Double-lung transplantation followed by delayed percutaneous repair for atrial septal defect-associated pulmonary arterial hypertension

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To the Editor:

Pulmonary arterial hypertension (PAH) is a rare but severe complication of unrepaired atrial septal defect (ASD) and appears to be among the strongest predictors of death in adults with Eisenmenger syndrome [1]. For decades, heart–lung transplantation (HLTx) has been considered the best treatment of last resort for patients with ASD-associated PAH and right ventricular failure. Nonetheless, over 25% of patients die within 1 year after the procedure [2]. In addition, severe organ shortages result in long waiting list times, during which the frequency of clinical deterioration or death exceeds 30% [3]. Double-lung transplantation (DLTx) with concomitant surgical cardiac-defect repair has been suggested as an attractive alternative for patients with ASD-associated PAH [4]. However, due to the limited number of patients with ASD-associated PAH treated by HLTx or DLTx, the available scientific evidence is insufficient to define the best strategy.

In 2015, we developed a multimodal strategy for treating patients with severe ASD-associated PAH, consisting of DLTx followed 3 to 6 months later by percutaneous ASD closure. We chose the 3–6 month interval because DLTx and concomitant surgical ASD repair would increase the operative time and because we expected that, during the interval, the pulmonary pressures would normalise and right heart function would recover, thereby decreasing peri-operative morbidity. We also waited at least 1 month after any clinically significant medical event before performing ASD closure. Furthermore, ASD closure right after DLTx may increase the right ventricular preload, thereby aggravating the right heart dysfunction. Here, we report on the feasibility and outcome of this strategy applied at our institution.

We retrospectively reviewed consecutive patients with ASD-associated PAH who were treated by either DLTx followed 3–6 months later by percutaneous ASD closure (between 2015 and 2020) or HLTx (between 2009 and 2014). Briefly, in the DLTx group, pretransplant echocardiography and right heart catheterisation (RHC) with balloon calibration of ASD size were performed to check the feasibility of ASD closure. The ASD was closed percutaneously after RHC performed 3–6 months after DLTx to confirm the absence of residual pulmonary hypertension. The Amplatzer septal occluder (size, number 16 to number 38) was used. Patients routinely received 75 mg of oral acetylsalicylic acid daily, starting on the day of ASD closure. Echocardiography was performed 1, 3, 6 and 12 months after closure. As part of our post-operative protocol, broad indications for extracorporeal membrane oxygenation (ECMO) were applied in the DLTx group to promote recovery of right heart function and to limit the development of primary graft dysfunction [5]. Exclusion criteria were as follows: non-*ostium secundum* ASD, infeasibility of percutaneous ASD closure, and complex cardiopathy. Baseline demographics were described as median with the first and third quartiles for continuous variables and as percentages for categorical variables. Baseline features were compared between groups using Fisher's exact test or the Kruskal–Wallis test, as appropriate. Given the 41-month median follow-up, we evaluated survival only during the first post-transplant year, using the Kaplan–Meier method with the log-rank test. The ethics review board of the scientific society *Société Française de Chirurgie Thoracique et Cardio-Vasculaire* approved the study (IRB00012919).

Shareable abstract (@ERSpublications)
In pulmonary hypertension with right heart failure due to atrial septal defect, double-lung transplantation then percutaneous defect closure 3–6 months later compared favourably with the standard approach consisting of heart–lung transplantation https://bit.ly/3BjdLzw

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Between 2009 and 2020, 21 patients underwent HLTx or DLTx for ASD-associated PAH. Among them, four were excluded due to non-*ostium secundum* ASD (n=2), previous surgical ASD closure (n=1) or complex cardiopathy (n=1). Of the 17 included patients, 10 had DLTx followed by percutaneous ASD closure after a median of 5.5 months and seven had HLTx. Transplantation was indicated for advanced right ventricular failure in 13 patients, life-threatening haemoptysis in three, and coronary compression due to pulmonary artery dilatation in one. Demographics and pre-operative clinical and haemodynamic severity parameters were comparable between groups. No between-group differences were found for primary graft dysfunction, post-operative ventilation duration, dialysis in the intensive care unit (ICU), or 3-month mortality (table 1); as noted above, post-operative ECMO use was more common after DLTx. In the DLTx group, median pulmonary arterial pressure was 17 mmHg and within the normal range in all patients before ASD closure, and right ventricle function improved significantly after transplantation. Of note, dialysis during the ICU stay, in-hospital death, and chronic lung allograft dysfunction occurred only in the HLTx group, although the differences were not significant (table 1). The waiting list time in the HLTx group was shorter, although not significantly. 1-year survival rates were 100% and 67% after DLTx plus delayed percutaneous ASD closure and after HLTx, respectively (p=0.09). During the median follow-up of 41 (10–80) months, four patients died, from multiorgan failure (n=1), bronchial fistula (n=1) or unknown cause (n=1) in the HLTx group and from multisystemic mucormycosis infection (n=1) in the DLTx group. No patient experienced ASD closure complications during follow-up.

