Suboptimal Donors Do Not Mean Worse Results: A Single-Center Study of Extending Donor Criteria for Lung Transplant

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ABSTRACT

Background. Lung transplant remains the only viable treatment for most of the end-stage lung diseases. It is believed that extending criteria for donor lungs would increase the number of lung transplants. The aim of the study was to compare the graft function by means of oxygenation index among recipients who received the lungs from donors of extended criteria with those whose received lungs from donors who met the standard criteria.

Methods. This retrospective study analyzed 71 donors whose lungs where transplanted into 71 first-time double lung recipients of 2 groups: patients who received transplants before and after 2018. The objective was to assess whether there is a significant difference in quality of the donor pool after applying extended criteria. The second objective was to compare results of recipients with lungs from donors of oxygenation index > 400 mm Hg with those obtained among recipients with this parameter < 400 mm Hg.

Results. In the case of transplants performed in 2018 to 2019, oxygenation indices were significantly lower in donors but significantly higher in recipients on the first day than those observed in 2015 to 2017. The number of transplants increased from 9 per year to 22 per year. Irrespective of whether the donor had PaO_2/fraction of inspired oxygen above or below 400 mm Hg, recipients showed similar oxygenation index values after transplant (mean oxygenation index, 462 vs 412 mm Hg, respectively). Short-term mortality did not differ either.

Conclusions. Extended criteria of lungs suitability as a potential grafts not only increases the donor pool but also proves that suboptimal donors are not associated with producing inferior results of the recipients.

LUNG transplant remains the only viable treatment for most of the end-stage lung diseases. According to the International Heart and Lung Registry, more than 69,000 adult lung transplants have been performed in 260 lung transplant centers so far [1]. The number of lung transplants in Poland has increased over the years, reaching 43 in 2018. However, the Polish National Transplantation Registry reports that the number of the procured lungs the same year was 52, meaning that some of those organs were not used. This issue is important as the National Registry also reports a steady decrease of reported and actual donors, while the number of potential candidates for such treatment increases [2]. Mean time spent on the Polish National Lung

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Transplant Waitlist is 216 days for nonemergency patients. Contrary to those unsettling trends, there is also a steady increase in multiorgan procurements in Poland (73% of all solid organ procurements performed in Poland in 2018). Such data indicate that extending a donor pool seems necessary. Certain criteria are believed to be describing the perfect lung donor, for example, age younger than 55 years, clear chest radiograph, arterial oxygen tension/fraction of inspired oxygen − oxygenation index (PaO_2/fraction of inspired oxygen [FiO_2]) > 300 mm Hg at positive end-expiratory pressure = 5 cm H_2O, less than 20 packs/y smoking history, absence of chest trauma, and purulent secretions on bronchoscopic visualization prior to procuring the lungs. Unfortunately, such donors are pretty uncommon [3]. Although oxygenation index exceeding 300 mm Hg provides satisfactory outcomes of lung transplant, the threshold for accepting the donor lungs in the biggest lung transplant facility was PaO_2/FiO_2 > 400 mm Hg until the year 2018. Since then, the aforementioned parameter was evaluated as less significant; therefore, the strict data-based approach, when it comes to lung assessment, was replaced with a more clinically led one. The aim of the study was to assess the graft function by means of oxygenation index at 3 time points: PaO_2/FiO_2 at official reporting of the available donor, first PaO_2/FiO_2 obtained after the procedure, and first PaO_2/FiO_2 after 24 hours since the end of the procedure among patients who underwent double lung transplant in a single center.

