	0.31

CF, cystic fibrosis; PF, pulmonary fibrosis; PH, pulmonary hypertension; LAM, lymphangiomyomatosis; OB, obliterans bronchiolitis; ECMO, extracorporeal membrane oxygenation; iLA, interventional lung assist device; In-hospital, percentage of recipients being hospitalized at the time of offer; Mechanical ventilation, percentage of recipients being mechanically ventilated at the time of offer; Sat O_2, median saturation before surgery; O_2, median amount of oxygen supply to the recipient at the time of saturation measurement.

Retrieval technique

Organs were inspected in situ after bronchoscopy. An antegrade flush perfusion was performed in 244 donors with low potassium dextran (Perfadex®) supplemented with trometamine 3.3 ml/l, Ca^{++}Chloride 0.6 ml/l, and epoprostenol sodium 2.5 ml/l after cannulation of the proximal pulmonary artery (PA) and incision of the left atrium. After

Table 2. Donor characteristics.

	Group I (N = 78)	Group II (N = 169)	P
Age (years)	52.5 (44;58)	42 (28.5;48.5)	<0.001
Gender (%)			
Female	69.2	58	0.06
Male	30.8	42	
DBD (%)	87.2	78.7	0.11
DCD (%)	12.8	21.3	
Cause of death (%)			
ICH	75.7	60.8	0.09
HBI	12.8	10.7	
TBI	5.1	10.7	
CVA	5.1	9.5	
Meningitis	1.3	5.9	
Other	0	2.4	
Smoking history (%)	57.7	41.3	0.02
Extensiveness of smoking (pack-year)	24 (15;30)	10 (3.75;14)	<0.001
Abnormal CXR (%)	21.8	27.6	0.33
Abnormal bronchoscopy (%)	32.9	24.2	0.16
Mechanical ventilation (days)	2 (1;3)	2 (1;3)	0.46
PaO_2/FiO_2 ratio (mmHg)	366 ± 116.1	455 ± 80.25	<0.001
EVLP (%)	5.1	3.6	0.73

ICH, intracranial bleeding; HBI, hypoxic brain injury; TBI, traumatic brain injury; CVA, cerebro-vascular accident; abnormal bronchoscopy, purulent secretions and/or mucosal inflammation; EVLP, lungs assessed/reconditioned using *ex-vivo* lung perfusion.

Table 3. Distribution of extended donor criteria.

	History of smoking (20 ≥ pack-years)	PaO_2/FiO_2 ratio (<300 mmHg)	Age ≥ 55 years
History of smoking (≥20 pack-years)	29 (37.2%)	(3.9%)	4 (5.1%)
PaO_2/FiO_2 ratio (<300 mmHg)		15 (19.2%)	7 (9.0%)
Age ≥ 55 years			20 (25.6%)

pneumonectomy and back table inspection, an additional retrograde flush was administered in 234 donors. Six organs were retrieved with antegrade perfusion only, and core cooling technique without pneumoplegia was used in seven cases.

All procured (DBD and DCD) lungs were stored in Perfadex® solution and placed on ice for transport. Total ischemic time was defined as time between cardiac arrest/aortic cross-clamp and reperfusion of the second implanted lung.

Analyzed data

Donor age, gender, cause of death, chest x-ray, bronchoscopy, history and extensiveness of smoking, PaO_2/FiO_2 ratio prior to the retrieval, duration of mechanical ventilation, and percentage of lungs assessed/reconditioned using *ex-vivo* lung perfusion (EVLP) were analyzed.

Recipient follow-up, age, gender, diagnosis, preoperative: O_2 saturation, in/out hospital status, mechanical ventilation, extracorporeal life support, type of the transplantation: DLTx/SLTx, and on-pump/off-pump surgery were analyzed as well as duration of postoperative mechanical ventilation, intensive care unit and hospital stay, prevalence of grade 3 primary graft dysfunction (PGD) over first 72 postoperative hours, prevalence and distribution of acute rejection, lung function tests, and freedom from grade 1 BOS and survival. The same postoperative parameters were compared during subgroup analysis: donors with PaO_2 < 300 mmHg versus Group II, donors older than 55 years versus Group II, and donors with smoking history >20 pack-year versus Group II.

