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Should we perform bilateral-lung or heart–lung transplantation for patients with pulmonary hypertension?

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Abstract

A best evidence topic was constructed according to a structured protocol. The following question was addressed: of the following two procedures, heart–lung transplantation or bilateral-lung transplantation (BLTx), which offers the best outcome for patients with pulmonary hypertension (PH) listed for thoracic transplantation? Of the 77 papers found using a report search for PH and thoracic transplantation, 9 represented the best evidence to answer this clinical question. Overall, 1189 (67%) lung transplantations and 578 (33%) heart–lung transplantations have been reported worldwide for idiopathic PH. For patients with Eisenmenger's syndrome, HLTx represents up to 70% of the transplantation procedures they undergo. On the whole, neither procedure demonstrated an overall survival benefit, when compared with the other. However, PH patients represent a heterogeneous population according to (i) the primary mechanism of PH and (ii) the consequences of PH on right or/and left heart function. With regard to the latter consideration, the current evidence shows that HLTx offers excellent functional and survival outcomes for patients with congenital heart disease and Eisenmenger's syndrome, severe right or/and left heart dysfunction, and who are chronically inotropic dependent. As far as heart dysfunction is concerned, the published evidence approximated cut-off values at 10–25% for the right ventricle ejection fraction (RVEF) and at 32–55% for the left ventricle ejection fraction (LVEF). In the case of lower values for RVEF and LVEF, HLTx should be performed. In all other patients with PH, the evidence demonstrated that BLTx offers a comparable outcome with the advantage of better organ sharing for other recipients. In order to reduce the waiting time on transplantation lists, cardiac repair and BLTx can be offered in experienced centres to patients with simple cardiac anomalies such as atrial septal defect, patent ductus arteriosus or perimembranous ventricular septal defect.

Keywords: Lung transplantation • Perioperative issues and risk analysis • Heart transplantation

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. The protocol is fully described in the *ICVTS* [1].

THREE-PART QUESTION

Of the following two procedures, [heart–lung transplantation] or [bilateral-lung transplantation], which offers the best survival for adult patients listed with [pulmonary hypertension] and how should the procedure be selected?

CLINICAL SCENARIO

A 43-year old male was referred to a transplantation centre with a New York Heart Association (NYHA) functional Class IV and rapidly progressive primitive pulmonary hypertension (PH). The patient was put under intravenous epoprostenol therapy associated with sildenafil. Despite maximal medical therapy, clinical improvement was limited to NYHA functional Class III. On the 6-min walk test, the patient performed <350 m and cardiac index measured <2 l/min/m^2. According to official guidelines, this patient met the criteria for thoracic transplantation [2]. An echocardiography measured the left ventricle ejection fraction (LVEF) at 40%. Concern regarding the possible recovery advantages of bilateral-lung transplantation (BLTx), or the need for heart–lung transplantation (HLTx), was raised. We therefore decided to look up the evidence in the literature.

SEARCH STRATEGY

Using the Ovid interface, Medline 1990–July 2012, our literature search was limited to English-language articles with the following key terms: ("pulmonary hypertension.mp) AND ("heart-lung transplantation.mp") AND ("lung transplantation.mp"). Finally, a manual search was used to follow-up on the references from the retrieved studies.

SEARCH OUTCOME

A total of 77 abstracts were found, from which 9 articles were selected for providing the best evidence on the topic. These articles are documented in Table 1.

