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Heart recovery and reverse remodeling following lung transplant in pulmonary artery hypertension

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Abstract

Background: Pulmonary artery hypertension (PAH) is a progressive disease that result in right heart dysfunction. Lung transplantation (LTx) improve survival in end-stage disease. The aim of this study is to assess heart recovery after LTx for patients with primary and secondary pulmonary hypertension.

Methods: We conducted a single center retrospective review for patients with primary and secondary PAH underwent LTx between the period of January 2015 and December 2020. Baseline characteristics and echocardiographic measures were assessed pre-operative and after 1 year follow-up. Survival comparison between primary and secondary PAH was estimated by Kaplan–Meier method.

Results: We identified 43 participants for the study. Among the participants, 11 case had primary PAH. Median age during transplant was 60 years (45.5, 65.5). Left atrium anterio-posterior dimensions, systolic right ventricle pressure tricuspid peal regurgitant velocity and severity of tricuspid regurgitation were found to be significantly improved post-operatively compared to pre-operative echocardiography (p value < 0.05). Overall mortality was not significant between primary and secondary PAH (p value $= 0.66$).

Conclusions: LTx can reverse heart remodeling and facilitate recovery in primary and secondary PAH. Our data confirm the importance of LTx as a viable option in PAH failing medical treatment.

Keywords: Lung transplantation, Pulmonary artery hypertension, Echocardiography

Background

Pulmonary artery hypertension (PAH) is a disease characterized by pulmonary vasculature remodeling resulting in right ventricular hypertrophy and remodeling [1]. Transplant surgery is the method of choice in patients failing medical management of PAH [2]. However, controversy whether lung transplant surgery (LTx) of heart–lung transplant would provide optimal therapy and organ allocation in patients with PAH [3, 4]. The aim of this study is to assess heart recovery after LTx for patients with primary and secondary pulmonary hypertension.

Methods

This is a single center retrospective review for patients with primary and secondary PAH underwent LTx in Brigham and Women's Hospital–Boston, Massachusetts, between the period of January 2015 and December 2020. The institutional board review (IRB) approved the study and waived informed consent. Chart review was carried out and we identified 43 cases operated in our center that were included in the statistical analysis. Among the 43 cases, 32 cases were diagnosed with secondary PAH. Causes of secondary PAH were due to chronic

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obstructive lung disease (16 cases), idiopathic pulmonary fibrosis (7 cases), hypersensitivity pneumonitis (5 cases), sarcoidosis (2 cases), bronchiolitis obliterans (1 case), and Langerhan's Histiocytosis (1 case).

PAH was diagnosed using right heart catheterization. Baseline characteristics and echocardiographic measures were assessed pre-operative and after 1 year from the LTx. All echocardiographic measurements were obtained from the mean of 3 consecutive beats. A subgroup analysis was done comparing the baseline characteristics and echocardiographic findings between primary and secondary PAH. Survival comparison between primary and secondary PAH was estimated by Kaplan–Meier method.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables normally distributed were presented as mean and standard deviation (SD). Skewed continuous variables were presented as median and interquartile range (IQR). Categorical variables were analyzed using χ2-test or Fisher's exact test. Continuous variables were analyzed using parametric and non-parametric tests (independent-sample *t* test and Mann–Whitney *U* test). Survival probability was estimated by the Kaplan–Meier method using the log-rank test. Statistical analysis was done using R version 4.1.2.