Primary graft dysfunction

The two groups were compared to differences in PaO_2/FiO_2 ratio on arrival in ICU, 24, 48, and 72 h after transplantation. The grade of PGD was defined based on ISHLT Working Group on Primary Dysfunction Report [7]. PaO_2/FiO_2 < 200 mmHg was considered as PGD three independently of findings on the chest X-ray.

Lung function and bronchiolitis obliterans syndrome

Lung function tests (LFTs) were performed on each hospital admission and transplant outpatient visit. The recipient was diagnosed with BOS grade 1 when the FEV_1 dropped permanently more than 20% of the maximum (the best achieved after transplantation) according ISHLT recommendations [8].

Immunosuppression and antimicrobial treatment

Patients receive immunosuppression according to standards guidelines which are thereafter adjusted according to target drug levels, and according to the presence of infections or renal toxicity. Patients do not receive induction immunosuppression at out center. Until October 2010, patients received cyclosporin (Neoral – Novartis), azathioprine, and prednisolone. Thereafter, patients receive tacrolimus (Prograf – Astellas), mycophenolate mofetil (Cellcept – Roche), and prednisolone.

Patients receive standard infection prophylaxis against CMV with valganciclovir (Valcyte – Roche) and for pneumocystis with co-trimoxazole. No routine antifungal prophylaxis is given unless the recipient is known to colonize with a fungal pathogen in which case they receive 6 weeks of voriconazole (Vfend – Pfizer) with dosing according to

blood levels. Routine antibacterial prophylaxis is with Piperacillin/Tazobactam or according to sensitivities in sputum cultures during pretransplant follow-up.

Statistical analysis

Distribution of quantitative data was analyzed using the Kolmogorov–Smirnov test. Normally distributed data are presented as a mean ± SD, not normally distributed as a median (interquartile range). Qualitative data are presented as percentage of the analyzed group. For comparison of quantitative data, the Student's *t*-test and Mann–Whitney *U*-test were used when appropriate. Qualitative data were compared using the Fisher's exact test and chi-square test. The Kaplan–Maier method was used for survival and freedom from BOS estimation. Propensity score matching (1 to 1) for recipient age and diagnosis was used for adjusted postoperative data analysis. A value of $P < 0.05$ was considered to be statistically significant. The analysis was performed using the SPSS for Windows software (IBM®, Armonk, New York, USA).

Results

Intraoperative variables

Intraoperative variables are displayed in Table 1. There were not significant differences observed between the groups.

Postoperative variables

In Group I versus Group II, there was no statistically significant difference observed in duration of postoperative mechanical ventilation: 38.5 (12;179.5) vs. 34 (20;350) hours ($P = 0.53$); prevalence of postoperative extracorporeal membrane oxygenation (ECMO) use: 8.9% vs. 7.7% ($P = 0.76$); intensive care unit: 6 (3;21) vs. 6 (3;22) days ($P = 0.55$); and hospital stay: 35 (24;57) vs. 33 (22;48) days ($P = 0.23$). After propensity score adjustment, these parameters were comparable as well: duration of mechanical ventilation: 38.5 (12;179.5) vs. 33 (17;463.5) hours ($P = 0.68$); prevalence of postoperative ECMO: 8.9% vs. 8.9% ($P = 1.0$); intensive care unit: 6 (3;21) vs. 5 (3;23) days ($P = 0.79$); and hospital stay: 35 (24;57) vs. 38 (25;54) days ($P = 0.98$).

Primary graft dysfunction

Comparison of prevalence of severe – grade 3 PGD: on arrival to intensive care unit, 24, 48, and 72 h after transplantation – is presented in Fig. 1a (unadjusted) and b (adjusted). There was no statistically significant difference observed at any point of observation between analyzed groups in unadjusted analysis. After adjustment, statistically significant difference was observed 72 h after LTx – Group I vs. II: 14.8 vs. 4.5 ($P = 0.046$).