Table 1: Overview of the studies

Authors, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Bando *et al.* (1994), J Thorac Cardiovasc Surg, USA [3]	*Study group:* all PH patients ($n = 57$) caused by PPH ($n = 27$) or ES ($n = 30$)	Survival	Significantly lower overall survival and actuarial allograft survival in SLTx patients compared with BLTx and HLTx	Small sample Short follow-up of 3 months for the last included patients
Prospective study (5-year period, January 1989–January 1994) (level 1b)	SLTx ($n = 11$) BLTx ($n = 22$) HLTx ($n = 24$)	Haemodynamic and functional recovery	Significant post-transplant improvement in confidence interval, mean PAP and NYHA functional class for BLTx and HLTx in comparison with SLTx	
		Infection and rejection episodes	No difference SLTx vs BLTx vs HLTx	
Conte *et al.* (2001), Ann Thorac Surg, USA [4] Retrospective review (4- to 5-year period, July 1995–January 2000) (level 2a)	*Study group:* BLTx patients *Comparative group:* SLTx patients PPH ($n = 15$) BLTx ($n = 9$) SLTx ($n = 6$) SPH ($n = 40$) BLTx: $n = 21$ of which $n = 12$ patients with mean PAP >40 mmHg SLTx: $n = 19$ of which $n = 6$ patients with mean PAP >40 mmHg	Survival	Better overall survival for BLTx in the indication of PPH No overall survival difference between SLTx and BLTx in SPH Patients with SPH and mean PAP >40 mmHg may benefit more from BLTx	The results can be considered relevant when addressing the difference between PPH and SPH. But in the subgroups of SPH, samples of patients become too small to actually lead to a definitive conclusion
		Infection Rejection Ventilation	No difference SLTx vs BLTx No difference in BOS No difference	
Stoica *et al.* (2001), Ann Thorac Surg, UK [5] Retrospective review (15-year period, July 1984–August 1999) (level 2a)	*Study group:* ES treated with HLTx ($n = 51$) *Comparative group:* Patients treated with HLTx for another indication than ES ($n = 212$)	Survival	No survival difference between ES patients and other patients No survival difference between simple and complex ES patients	No comparison made with ES patients undergoing BLTx
Pielsticker *et al.* (2001), J Heart Lung Transplant, USA [6] Prospective study (level 1b)	*Study group:* 35 LTx centres worldwide (Europe, North America, Israel and Japan)	Tx practice patterns worldwide addressing PH	*Preferred procedure:* USA/Ca: BLTx Europe/Israel: HLTx BLTx preferred by 83% of centres *Criteria for HLTx:* • In 45% of centres, RV function with RVEF measurement cut-off range 10–25% • In 76% of centres, LV function with LVEF measurement cut-off range 32–55% • Severity of tricupsid valve regurgitation in 24% of centres Longest waiting time for HLTx was in the USA, shortest was in Canada	Heterogeneous practice pattern across the world. However, not exhaustive. Only 37 of the 46 surveyed centres answered the questionnaire
Waddell *et al.* (2002), J Heart Lung Transplant, Canada [7] and UNOS/ISHLT joint Transplant Registry	*Patients:* $n = 605$ end-stage ES ASD: ($n = 171$) VSD: ($n = 164$) MCA: ($n = 68$) PDA: ($n = 32$)	Survival	Overall, including any type of ES patients, significantly better survival for HLTx in comparison with LTx ($P = 0.002$) Highly significant benefit of HLTx for ES patients with VSD ($p = 0.0001$)	Unequal sample size between patients who underwent HLTx or LTx. ES patients form a heterogeneous group according to the involved cardiac anomalies

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Table 1: (*Continued*)

Authors, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Prospective registry (10-year period, 1988 and 1998) (level 1b)	*Study group:* HLTx *n* = 430 (71%) *Comparative group:* BLTx *n* = 106 (18%) SLTx *n* = 69 (11%)		VSD and MCA patients had the best prognosis and 96% of them were treated with HLTx Increased mortality risk for patients with VSD when treated with LTx (relative risk = 1.817, *P* = 0.035) All ES patients with more than ASD, PDA or perimembranous VSD are evaluated for HLTx	
Toyoda *et al.* (2008), Ann Thorac Surg, USA [8] Retrospective review (11-year period) (level 2a)	*Study group:* all HLTx (*n* = 49) and LTx (BLTx = 11, SLTx = 7) performed for IPAH between 1982 and 1993 at the same institution *Comparative group:* all HLTx (*n* = 8) and LTx (BLTx = 20, SLTx = 2) performed for IPAH between 1994 and 2006 at the same institution	Survival Incidence of BOS	Survival improvement by era No overall difference in survival when comparing BLTx with HLTx Improved by era *P* < 0.01 No difference HLTx vs BLTx	Vague criteria for choosing HLTx: chronically inotropic-dependent patients Small sample size and unequal repartition of the procedures from one era to the other
Fadel *et al.* (2010), Eur J Cardiothorac Surg, France [9] Retrospective review (10-year period, June 1998 and December 2008) (level 2a)	*Study group:* HLTx (*n* = 152) performed for PH Decision for HLTx was made because of: • Severe right heart failure, enlargement or dysfunction • Cardiac index <2.2 l/min/m^2 • Severe preoperative renal failure • Patients chronically dependent on inotropic support • CSPS *Comparative group* BLTx (*n* = 67) performed for PH during the same period in all other patients	Survival Waiting time Functional recovery Perioperative outcome	No overall survival difference Freedom of BOS survival was significantly better in HLTx No significant difference in waiting duration for a suitable graft Significantly more PGD in BLTx patients (left heart failure on echocardiography with severe pulmonary oedema and recurrent PH during the first 24–36 h following Tx) Need for cardiopulmonary bypass (*P* = 0.55) Postoperative mortality (*P* = 0.24) Early surgical complication (*P* = 0.85) *Mechanical ventilation:* HLTx < BLTx (*P* = 0.02) *Bronchial complications:* HLTx < BLTx (*P* < 0.001)	Unequal sample groups No cut-off definition for right heart failure such as RVEF measurement Different graft preservation methods over the study period No patient with left heart disease
Christie *et al.* (2011), J Heart Lung Transplant, ISHLT Registry [10] Prospective study (level 1b)	*Study groups:* BLTx from 1994 to 2009 (*n* = 16 628) HLTx from 1982 to 2009 (*n* = 3303) IPAH patients from 1990 to 2009: LTx *n* = 1189 (67%) HLTx *n* = 578 (33%)	*Survival:* half-life survival and conditional half-life survival (time to 50% survival for patients alive 1 year after Tx)	*BLTx:* Half-life 6.8 years Conditional half-life 9.3 years *HLTx:* • Half-life 5 years Conditional half-life 12 years • *LTx for IPAH*: half-life 4.9 years Conditional half-life 9.5 years • *HLTx for IPAH*: Half-life 5 years Conditional half-life 10.1 years	No direct comparative test on survival data No information on criteria for the choice of the Tx procedure No information about waiting time on transplantation list for a suitable graft according to the procedure
De Perrot *et al.* (2012), J Thorac Cardiovasc Surg, Canada [11]	All patients with PH *Study group:* Tx 1997–2004	Survival	No difference BLTx vs HLTx No difference regarding indication	*Criteria for HLTx decision:* LVEF<40%

