Original Article on Extracorporeal Life Support in Thoracic Surgery

# Off-pump lung re-transplantation avoiding clamshell thoracotomy is feasible and safe: a single-center experience

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**Background:** Lung re-transplantation (re-LTx) is the only therapeutic option for selected patients with advanced allograft dysfunction. This study aims to describe our center's experience to illustrate the feasibility and safety of off-pump re-LTx avoiding clamshell incision.

**Methods:** We performed a retrospective analysis of 42 patients who underwent bilateral re-LTx between 2007 and 2021. Patients were classified according to their surgical approach and extracorporeal life support (ECLS)-use. Demographics, surgical technique, and short- and long-term outcomes were compared between groups. Continuous data were examined with an independent-sample *t*-test or non-parametric test. Pearson's chi-squared and Fisher's exact were used to analyze categorical data.

**Results:** Twenty-six patients (61.9%) underwent re-LTx by anterior thoracotomy without ECLS. Compared to the more invasive approach (thoracotomy with ECLS and clamshell with/without ECLS, n=16, 38.1%), clamshell-avoiding off-pump re-LTx patients had a shorter operative time (471.6±111.2 *vs.* 704.0±273.4 min, P=0.010) and less frequent grade 3 primary graft dysfunction (PGD-3) at 72 h (7.7% *vs.* 37.5%, P=0.038). No significant difference was found in PGD-3 incidence within 72 h, mechanical ventilation, intensive care unit (ICU) and hospital stay, and the incidence of reoperation within 90 days between groups (P>0.05). In the long-term, the clamshell-avoiding and off-pump approach resulted in similar 1- and 5-year patient survival *vs.* the more invasive approach.

**Conclusions:** Our experience shows that clamshell-avoiding off-pump re-LTx is feasible and safe in selected patients on a case-by-case evaluation.

**Keywords:** Extracorporeal life support (ECLS); lung transplantation; re-transplantation

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## Introduction

Chronic lung allograft dysfunction (CLAD), including bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), is the main cause hindering the long-term survival of lung transplant (LTx) patients (1). Lung re-transplantation (re-LTx) is the only viable option in selected patients with severe CLAD comprising about 5% of the annual LTx activity worldwide. Considering the patient's status and previous thoracic surgical intervention(s), re-LTx is usually more complex than the initial LTx procedure. Therefore, 1-year patient survival of re-LTx patients is 78%, which seems less than the internationally reported 85% of primary LTx (2-5).

Due to the limited number of patients and reported experience, the criteria for patient selection and surgical approach in re-LTx are debatable and center-dependent. Due to expected severe adhesions and difficulty in exposure following previous thoracotomy, the clamshell approach and the use of extracorporeal life support (ECLS) could be preferred for re-LTx procedures (6-8). However, this more invasive approach comes with related complications (bleeding, thrombosis, sternal malunion and wound problems, etc.). Limited experience with off-pump clamshell-avoiding re-LTx has been reported.

### Highlight box

**Key findings**

- Our experience shows that clamshell-avoiding off-pump lung re-transplantation (re-LTx) is feasible and safe in selected patients on a case-by-case evaluation.

**What is known and what is new?**

- Re-LTx is the only therapeutic option for selected patients with advanced allograft dysfunction. The clamshell approach with extracorporeal life support (ECLS) is more common in this kind of surgery considering the surgical complexity.
- Our experience shows that clamshell-avoiding off-pump re-LTx is feasible and safe in selected patients on a case-by-case evaluation.

**What is the implication, and what should change now?**

- Our experience showed that off-pump ECLS-avoiding re-LTx is possible and safe in the majority of selected patients and could be considered as a first step during re-LTx.

At the University Hospitals Leuven, the general routine in primary sequential single-lung transplantation (Tx) is the off-pump technique through a bilateral anterior thoracotomy. We aim to retrospectively analyze our surgical experience and short- and long-term outcomes after re-LTx comparing the less invasive to the more invasive approach, illustrating the feasibility and safety of off-pump clamshell-avoiding re-LTx.

## Methods

We performed a single-center retrospective cohort study including all patients undergoing re-LTx at the University Hospitals Leuven (UZ Leuven), Belgium between January 2007 and December 2021. The exclusion criteria were patients with incomplete data, multi-organ transplant or single re-LTx. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee UZ/KU Leuven (No. S51577). There is no experiment in this paper as it is a retrospective study of clinical strategies, therefore informed consent is not required.