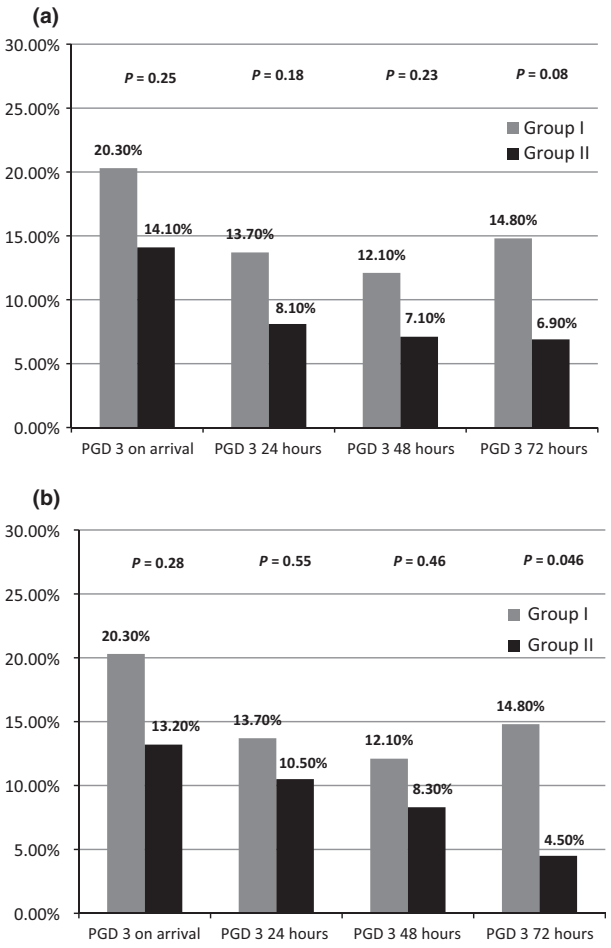


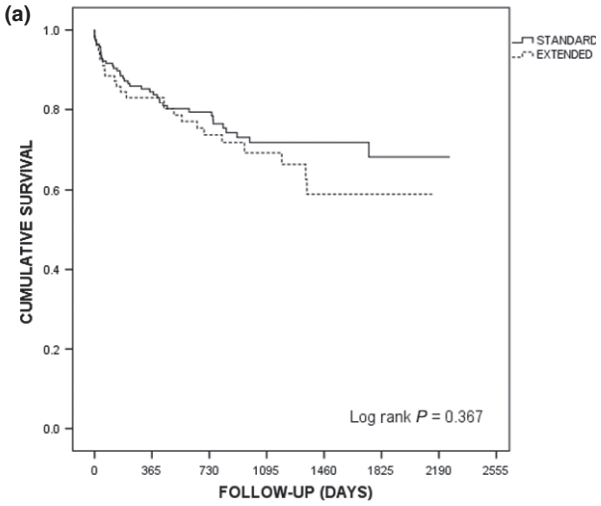
Figure 1 Prevalence of primary graft dysfunction (PGD) grade 3 over first 72 h after lung transplantation – (a) unadjusted and (b) adjusted.

Follow-up

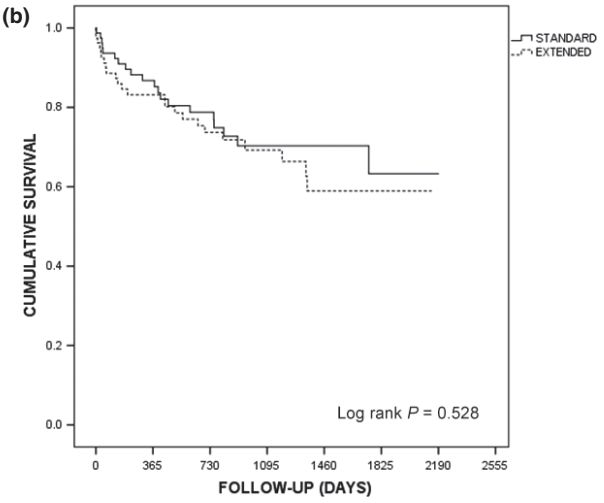
Median follow-up was comparable between Group I and II: 985 (441;1497) vs. 873 (462;1442) days ($P = 0.79$).