Table 1 Pre-operative data

Patients characteristics	
Age (years, IQR)	60 (45.5–65.5)
Sex	
Female, *n* (%)	23 (53.5)
BMI, (SD)	26.87 (7.17)
Diagnosis, *n* (%)	
Primary PAH	11 (25.6)
Secondary PAH	32 (74.4)
Serum creatinine, mg/dl	0.55 (0.63–0.94)
Total bilirubin mg/dL	0.55 (0.3–0.92)
Albumin, g/dl	3.7 (3.25–4.3)
LAS (IQR)	44.64 (38.4–54.4)
Karnofsky score (IQR)	70 (50–70)
Days to LTx (IQR)	309 (118–777)
Right heart catheterization (IQR)	
Mean PAP, mmHg	37.5 (30.25–47.75)
Mean RAP, mmHg	8 (6–11)
Mean PCWP, mmHg	12.5 (8–16)
Systolic RVP, mm Hg	54 (42.5–79.25)
Tricuspid annuloplasty, *n* (%)	2 (5)

yrs Years, *IQR* Interquartile range, *SD* Standard deviation, *PAH* Pulmonary artery hypertension, *LAS* Lung allocation score, *LTx* Lung transplant surgery, *PAP* Pulmonary artery pressure, *RAP* Right atrium pressure, *PCWP* Pulmonary capillary wedge pressure, *BMI* Body mass index

Results

Table 1 describes the overall baseline characteristics in the 43 patients with PAH irrespective to the type of hypertension. Median age of those who received LTx was 60 years old. Among those who received LTx, 11 (25.6%) had primary PAH. Females composed 53.5% of the study population. Mean body mass index (BMI) 26.87 (SD = 7.17). Median laboratory findings (total bilirubin, creatinine, albumin) were within normal limits. Only 2 patients underwent tricuspid annuloplasty along with LTx for severe tricuspid regurgitation as noted in the echocardiography.

Comparison between echocardiographic findings preoperatively and postoperatively were described in Table 2. Patients received LTx had significant increase in the left ventricle anterio-posterior (A-P) dimension leading to improved left ventricle filling. In addition, reduction in the Systolic right ventricular pressure (RVP), right ventricle (RV) basal diameter, right atrium (RA) diameter, and tricuspid valve (TV) peak regurgitant velocity was noticed in the echocardiographic findings. No statistical change was noted with respect to preoperative ejection fraction (EF) and body surface area (BSA) and 1 year follow-up. Twelve patients (27.9%) had moderate to severe tricuspid regurgitation pre-operative. Severity of the regurgitation improved during the 1-year echocardiography follow-up and only 1 patient did not have improvement in the regurgitation severity.

Table 3 compare the baseline characteristics between primary and secondary PAH. It is noted that primary PAH patients have statistically significant higher baseline bilirubin (1.5 vs 0.4) and lower baseline albumin (3.2 vs 4.2). In addition, right heart catheterization showed higher median pulmonary artery and right ventricular pressure in the primary PAH.

Pre-operative and 1 year follow-up post-operative echocardiography measurements comparing primary and secondary hypertension were described in Table 4. Pre-operative right heart echocardiography findings showed a comparable similarity with the previously described right heart catheterization findings. Systolic RVP, RV basal diameter, RA diameter, and TV peak regurgitant velocity where significantly higher in the primary PAH group. Post-operative echocardiographic findings did not show any significant difference between the 2 groups.

Tables 5 and 6 describe the 1 year heart changes following LTx in patients diagnosed with primary and secondary PAH respectively. Patients with primary PAH had increase in the median LA A-P dimension and decrease in the systolic RVP, RV basal diameter, RA diameter, and TV peak regurgitant velocity.

Table 2 Pre-operative vs post-operative echocardiography measurements

Variable	Pre-operative ($n=43$)	Post-operative ($n=31$)	*P* value
Ejection fraction	61 (59–65)	62 (57–65)	0.72
Body surface area, m^2	1.9 (1.68–2.03)	1.89 (1.65–2.1)	0.57
Left atrium A-P dimension, mm	33 (31–39)	39 (35.5–42)	0.008
Systolic RVP, mm Hg	52 (34.24–71)	28 (24–31)	< 0.001
RV basal diameter, mm	42 (38–52)	36 (33–42)	< 0.001
RA diameter, mm	40 (34–52.5)	36 (33–40)	< 0.01
TV peak regurgitant velocity	3.37 (2.67–3.9)	2.28 (2.16–2.52)	< 0.001
Tricuspid regurgitation			< 0.001
Moderate–severe, *n* (%)	12 (27.9)	1 (3.7)	