MATERIALS AND METHODS

This retrospective study analyzed 71 donors whose lungs where transplanted into 71 first-time double lung recipients. Inclusion criteria were as follows: primary double lung transplant procedure, performed between January 1, 2015, and December 31, 2017 (group 1: 27 patients) and between January 1, 2018, and November 30, 2019 (group 2: 44 patients) in Silesian Center for Heart Diseases. Patients who received transplants before 2015 as well as those who underwent single lung transplant, underwent retransplant, or did not survive the procedure were excluded from the study. Detailed demographic and clinical characteristics of studied donor-recipient pairings are presented in Table 1. The first objective was to assess whether there is a significant difference in quality of the donor pool, measured by mean oxygenation index of the given period and how it affected the PaO_2/FiO_2 at the 2 remaining recipient-associated time points. The second objective was to evaluate the quality of the lungs by means of oxygenation index after the transplant for those who had received the double lung graft of PaO_2/FiO_2 > 400 mm Hg at reporting of the donor. The third objective was to compare aforementioned results with those obtained among recipients with donor oxygenation index < 400 mm Hg. The second and third objectives were performed only among patients from group 2 with available data (n = 32). Detailed demographic and clinical characteristics of this particular donor-recipient pairings are presented in Table 2.

Statistical Analysis

Data with normal distribution were presented as mean and standard deviation. Data not presenting the normal distribution were presented as median and interquartile range. Statistical analyses were carried out using the TIBCO Statistica 13.3 software (TIBCO Software, Palo Alto, Calif, United States). With its use, basic descriptive statistics were analyzed along with Shapiro-Wilk tests as well as Student *t* test analysis for independent samples and the Mann-Whitney *U* test. The classic threshold $\alpha = .05$ was considered the level of significance.

Table 1. General Characteristics With Demographic and Clinical Features of the Entire Study Group

All Patients (n = 71)	2015-2019
Recipient age, median (IQR)	35 (28)
Recipient BMI, median (IQR)	18 (4)
Donor age, mean (SD), y	43.12 (12)
Donor BMI, mean (SD)	24.12 (3)
Recipient pulmonary function at qualification	
FEV_1, median (IQR), %	24 (17)
FVC, mean (SD), %	46.84 (19)
6MWD, median (IQR), m	323.1 (247.5)
Oxygenation index, mean (SD), mm Hg	462.37 (77)
Donor hemoglobin, mean (SD), g%	10.96 (3)
Donor serum creatinine, median (IQR), mg%	1.1 (0.88)
Recipient length of hospital stay, median (IQR), d	41 (22)
Duration of operation, median (IQR), h	12.92 (2.34)
Ventilation time, median (IQR), h	24.8 (8.25)
Total ischemic time, mean (SD), min	754 (472)
Recipient sex, No. (%)	
Female	35 (49.3)
Male	36 (50.7)
Donor sex, No. (%)	
Female	32 (45.07)
Male	39 (54.93)
Blood type of recipient, No. (%)	
0	19 (26.76)
A	28 (39.43)
AB	12 (16.9)
B	12(16.9)
Underlying disease, No. (%)	
Chronic obstructive pulmonary disease	8 (11.27)
Cystic fibrosis	39 (54.92)
Idiopathic pulmonary fibrosis	2 (2.82)
Interstitial lung disease (other than IPF)	5 (7.05)
Idiopathic pulmonary arterial hypertension	5 (7.05)
Combined pulmonary fibrosis and emphysema	1 (1.41)
Bronchiolitis obliterans syndrome	1 (1.41)
Emphysema	3 (4.23)
Bronchiectasis	2 (2.82)
Pneumoconiosis	1 (1.41)
Hypersensitivity pneumonitis	2 (2.82)
Langerhans cell histiocytosis	1 (1.41)
Hereditary hemorrhagic telangiectasia	1 (1.41)

Abbreviations: 6MWD, 6-minute walk distance; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; IPF, idiopathic pulmonary fibrosis.

RESULTS

Comparison of Donor and Recipient Oxygenation Index Depending on the Year of Surgery

The first assessment was to determine how the oxygenation indices of donors and recipients differ for procedures

Table 2. Donor and Recipient Demographic and Clinical Features Among Patients Who Underwent Double Lung Transplant Between 2018-2019, Divided Into Groups According to Donor Oxygenation Index