Survival

Twenty-four patients (30%) from Group I died during follow-up vs. 40 (23.7%) from Group II. Estimated survival in 1, 3, and 5 years after LTx in Group I vs. II is 83.2%, 69.2%, and 59% vs. 84.6%, 71.8%, and 68.2% (log rank $P = 0.367$) (unadjusted) and 83.2%, 69.2%, and 59% vs. 86.7%, 70.3%, and 63.3% (log rank $P = 0.528$) (adjusted). Survival estimate is presented in Fig. 2a (unadjusted) and b (adjusted).

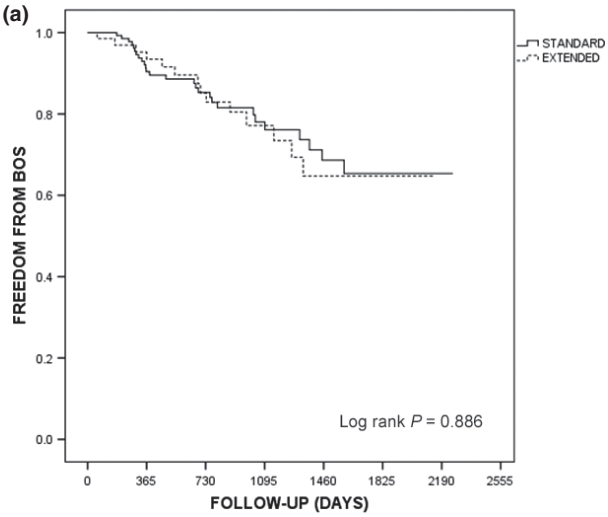


Group	1 year	2 years	3 years	4 years	5 years
Standard					
Survival (%)	84.6	79.4	71.8	71.8	68.2
Patients at risk	119	84	49	32	17
Extended					
Survival (%)	83.2	73.7	69.2	59.0	59.0
Patients at risk	58	42	24	11	6

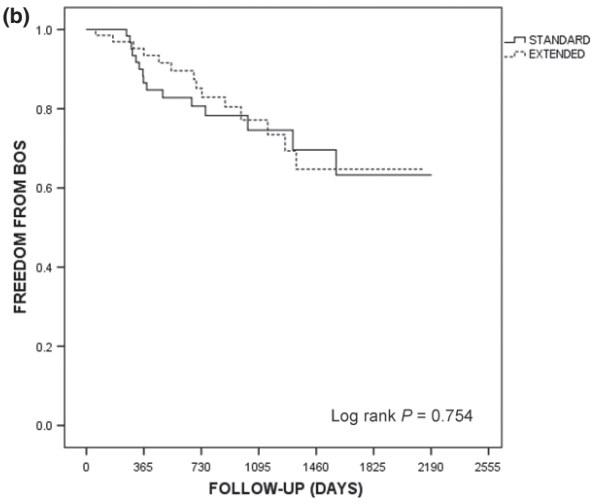


Group	1 year	2 years	3 years	4 years	5 years
Standard					
Survival (%)	86.7	78.7	70.3	70.3	63.3
Patients at risk	57	42	23	15	9
Extended					
Survival (%)	83.2	73.7	69.2	59.0	59.0
Patients at risk	58	42	24	11	6

Figure 2 Kaplan–Meier survival estimate – (a) unadjusted and (b) adjusted.