A-P Lung transplant surgery: anterio-posterior, *RVP* Right ventricular pressure, *RV* Right ventricle, *RA* Right atrium, *TV* Tricuspid valve

Table 3 Pulmonary artery hypertension primary vs secondary: baseline characteristics

Patients characteristics	Primary ($n=11$)	Secondary ($n=32$)	*P* value
Age (years, IQR)	62 (46–64.5)	60 (45.8–66)	0.91
Sex			0.25
Female, *n* (%)	8 (72.7)	15 (46.9)	
BMI, mean (SD)	29.6 (6.9)	25.9 (6.7)	0.14
Serum creatinine,	0.89 (0.82–0.97)	0.7 (0.61–0.89)	0.05
Total bilirubin mg/dL	1.5 (1.27–2)	0.4(0.25–0.6)	< 0.001
Albumin, g/dl	3.2 (3.15–3.45)	4.2 (3.7–4.35)	< 0.001
LAS (IQR)	44.6 (40.4–54.9)	45.1 (37.9–56.1)	0.69
Karnofsky score (IQR)	70 (60–70)	60 (50–70)	0.36
Days to LTx (IQR)	233 (101–1367)	368 (124–628)	0.97
Right heart catheterization (IQR)			
Mean PAP, mmHg	59 (47–67)	33 (28.5–40)	< 0.001
Mean RAP, mmHg	8 (7–16)	8 (6–10)	0.35
Mean PCWP, mmHg	11 (8.5–14.5)	14 (8–16.5)	0.57
Systolic RVP, mm Hg	88 (76–99)	48 (40.5–58.5)	< 0.001
Tricuspid annuloplasty, *n* (%)	2 (18.2)	0 (0)	0.1

yrs Years, *IQR* Interquartile range, *SD* Standard deviation, *PAH* Pulmonary artery hypertension, *LAS* Lung allocation score, *LTx* Lung transplant surgery, *PAP* Pulmonary artery pressure, *RAP* Right atrium pressure, *PCWP* Pulmonary capillary wedge pressure, *BMI* Body mass index

Survival comparison between primary and secondary PAH was estimated by Kaplan–Meier method (Fig. 1). Five-year survival probability for the primary and secondary PAH were 62% and 64% respectively. Overall mortality was not significant between primary and secondary PAH following LTx (p value = 0.66).

Discussion

The results of this study suggest the improved heart function and morphology following LTx in patients with primary or secondary PAH. Patients cardiac function improvement was shown and confirmed with the 1-year echocardiography follow-up assessment. Improvement of the right heart function was assessed by measuring RV systolic pressure, RV basal diameter, RA diameter, and tricuspid valve peak regurgitant velocity.

None of the patients had moderate to severe tricuspid regurgitation during the follow-up echocardiography. Such improvement in the tricuspid function was also described using echocardiographic findings [5]. Shigemura et al. described the improved outcome of combining tricuspid valve repair with double LTx in patients with severe PAH [6, 7]. It is noted in our study that only 2 cases underwent tricuspid annuloplasty during the transplant indicating the possibility of functional TV regurgitation improvement without the need of surgical intervention.

Salman et al. described the improvement in right heart function in PAH following LTx 3 weeks following transplantation [8]. Our present data add on the previous presented data by assessing the right and left heart structures 1 year after transplant.

Left heart function was assessed in our study, in addition to the right heart function, due to the potential impact on mortality and treatment failure suggested by Wolferen et al. [9]. In our study, improvement in the left atrium A-P diameter was significantly seen in primary PAH. This improvement is not limited to heart function but extend to secondary organs [10].