### *Demographics and outcomes*

Donor data [type, age, gender, cause of death, and partial pressure of oxygen to fraction of inspiratory oxygen ($PaO_2$/$FiO_2$) ratio] were collected from the donor report. Recipient characteristics [including gender, age at (re-)LTx, years between the initial LTx and re-LTx, body mass index (BMI), and days on the waiting list), indication for re-LTx, the ratio of preoperative forced expiratory volume in 1 second/forced vital capacity (FEV1%), the ratio of forced vital capacity/prediction (FVC%), 6-minute walking distance (6MWD), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) status, human leukocyte antigen (HLA) mismatch, panel reactive antibody (PRA), complement-dependent cytotoxic (CDC)-crossmatch, post-re-LTx donor-specific antibodies (DSA)], short-term outcome [operative time, ECLS application, grade 3 primary graft dysfunction (PGD-3) within and at 72-h post-transplant, mechanical ventilation in days, intensive care unit (ICU) and hospital stay, 90-day reoperation incidence], and long-term outcome

(1- and 5-year patient survival) were collected from the prospectively collected UZ Leuven LTx database.

### *Criteria for re-LTx*

Re-LTx is performed in carefully selected candidates meeting the same general eligibility criteria as for primary LTx regarding absolute/relative contraindications and risk factors from the consensus statement of selecting LTx candidates by ISHLT in 2021 (Table S1) (9). All cases were discussed at the multidisciplinary team meeting. Moreover, additional requirements are considered when deciding on re-LTx eligibility to reduce risks and ensure a better outcome and survival of patients:

(I) >2 years post-CLAD onset;
(II) BOS, rather than RAS;
(III) Younger patients (<60 years old);
(IV) Ambulatory, rather than hospitalized status;
(V) Estimated glomerular filtration rate >60 mL/min/1.73 $m^2$;
(VI) No important HLA immunization (unless acceptable virtual PRA and virtual crossmatch possible);
(VII) No non-adherence during postoperative follow-up and adequately treated comorbidities (including gastro-esophageal reflux disease, diabetes mellitus, etc.).

### *Surgical approach and use of ECLS*

During surgery, the patient is placed in a supine position and intubated with a double-lumen tube. Sequential single-LTx is performed via a bilateral anterior thoracotomy (10). Reasons for conversion to clamshell thoracotomy are:

(I) Preoperative CT scan showing severe fibrotic chest cavity limiting exposure;
(II) Intraoperative hemodynamic instability requiring maximal hilar exposure.

In the off-pump LTx strategy, ECLS using veno-arterial extracorporeal membrane oxygenation (VA-ECMO) or cardio-pulmonary bypass (CPB) is only considered intraoperatively when there is (11):

(I) Mechanical ventilatory support failure;
(II) Pulmonary artery pressure reaching ≥2/3 systolic pressure;
(III) Hemodynamic instability;
(IV) Bleeding complications.

Central VA-ECMO is the preferred strategy and ECLS is removed after reperfusion.

### *Statistical analysis*

Baseline donor, recipient, and operative variables were compared between patients undergoing re-LTx through sequential anterior thoracotomy without ECLS *vs.* the more invasive approaches (thoracotomy with ECLS or clamshell with/without ECLS). Continuous variables were expressed as mean ± standard deviation (SD) or median (minimum to maximum) examined with independent-samples *t*-test (normal distribution) or the Mann-Whitney rank sum test (abnormal distribution), respectively. Pearson's chi-squared test and Fisher's exact test were used to analyze categorical variables. All data were analyzed by IBM SPSS version 22.0 for Windows (SPSS IBM, Armonk, NY, USA). P<0.05 was considered statistically significant.

## Results

From January 1st, 2007 to December 31st, 2021, 48 re-LTx were performed. One patient with incomplete data, two multi-organ transplants and three single re-LTx were excluded resulting in 42 sequential single (bilateral) re-LTx cases (*Figure 1*).

Twenty-six patients (61.9%) received re-LTx by bilateral thoracotomy without ECLS. Sixteen patients (38.1%) had re-LTx through a more invasive approach, among which 14 (eight thoracotomy and six clamshell) were performed with ECLS and two by clamshell approach without ECLS. Donor and recipient pre-operative characteristics are summarized in *Tables 1-3*.