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Table 1: (*Continued*)

Authors, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments/weaknesses
Retrospective review (13-year period, January 1997–September 2010) (level 2b)	*Comparative group:* Tx 2005–2010 BLTx patients *n* = 57 (72%) HLTx patients *n* = 22 (28%)		Majority of HLTx were performed for PH related to CHD	Previsible surgical obstacle to BLTx

ASD: atrial septal defect; BLTx: bilateral lung transplantation; BOS: bronchiolitis obliterans syndrome; CHD: congenital heart disease; CSPS: congenital systemic-to-pulmonary shunt; ES: Eisenmenger's syndrome; HLTx: heart–lung transplantation; IPAH: idiopathic pulmonary artery hypertension; ISHLT: International Society for Heart–Lung Transplantation; LTx: lung transplantation; LV: left ventricle; LVEF: left ventricle ejection fraction; MCA: multiple congenital anomalies; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PDA: patent ductus arteriosus; PGD: primary graft dysfunction; PH: pulmonary hypertension; PPH: primitive pulmonary hypertension; RV: right ventricle; RVEF: right ventricle ejection fraction; SLTx: single-lung transplantation; SPH: secondary pulmonary hypertension; Tx: transplantation; UNOS: United Network for Organ Sharing; VSD: ventricular septal defect.

RESULTS

Bando *et al.* [3] conducted a prospective study of patients who underwent single-lung transplantation (SLTx), BLTx or HLTx. The indication was PH caused either by primary PH (PPH) or by Eisenmenger's syndrome (ES). HLTx was performed when LVEF measured <35%, or when significant coronary artery disease, or ES, caused by surgically irreparable complex congenital heart disease (CHD), was diagnosed. Survival was better in BLTx and HLTx than in SLTx recipients (P = ns). Allograft actuarial survival was better in BLTx and HLTx ($P < 0.05$) patients, when compared with SLTx patients. BLTx and HLTx patients demonstrated an improvement in NYHA functional class ($P < 0.05$), cardiac index increase ($P < 0.05$) and in reducing mean pulmonary artery pressure ($P < 0.05$).

Conte *et al.* [4] compared the survival of patients with PPH or secondary PH (SPH), according to the procedure they had undergone (BLTx or SLTx). In the PPH group, BLTx patients had a better overall survival ($P < 0.05$). In the SPH group, no significant difference in survival, related to the procedure, was shown. There were no differences in the incidence of rejections, infections or other complications between patients who had undergone SLTx or BLTx. The authors reported a better survival for BLTx patients with a mean pulmonary artery pressure superior to 40 mmHg, prior to transplantation ($P = 0.19$).