Although few papers investigated the potential impact of secondary PAH as a prognostic factor in patients with end-stage lung diseases [11, 12], little known on the difference in outcome between primary and secondary PAH following LTx. It is interesting to note that, although patients with primary PAH tended to have a higher

Table 4 Pulmonary artery hypertension primary vs secondary: echocardiography measurements and outcome

Patients characteristics	Primary ($n=11$)	Secondary ($n=32$)	*P* value
Pre-operative echocardiography			
Ejection fraction	65 (65–68)	65 (60–70)	0.91
Body surface area, m^2	1.9 (1.65–2.02)	1.86 (1.76–2.01)	0.98
Left atrium A-P dimension, mm	34 (30.5–38)	33 (31–39)	0.89
Systolic RVP, mm Hg	71 (63–80.5)	40 (34–60)	0.004
RV basal diameter, mm	53 (46–55)	40 (38–35)	0.006
RA diameter, mm	60 (49–65.5)	38.5 (31.75–45.25)	0.001
TV peak regurgitant velocity	3.97 (3.52–4.17)	2.97 (2.67–3.64)	0.02
Post-operative echocardiography			
Ejection fraction	64 (60–65)	61.5 (56.2–65)	0.95
Body surface area, m^2	1.7 (1.7–2.1)	1.92 (11.62–2.07)	0.79
Left atrium A-P dimension, mm	38 (37–43)	39 (33.5–41.7)	0.40
Systolic RVP, mm Hg	31 (27–34.5)	26 (23.75–30)	0.14
RV basal diameter, mm	34 (28–36)	36 (34–44)	0.13
RA diameter, mm	35 (33–42)	37 (33–40)	0.67
TV peak regurgitant velocity	2.4 (2.24–2.52)	2.27 (2.16–2.42)	0.35

A-P Lung transplant surgery: anterio-posterior, *RVP* Right ventricular pressure, *RV* Right ventricle, *RA* Right atrium, *TV* Tricuspid valve

Table 5 Primary pulmonary artery hypertension: pre-operative vs post-operative echocardiography

Variable	Pre-operative ($n=11$)	Post-operative ($n=9$)	*P* value
Ejection fraction	65 (65–68)	64 (60–65)	0.78
Body surface area, m^2	1.9 (1.64–2.02)	1.7 (1.7–2.1)	0.86
Left atrium A-P dimension, mm	34 (28.5–38)	38 (37–43)	0.04
Systolic RVP, mm Hg	71 (64–80)	31 (27–34.5)	0.004
RV basal diameter, mm	53 (46–55)	34 (28–36)	< 0.001
RA diameter, mm	60 (49–64.5)	35 (33–42)	0.001
TV peak regurgitant velocity	3.97 (3.52–4.17)	2.4 (2.24–2.52)	< 0.001
Tricuspid regurgitation			< 0.001
Moderate–severe, *n* (%)	8 (72.7)	0 (0)	

A-P Lung transplant surgery: anterio-posterior, *RVP* Right ventricular pressure, *RV* Right ventricle, *RA* Right atrium, *TV* Tricuspid valve

Table 6 Secondary pulmonary artery hypertension: pre-operative vs post-operative echocardiography

Variable	Pre-operative ($n=32$)	Post-operative ($n=22$)	*P* value
Ejection fraction	60 (56–63)	61 (57–63)	0.25
Body surface area, m^2	186 (1.76–2.01)	1.92 (1.2–2.07)	0.74
Left atrium A-P dimension, mm	33 (31–39)	39 (33.5–41.75)	0.14
Systolic RVP, mm Hg	40 (34–60)	26 (23.7–30)	< 0.001
RV basal diameter, mm	40 (38–45)	36 (34–44)	0.01
RA diameter, mm	38.5 (31.75–45.25)	37 (33–40)	0.35
TV peak regurgitant velocity	2.97 (2.67–3.64)	2.27 (2.16–3.78)	< 0.001
Tricuspid regurgitation			0.03
Moderate–severe, *n* (%)	5 (15.6)	0 (0)	

A-P Lung transplant surgery: anterio-posterior, *RVP* Right ventricular pressure, *RV* Right ventricle, *RA* Right atrium, *TV* Tricuspid valve