Variables	> 400 mm Hg	≤ 400 mm Hg	*P* Value
Recipient age, mean (SD), y	39 (14)	37.5 (14)	.732
Recipient BMI, mean (SD)	18.19 (3)	19.21 (4)	.365
Donor age, mean (SD), y	43.11 (16)	44.75 (10)	.686
Donor BMI, mean (SD)]	23.99 (3)	24.33 (3)	.714
Recipient pulmonary function at qualification			
FEV_1, mean (SD), %	22.26 (7)	30.04 (15)	.098
FVC, mean (SD), %	43.9 (17)	49.41 (22)	.577
6MWD, mean (SD), m	274.85 (166)	353.94 (160)	.254
Donor hemoglobin, mean (SD), g %	11.56 (3)	11.18 (3)	.725
Donor serum creatinine, median (IQR), mg%	0.97 (0.63)	1.05 (0.82)	.886
Duration of operation, median (IQR), h	12.58 (2.34)	12.71 (3.75)	.765
Ventilation time, median (IQR), h	28.58 (62.59)	26 (29.83)	.396
Total ischemic time, mean (SD), min	596.73 (469)	821.14 (488)	.217
Recipient sex, No. (%)			.674
Female	14 (48.28)	4 (57.14)	
Donor sex, No. (%)			.125
Female	9 (31.03)	5 (71.42)	
Underlying disease, No. (%)			.846
Chronic obstructive pulmonary disease	2 (6.90)	2 (28.57)	
Cystic fibrosis	19 (65.52)	3 (42.86)	
Interstitial lung disease (other than IPF)	3 (10.35)	1 (14.28)	
Idiopathic pulmonary arterial hypertension	1 (3.457)	0 (0)	
Emphysema	2 (6.90)	0 (0)	
Bronchiectasis	1 (3.45)	0 (0)	
Pneumoconiosis	0 (0)	1 (14.29)	
Hypersensitivity pneumonitis	1 (3.45)	0 (0)	

Abbreviations: 6MWD, 6-minute walk distance; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range.

performed in 2015 to 2017 (group 1) and 2018 to 2019 (group 2). Analyses were performed using the Student *t* test for independent samples, comparing the PaO_2/FiO_2 of the donor (first time point) and recipient (second time point) in the mentioned groups. The analysis was performed only on patients who underwent double lung transplant, excluding retransplant.

It showed that in the case of operations performed in 2018 to 2019, oxygenation rates were significantly lower in donors while significantly higher in recipients on the first day than those observed in 2015 to 2017. The strength of dependence for donors was large and was very large for recipients. Detailed results of this part of the study are presented in Table 3.

Comparison of Recipient Oxygenation Index Depending on Donor Oxygenation Index

Subsequently, it was analyzed how the recipient mean oxygenation index differs among those who received transplants between 2018 and 2019, depending on whether PaO_2/FiO_2 was observed above or below 400 mm Hg in the donor. Analyses were performed using Student *t* test for independent samples, comparing the recipient oxygenation index (on the first and second days) in these groups. The analysis was performed only on patients who underwent double lung transplant, excluding retransplant.

The results were not statistically significant. This means that irrespective of whether the donor had PaO_2/FiO_2 above or below 400 mm Hg, recipients showed similar oxygenation index values both on the first and the following days. Detailed results of this analysis are demonstrated in Table 4.

Extending the donor pool allowed more lungs to be procured. Such change of approach led to increase of double lung transplant from 9 per year to 22 per year and counting. Replacing the strict oxygenation index policy from previous years with the more liberal one alone led to additional 7 double lung transplants between 2018 and 2019.

Short-term Mortality

One-year mortality among double lung recipients who received transplants between 2015 and 2017 was approximately 18.75%. The same parameter among the patients who received transplants in 2018 was 8.7%. All 7 patients with PaO_2/FiO_2 of less than 400 mm Hg are alive at the time of submitting this article (5 received transplants in 2018).