Stoica *et al.* [5] retrospectively reviewed all ES patients undergoing HLTx ($n = 51$). The outcomes of these patients were compared with those of all the other patients ($n = 212$) undergoing the same procedure in the same institution for another indication. No significant difference in overall survival between the two groups ($P = 0.54$) was shown. A subgroup analysis could not demonstrate any difference between simple and complex ES patients who had undergone HLTx.

Pielsticker *et al.* [6] conducted a survey of worldwide practice patterns for treating PH with a transplantation procedure. Thirty-five PH centres answered with the complete data. For 83% of the centres, the preferred procedure was BLTx. Criteria for choosing HLTx was most frequently left ventricle (LV) function (76%), RV function criteria (45%) and the degree of tricuspid valve regurgitation (27%). The measured LVEF and right ventricle ejection fraction (RVEF) cut-off ranged from 32 to 55% and 15 to 25%, respectively.

Wadell *et al.* [7] analysed the United Network for Organ Sharing/International Society for Heart–Lung Transplantation (ISHLT) joint transplant registry to assess the relevance of HLTx for ES patients, in comparison with lung transplantation (LTx) with cardiac repair. The authors compared the survival of 605 end-stage ES patients according to the transplantation procedure. HLTx appeared to be the safest procedure, with a significantly higher survival rate in comparison with LTx ($P = 0.002$). Survival of ventricular septal defect (VSD) patients was significantly better for those who underwent HLTx than those who underwent LTx ($P = 0.0001$).

Toyoda *et al.* [8] carried out a retrospective review of all patients transplanted (HLTx or LTx) for idiopathic pulmonary arterial hypertension (IPAH). The authors compared long-term outcome by the era of transplantation. Survival improved for the most recently transplanted patients ($P = 0.004$). There was no survival difference between the different types of procedures (HLTx, BLTx or SLTx).

Fadel *et al.* [9] reviewed all patients who underwent HLTx or BLTx for PH. They reported 152 HLTx procedures in comparison with 67 BLTx procedures. HLTx was selected in the case of severe right-heart enlargement and dysfunction, congenital systemic-to-pulmonary shunt (CSPS, i.e. ES), lowered cardiac index (<2.2 l/min/m^2), severe preoperative renal failure or if patients were chronically dependent on inotropic support. Otherwise, BLTx was performed. No difference in overall survival was found between the two procedures ($P = 0.46$) performed. There also was no difference in the mean waiting time for a suitable graft (HLTx 8.7 ± 11.8 vs BLTx 6.7 ± 7.5 months; $P = 0.2$).

Christie *et al.* [10] reported on the data collected from the ISHLT registry. Half-life and conditional half-life survivals calculated for BLTx and HLTx showed similar results (no comparative test was performed). The same observation can be made about HLTx and LTx performed for IPAH. Both procedures appear to offer the same level of safety for PH patients.

De Perrot *et al.* [11] reported their experiences with HLTx and BLTx for all types of PH patients. HLTx was selected in the case of severe LV dysfunction (LVEF <40% and/or the presence of technical limitations for conducting BLTx). The procedure outcomes did not indicate any difference in overall survival between HLTx and BLTx for PH patients, or any difference in survival according to the type of PH indication. CHD patients mainly underwent HLTx, but had to wait longer for a suitable graft (378 ± 306 days; $P < 0.0001$). However, mortality on the waiting list remained lowest (9%; $P = 0.01$).

CLINICAL BOTTOM LINE

On the whole, none of the published research confirms an overall survival benefit for HLTx, in comparison with BLTx. BLTx and HLTx are the safest procedures for PH patients. BLTx and HLTx are not alternative procedures, but rather, each is suited for a different type of patient. Indeed, PH patients constitute a heterogeneous group of patients not only due to the mechanisms involved in the development of PH, but also because of the various consequences PH have on right and left ventricle function. In this context, HLTx can offer excellent early and long-term outcomes to patients with CHD and ES, severe right heart dysfunction and/or severe left heart dysfunction, and to those who are chronically dependent on inotropic support. In all other patients, BLTx can provide comparable outcomes with the advantage of better organ sharing for other recipients. Regarding the perioperative risks and rejection rates, the results are quite different from one publication to another. Some authors reported a lower primary graft dysfunction rate and better survival, without bronchiolitis obliterans, when HLTx was performed. As far as waiting time is concerned, PH patients with simple cardiac anomalies such as atrial septal defect, patent ductus arteriosus or perimembranous VSD can be treated with a combination of BLTx and cardiac repair. Cut-off values can be approximated at 10–25% for the RVEF and 32–55% for the LVEF. For any lower values, HLTx should be performed.

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