Group	1 year	2 years	3 years	4 years	5 years
Standard					
Survival (%)	90.4	85.3	78.0	68.6	65.4
Patients at risk	107	74	40	25	14
Extended					
Survival (%)	93.5	85.2	77.1	64.7	64.7
Patients at risk	54	38	21	11	6



Group	1 year	2 years	3 years	4 years	5 years
Standard					
Survival (%)	86.5	80.7	74.6	69.6	63.3
Patients at risk	50	36	19	12	7
Extended					
Survival (%)	93.5	85.2	77.1	64.7	64.7
Patients at risk	54	38	21	11	6

Figure 3 Kaplan–Meier estimation of freedom from bronchiolitis obliterans syndrome (BOS) grade 1 – (a) unadjusted and (b) adjusted.

Acute rejection

Unadjusted prevalence and distribution of the highest recorded acute rejection (AR) episode during follow-up was comparable in Group I vs. II: AR grade 0 – 74.7% vs. 74.5%; AR grade 1 – 8.9% vs. 9.5%; AR grade 2 – 13.9% vs. 12.4%; and AR grade 3 – 2.5% vs. 3.6% ($P = 0.96$). After adjustment, there were no significant differences observed as well: AR grade 0 – 74.7% vs. 72.1%; AR grade 1 – 8.9% vs. 11.4%; AR grade 2 – 13.9% vs. 15.2%; and AR grade 3 – 2.5% vs. 1.3% ($P = 0.88$).

Lung function tests and BOS

Kaplan–Meier estimation of freedom from BOS [Fig. 3a (unadjusted) and b (adjusted)] showed no statistically significant difference between evaluated groups.

Table 4. Subgroup analysis.

	Subgroup I (N = 31; age > 55 years)	Subgroup II (N = 36; smoking > 20 pack-years)	Subgroup III (N = 25; PaO_2/FiO_2 < 300)	Standard (N = 169)	P*
Estimated survival (%)					
1-year	76.6	97.2	67.1	84.6	NS
2-years	67.3	76.7	67.1	71.8	
5-years	67.3	61.4	67.1	68.2	
BOS free survival (%)					
1-year	96	94	92.9	90.4	NS
2-years	61.9	81.1	92.9	78	
3-years	61.9	62.4	92.9	65.4	
PGD 3 (%)					
On arrival	20.7	14.1	31.8	14.1	P†
24 h	10.7	5.7	18.2	8.1	
48 h	13	5.9	23.8	7.1	
72 h	19	6.5	25	6.1	
Acute rejection (%)					
AR0	74.2	72.2	80	74.5	NS
AR1	12.9	11.1	4	9.5	
AR2	9.7	13.9	16	12.4	
AR3	3.2	2.8	0	3.6	
Postoperative mechanical ventilation (hours)	32 (12.5;156)	31 (8;84)	82 (25;504)	34 (20;350)	NS
ICU stay (days)	5 (3;25)	5.5 (3;20)	11 (4.5;24)	6 (3;22)	NS
Hospital stay (days)	31 (20;55)	39.5 (28.5;56.5)	44 (24;67)	33 (22;48)	NS

*P value for comparison of subgroups I; II, and III to "standard donors".
†PGD 3 subgroup III versus standard – 48 h P = 0.028 and 72 h P = 0.022. Other subgroups and time points for subgroup III P = NS.

Subgroup analysis

Three subgroups, I – recipients who received lungs from donors more than 55 years of age (N = 31); II – recipients who received lungs from donors with history of smoking more than 20 pack-years (N = 36); and III – recipients who received lungs from donors with PaO_2 below 300 mmHg in last preretrieval measurement (N = 25), were compared with Group II – recipients who received standard criteria lungs (N = 169). Median age of the donors subgroup I versus Group II: 59 (57;61) vs. 42 (28.5;48.5) P = 0.001; median pack-year of cigarettes subGroup II vs. Group II: 30 (24;30) vs. 10 (5;14.75) P < 0.001; and median preretrieval PaO_2/FiO_2 ratio subgroup 3 vs. Group II: 233.3 ± 52.5 vs. 455.3 ± 80.3 P < 0.001. The postoperative results are shown in Table 4. There were no statistically significant differences when subgroups I and II were compared with Group II. Recipients from subgroup III experienced statistically more often PGD grade 3, 48 and 72 h after operation: 23.8% vs. 7.1% (P = 0.028) and 25% vs. 6.9% P(0.022).