DISCUSSION

Ideal PaO_2 ($PaO_2 > 300$ mm Hg on $FiO_2 = 1.0$, positive end-expiratory pressure = 5 cm H_2O) was believed to be the most important factor to evaluate lung quality. Several researches have shown that poor oxygenation index (PaO_2/

Table 3. Comparison of Donor and recipient oxygenation indices (PaO_2/FiO_2) Depending on Year of Surgery

Variable	2015-2017 (n = 27)		2018-2019 (n = 44)				95% CI		
	Mean	SD	Mean	SD	*t*	*P* Value	LL	UL	Cohen *d*
Donor PaO_2/FiO_2 (first time point)	487.13	72.37	447.51	78.66	2.12	.037	3.01	76.23	0.88
Recipient PaO_2/FiO_2 (second time point)	323.02	114.97	473.21	244.13	−3.33	.001	−240.26	−60.12	2.16

Abbreviations: FiO_2, fraction of inspired oxygen; LL, lower limit; UL, upper limit.

Table 4. Comparison of Recipient Oxygenation Indices Depending on Donor Oxygenation Index

Variables	> 400 mm Hg (n = 29)		< 400 mm Hg (n = 7)		t	P Value	95% CI		Cohen d
	Mean	SD	Mean	SD			LL	UL	
Recipient PaO_2/FiO_2 (second time point)	462.89	208.71	412.24	216.23	0.57	.571	−154.30	255.59	0.27
Recipient PaO_2/FiO_2 (third time point)	429.41	165.80	454.53	153.37	−0.25	.808	−344.89	294.65	0.16

Abbreviations: FiO_2, fraction of inspired oxygen; LL, lower limit; UL, upper limit.

FiO_2) should not be the reason of immediate exclusion of the donor [4,5]. First research assessing the issue of oxygenation index dated back to 1995 [6]. Sundaresan et al concluded that successful outcome of lung transplant can be achieved with the use of marginal donor lungs. More data were provided by the review article assessing more than 12,000 donors. Patients were divided into 3 groups: donor PaO_2/FiO_2 greater than 300 mm Hg, PaO_2/FiO_2 201 to 300 mm Hg, and PaO_2/FiO_2 of less than 200 mm Hg. The conclusion of the article was that donor oxygenation index did not affect survival of graft recipients, and it may play much less vital role that previously believed [4]. Disqualifying a donor solely on this result seems irrational. Sometimes, lower oxygenation index may be an effect of an easily reversible process such as pulmonary edema or retained secretion. Customized lung donor management protocols (eg, diuresis, lung recruitment maneuvers) may improve lungs functioning and help the donors to meet the oxygenation requirement [7]. Nevertheless, harvesting and transplanting the organs from donors with PaO_2/FiO_2 levels lower than 300 mm Hg does not seem to affect the results of the transplant in a negative way [8–10]. Another review published by Schiavon et al also assesses marginal donors. Its conclusion states that majority of articles report comparably positive outcomes of lung transplant after donation from donors of oxygenation index of less than 300 mm Hg [11]. On the other hand, the nonlinear model of Thalbut et al showed a steep increase in the relative risk of death when donor PaO_2/FiO_2 before harvest was below 350 mm Hg [12]. However, available data of more recent studies and review assessing greater number of patients rule in favor of extending the oxygenation index values as well as taking a more liberal approach on its importance. All of those findings were taken into consideration at the end of 2017 before it was decided to change the policy pertaining the oxygenation index in our facility. Our results are consistent with available literature that oxygenation index of less than 400 mm Hg does not mean that the quality of the lungs will provide worse function than those of PaO_2/FiO_2 exceeding 400 mm Hg. Our study also demonstrated that 5 of those 7 patients with oxygenation index of less than 400 mm Hg had mean PaO_2/FiO_2 of 310 mm Hg. All of the 7 patients are still alive up to this day; 5 of them reached 1-year survival as they received transplants in 2018. What is more, 2 of our recipients received lungs with PaO_2/FiO_2 less than 300 mm Hg. Both reached 1-year survival and are in general good condition.

CONCLUSIONS

A more liberal clinically based approach for assessment of lung suitability as a potential graft not only increases the donor pool but also proves that suboptimal donors are not associated with producing inferior results for the recipients. Moreover, short-term mortality of patients receiving lungs of lesser oxygenation index of the donor at reporting does not differ from those with supposedly better lungs among double lung transplant recipients. This issue requires further study on a larger group with increased follow-up time.

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