To date, this is the largest cohort of patients with ASD-associated PAH treated with DLTx followed by percutaneous ASD closure after 3 to 6 months. Our results support the feasibility and safety of this multimodal sequential approach. Early survival was better and in-hospital complications less common with DLTx, although the differences were not statistically significant in this small case series. In addition to sparing the heart allograft for another recipient [6], DLTx is associated with a lower rate of peri-operative bleeding compared to HLTx [4]. However, the best time for ASD closure after DLTx is not agreed upon. Pre-operative ASD closure in patients with severe PAH carries a high risk of worsening PAH with life-threatening right ventricular failure and should therefore be discouraged. ASD closure immediately

TABLE 1 Main features of the overall population and two treatment groups

	Overall population	DLTx and ASD closure	HLTx	p-value[#]
Total subjects, n	17	10	7	0.41
Females	16 (94)	10 (100)	6 (86)	0.41
Age (years)	35 (26–38)	34 (24–38)	35 (26–42)	0.80
Blood group O/A/B	7 (41)/8 (47)/2 (12)	3 (30)/6 (60)/1 (10)	4 (57)/2 (29)/1 (14)	0.52
Size of the atrial septal defect (mm)	18 (23–32)	18 (23–32)	25 (7–40)	0.91
WHO functional class III/IV	8 (47)/9 (53)	5 (50)/5 (50)	3 (42)/4 (58)	0.65
6-min walk distance (m)	388 (345–443)	388 (364–436)	345 (365–443)	0.19
Right heart catheterisation				
Right atrial pressure (mmHg)	6 (4–8)	6 (5–8)	7 (3–8)	0.44
Mean pulmonary artery pressure (mmHg)	65 (56–92)	65 (56–92)	65 (64–89)	0.67
Pulmonary capillary wedge pressure (mmHg)	6 (4–8)	5 (4–11)	7 (1–7)	0.26
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.7 (2.1–3.2)	2.7 (2.0–3.2)	2.6 (2.1–3.8)	0.94
Pulmonary vascular resistance (WU)	17 (13–27)	15 (13–23)	23 (17–36)	0.49
Intravenous prostacyclin	11 (65)	6 (60)	5 (71)	0.99
High emergency allocation programme	8 (47)	3 (30)	5 (71)	0.15
Time on the waiting list (months)	11.2 (1.1–17.5)	11.2 (7.8–17.5)	3.8 (0.4–17.7)	0.58
Pre-operative veno-arterial ECMO (n=10)	1 (6)	0 (0)	1 (14)	0.10
Primary graft dysfunction score grade 3 at 72 h[¶] (n=14)	6 (42)	5 (71)	1 (14)	0.10
Haemothorax	5 (29)	2 (20)	3 (43)	0.59
Ventilation time in the ICU (days)	11 (5–20)	11 (8–20)	8 (4–30)	0.71
Post-operative veno-arterial ECMO	9 (53)	8 (80)	1 (14)	0.01
Dialysis in the ICU	1 (6)	0 (0)	1 (14)	0.41
In-hospital mortality	1 (6)	0 (0)	1 (14)	0.41
Chronic lung allograft dysfunction at last follow-up (n=13)	2 (12)	0 (0)	2 (28)	0.15
Follow-up (months)	41 (10–80)	26 (10–54)	62 (9–151)	0.09

Data are presented as n (%) or median (interquartile range), unless otherwise stated. DLTx: double-lung transplantation; ASD: atrial septal defect; HLTx: heart–lung transplantation; WHO: World Health Organization; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit. [#]: comparison of the DLTx plus ASD closure and HLTx groups (Fisher or Kruskal–Wallis test, as appropriate); [¶]: ungradable in three of the eight patients with post-operative veno-arterial ECMO in the DLTx plus ASD closure group.

before DLTx during the same surgical procedure has been described [7–10]. This strategy, although feasible [4], is associated with a higher risk of primary graft dysfunction [7] promoted by pulmonary hypertension [11]. However, the risk of primary graft dysfunction can be limited by post-operative ECMO [12, 13].