Discussion

Lack of donor lungs is a major limitation of Ltx. Any initiatives increasing organ availability are vital for development of transplantation. Undoubtedly, utilization of organs from ECD has a pivotal role in increasing of the number of performed LTx. Based on data published by Reyes and colleagues, 56% of donor lungs registered in United Network of Organ Sharing (UNOS) within the period July 1999 to July 2008 were not compliant with at least 1 standard donor criterion [6]. In our practice, over the last 6 years, this number is 58% raising the question about its possible influence on outcome.

In our analysis, we have chosen 3 inclusion criteria for ECD group: age over 55 years, history of smoking more than 20 pack-year, and the last preretrieval $Pa0_2/FiO_2$ < 300 mmHg. The three criteria were chosen on the basis of the objectivity, excluding variables which may be influenced by interpretation, significantly. For example, Bolton and colleagues demonstrated the subjectivity of chest x-rays (CXR) as a criterion for lung acceptability for transplantation. There was very high variability of interpretation of CXR findings among the surgeons and only a moderate agreement among pulmonologists [9]. We assume that the same variability exists pertaining to other criteria, for example bronchoscopy or presence of aspiration. Thus, defining the marginal donors based only on fully objective criteria makes our analysis more reliable.

First institutional reports about breaching the standard lung donor criteria were published in the early 90's. Kron and colleagues prospectively evaluated an outcome of nine lung transplantations using ECD lungs with no detrimental effect on early survival [10]. Similar observations regarding early and mid-term survival were published by Sundaresan and colleagues [11]. Other reports evaluating single-center cohorts including 24–54% of donors outside the standard acceptability criteria revealed similar observations: no differences in 30-day and 1-year mortality when standard and marginal donor lungs were used [12–14]. Not all reports, however, support those findings. Pierre and colleagues evaluating 123 donors of which 50% were considered ECD revealed significant difference in 30-day survival in favor to standard donors [15]. This finding was supported by Botha and colleagues who identified a higher 90-day organ-specific mortality rate in ECD group [16]. Our analysis did not show any statistically significant difference in survival after LTx whether standard or marginal donor lungs were utilized. However, it is important to note that our recipient groups were not the same: patients who received extended donor criteria lungs were significantly older ($P = 0.01$), with a trend toward fewer cystic fibrotic and more emphysematous recipients observed ($P = 019$). These differences – recipients' age and trend toward different diagnosis distribution – were not driven by any intentional action. They appeared by chance. To investigate a potential influence of them, we performed propensity score matching for age and diagnosis for adjusted survival analysis. After adjustment, the difference in survival remained nonsignificant: unadjusted versus adjusted log rank $P = 0.367$ vs. $P = 0.528$ corroborating our hypothesis that survival is not detrimentally affected by the use of ECD lungs.

PGD is a major complication in early postoperative period after Ltx increasing both morbidity and early mortality [17]. Data from a prospective, multicenter study published by Christie and colleagues revealed that PGD grade 3 appears in 28.4% of the studied patients at 24 h, 22.8% at 48 h, and 18% at 72 h after LTx. PGD grade 3 at any point of observation was associated with the highest risk of early death and worse long-term survival. Also, grade of PGD at 48 and 72 h was better predictor of mortality than at 24 h after LTx [18]. In our analyses, we have not observed any statistically significant difference of the prevalence of grade 3 PGD between ECD and standard donor groups at any time point. However, there was a trend toward more frequent PGD grade 3 at 72 h in ECD group: 14.8% vs. 6.8% ($P = 0.07$).When adjusted using a propensity score, the difference at 72 h becomes significant 14.8% vs. 4,5% ($P = 0.046$). However, we observed no difference in duration of mechanical ventilation, intensive care and hospital length of stay, and survival either in unadjusted or in adjusted analysis. While evaluating the subgroups results, there were no differences in PGD 3 and other parameters as a compare to Group II – "standard donor criteria" when donors over 55 years of age and heavy smokers were compared. In case of subgroup of donors with PaO_2/FiO_2 ratio < 300 mmHg, PGD grade 3 was observed significantly more frequently at 48 h: 23.8% vs. 7.1% ($P = 0.028$), and at 72 h: 25% vs. 6.9% ($P = 0.022$). No any other statistically significant differences in other parameters of outcome were observed. However, noticeably better results were noticed in standard criteria donors. PGD was analyzed in detail by one group only, evaluating ECD lungs previously. Botha and colleagues found significantly higher rate of severe PGD in ECD group, corresponding to a higher 30-day mortality rate [16]. There were no difference in PaO_2/FiO_2 ratio on arrival to intensive care unit observed by Pierre and colleagues and in alveolar-arterial oxygen difference at 0 and 24 h after transplantation as reported by Sundaresan and colleagues between standard and ECD groups [11,15].