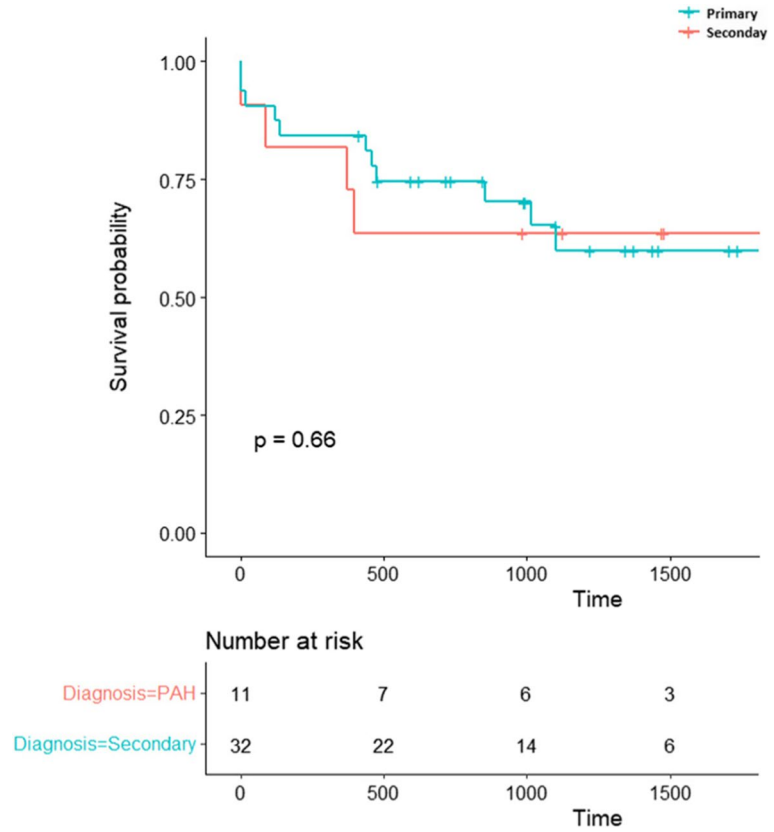

Fig. 1 Comparison between primary vs secondary PAH survival probability after LTx

pre-operative right heart echocardiographic findings compared to secondary PAH. Improvement to normalization of the right heart function post-operatively with no difference in mortality was noted between the two groups. It should be noted that meticulous peri-operative and post-operative management of PAH is essential to improve survival in experienced centers [13].

Limitations of the study includes the following: this study is a retrospective chart review and potential bias might be seen. Our work is limited to a small sample size which limited further analysis. In addition, loss of echocardiography follow-up after the transplant was noted in a few cases.

Conclusions

LTx can reverse heart remodeling and facilitate recovery in primary and secondary PAH. Our data confirm the importance of LTx as a viable option in PAH failing medical treatment.

Abbreviations

LTx: Lung transplant surgery; PAH: Pulmonary artery hypertension; IRB: The institutional board review; IQR: Interquartile range; SD: Standard deviation; A-P: Anterio-posterior; RVP: Right ventricular pressure; RV: Right ventricle; RA: Right atrium; TV: Tricuspid valve; EF: Ejection fraction; PAP: Pulmonary artery pressure; RAP: Right atrium pressure; PCWP: Pulmonary capillary wedge pressure; LAS: Lung allocation score; BMI: Body mass index.

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Authors' contributions

HA contributed to the research question formulation, and is the corresponding author. AC, MK, JY, AK, HG, and NS reviewed the paper. HM reviewed and edited the research article. All authors read and approved the final manuscript.

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Availability of data and materials

All data are available for the publication and sharing.

Declarations

Ethics approval and consent to participate

This study was approved by the Brigham and Women's Hospital institutional board review. Patient consent was waived by the IRB.

Consent for publication

All authors consent submission and publication to 'The Cardiothoracic Journal'.

Competing interest
The authors declare that they have no competing interests.

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