In the largest cohort comparing HLTx to DLTx associated with concomitant surgical cardiac defect repair, the patients with ASD-associated PAH managed by DLTx and ASD closure (n=56) had better survival to that in patients treated with HLTx (n=79) [4]. However, whether ASD closure was performed before or during DLTx was not specified. Interestingly, in our cohort, perhaps due to extended post-operative ECMO use in the DLTx group, primary graft dysfunction rates were not significantly different between the two groups. Closing the ASD a few months after DLTx allows the pulmonary artery pressures to normalise and right heart function to recover [14], as confirmed by our RHC data obtained just before ASD closure. In these circumstances, percutaneous ASD closure appears safer than open surgical closure in recently transplanted patients. One patient in the HLTx group died from multiorgan failure, but the three other causes of death were not specific to the surgical procedure.

In conclusion, our study confirms the safety and feasibility of treating ASD-associated PAH with DLTx followed 3–6 months later by percutaneous ASD closure. Studies in larger samples are needed to further assess survival and to better determine the optimal timing of percutaneous ASD closure.

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References

1 Kempny A, Hjortshøj CS, Gu H, *et al.* Predictors of death in contemporary adult patients with Eisenmenger syndrome: a multicenter study. *Circulation* 2017; 135: 1432–1440.

2 Chambers DC, Cherikh WS, Harhay MO, *et al.* The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult lung and heart–lung transplantation report—2019; focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019; 38: 1042–1055.

3 Agence de la biomédecine. Le rapport annuel médical et scientifique 2016. Le rapport médical et scientifique du prélèvement et de la greffe en France. www.agence-biomedecine.fr/annexes/bilan2016/donnees/organes/04-coeur-poumon/synthese.htm Date last accessed: 2 February 2018.

4 Sertic F, Han J, Diagne D, *et al.* Not all septal defects are equal: outcomes of bilateral lung transplant with cardiac defect repair *vs* combined heart–lung transplant in patients with Eisenmenger syndrome in the United States. *Chest* 2020; 158: 2097–2106.

5 Christie JD, Kotloff RM, Ahya VN, *et al.* The effect of primary graft dysfunction on survival after lung transplantation. *Am J Respir Crit Care Med* 2005; 171: 1312–1316.

6 Lund LH, Khush KK, Cherikh WS, *et al.* The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult heart transplantation report—2017; focus theme: allograft ischemic time. *J Heart Lung Transplant* 2017; 36: 1037–1046.

7 Urban M, Booth K, O'Sullivan J, *et al.* Novel management of atrial septal defect at time of lung transplantation. *Ann Thorac Surg* 2018; 106: e1–e2.

8 Goerler H, Simon A, Gohrbandt B, *et al.* Heart-–lung and lung transplantation in grown-up congenital heart disease: long-term single centre experience. *Eur J Cardiothorac Surg* 2007; 32: 926–931.

9 Hjortshøj CS, Gilljam T, Dellgren G, *et al.* Outcome after heart–lung or lung transplantation in patients with Eisenmenger syndrome. *Heart* 2020; 106: 127–132.

10 Matsuda H, Minami M, Ichikawa H, *et al.* Living-related lobar transplantation and simultaneous atrial septal defect closure in a young patient with irreversible pulmonary hypertension: a case report. *Heart Vessels* 2004; 19: 203–207.

11 Porteous MK, Lee JC, Lederer DJ, *et al.* Clinical risk factors and prognostic model for primary graft dysfunction after lung transplantation in patients with pulmonary hypertension. *Annals ATS* 2017; 14: 1514–1522.

12 Salman J, Ius F, Sommer W, *et al.* Mid-term results of bilateral lung transplant with postoperatively extended intraoperative extracorporeal membrane oxygenation for severe pulmonary hypertension. *Eur J Cardiothorac Surg* 2017; 52: 163–170.

13 Hoetzenecker K, Schwarz S, Muckenhuber M, *et al.* Intraoperative extracorporeal membrane oxygenation and the possibility of postoperative prolongation improve survival in bilateral lung transplantation. *J Thorac Cardiovasc Surg* 2018; 155: 2193–2206.e3.

14 Gorter TM, Verschuuren EAM, van Veldhuisen DJ, *et al.* Right ventricular recovery after bilateral lung transplantation for pulmonary arterial hypertension. *Interact Cardiovasc Thorac Surg* 2017; 24: 890–897.