As PGD is a major factor responsible for early morbidity and mortality, after LTx BOS remains the main cause of late mortality. According to the annual ISHLT report, BOS is responsible for a quarter of death upon 1 year after transplantation [1]. Our observation did not show any influence of utilization of marginal lungs on BOS grade 1 free survival and was similar to the results of other groups [12,16].

Recently, a few institutional reports analyzing the use of EVLP to asses or, in some situations, to recondition the organs initially rejected for transplantation or defined as a "high-risk organs" have been published. The number of organs evaluated in this way was relatively small and follow up short, but the results are comparable to transplantation with standard donor lungs. The development of this technology may increase the confidence in the utilization of marginal lungs further and make the early postoperative course more predictable, especially regarding the PGD rate [19–24]. Further developments in this field – mobile EVLP – for example, the Transmedics Organ Care System (OCS) could possibly be a new tool decreasing an ischemic and cold storage time to a minimum and allowing for early *ex-vivo* lung assessment and reconditioning [25].

Majority of our donors did not fulfill only one standard acceptability criterion. Analyzing the results we believe that lungs from the donors over 55 years of age or with smoking history >20 pack-years should no longer be called "marginal" because of excellent results achieved and widespread acceptance among many transplant centers. More caution is necessary when considering the donor lungs with PaO_2/FiO_2 ratio < 300 mmHg. The results, especially early outcome seems to be adversely affected but without significant influence on mid-term results.

We realize that this study has limitations. Its retrospective nature (some data were missed and excluded from

analysis) and the relatively short follow-up period as well as difference in recipients age and trend toward different diagnosis (corrected using the propensity score matching) of the patients receiving standard versus marginal lungs may potentially bias our observations. In our material compare to ISHLT data, pulmonary fibrosis patients are relatively less common. It is the reflection of our waiting list where cystic fibrosis and emphysema patients are the majority. Distribution of ECD among PF patients was comparable; thus, we do not think if it causes any bias. However, due to this difference, extrapolation of our results on all LTx population may be affected. Nonetheless, we advocate more liberal approach for donor acceptance criteria for Ltx. The ECD lungs should be treated with caution, especially facing the donor with PaO_2/FiO_2 ratio < 300 mmHg, and the whole clinical picture should be taken into account when the organ is accepted or rejected for transplantation. Recently published data from Hannover group suggest that ECD can be safely utilized when recipient is from low-risk group [26]. When the recipient risk is recognized as high, for example, in case of bridging to transplant with extracorporeal support should rather not be used. Additional tools like EVLP or OCS may be helpful to asses and/or recondition suboptimal organs and in this way avoid unnecessary organ loss.

Authorship

BZ: designed research/study, performed research, collected data, wrote the paper. DGS: designed research/study, collected data, performed research. AS: designed research/study, collected data, performed research, analyzed data. FDR, MA and TB designed research/study. PNM and NPP: collected data. AW and AFP: performed research. AR: designed research/study, performed research. MC: designed research/study, performed research, wrote the paper. ARS: designed research/study, supervised research.

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