Emphysema, cystic fibrosis and pulmonary fibrosis were the main indications for their primary LTx. Thirty-eight patients were performed with double-lung Tx, three with heart-lung Tx and one with single-lung Tx. Among all cases, 34 patients underwent their primary LTx through bilateral anterior thoracotomy approach and 28 without ECLS, in total, 26 patients with a full minimally invasive approach. There is no relationship of the use of clamshell or ECLS between the primary and re-LTx (P>0.05, *Table 1*). FVC% of patients from the bilateral anterior thoracotomy off-pump re-LTx group was higher than patients from the invasive approach group (59.0±22.60 *vs.* 44.0±16.8 and 34.1±12.3, P=0.004, *Table 1*). There was no significant difference in indication, FEV1%, 6MWD, ambulatory status, surgical approach and ECLS application between groups during the primary Tx.

For re-LTx, the majority of lungs (33/42; 78.6%) was from donation after brain death (DBD). Cerebrovascular

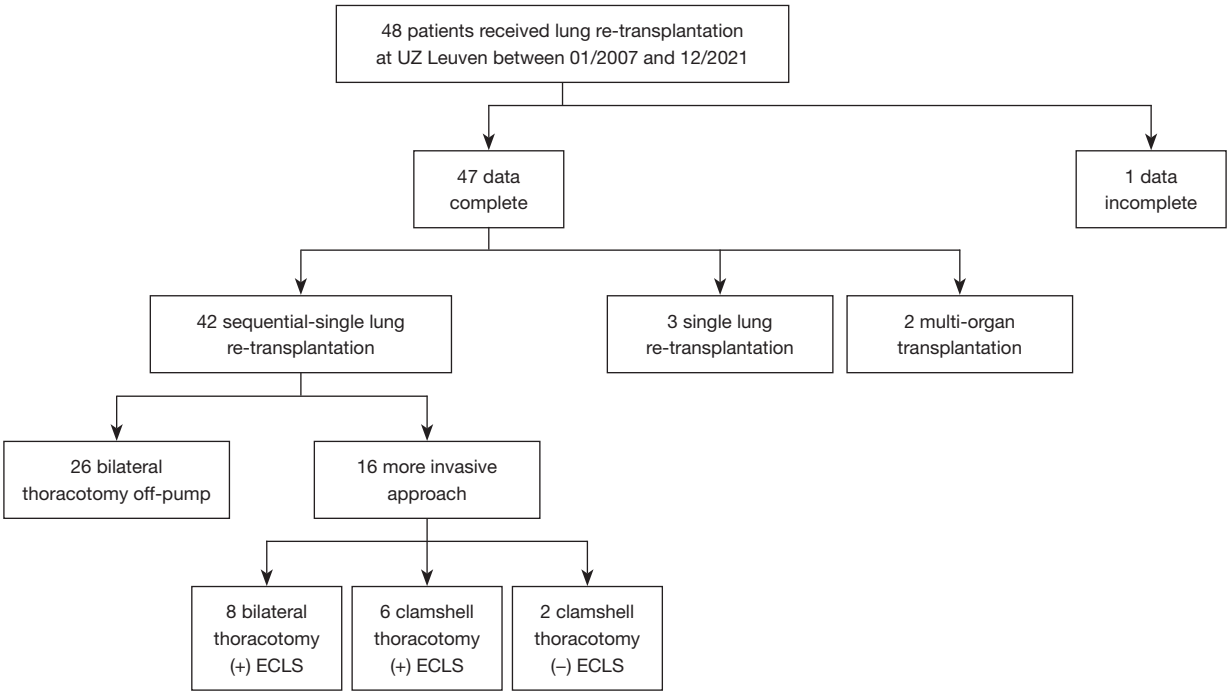


**Figure 1** Flowchart of the study population. ECLS, extracorporeal life support.

accident (CVA, 21/42; 50.0%) was the most common cause of death. There was no significant difference in donor type, age, gender, cause of death, and $PaO_2/FiO_2$ between groups (*Table 2*).

The overall male/female ratio was 22/20. The mean interval between primary and re-LTx was 5.6 years. The indication for re-LTx was mostly BOS (37/42; 88.1%). Patients in the minimally invasive approach group were more at home before the re-LTx (ambulatory) than the invasive approach group (76.9% *vs.* 25.0%, P=0.001, *Table 3*). Four re-LTx recipients (9.5%) were sensitized for HLA I (A, B or C) antibody and 13 (31.0%) for HLA II (DP, DM, DO, DQ or DR) antibody at the time of their primary LTx. Twenty-four recipients (57.1%) were HLA antibody sensitized at pre-re-LTx, including 8 for HLA I antibody (19.0%) and 16 for HLA II antibody (38.1%). PRA level >25% was observed in 7 patients (31.8% of 22 tested patients) and the CDC-crossmatch was positive in 6 patients (14.3%). Between groups, there was no significant difference in recipient's gender, age, the time between primary LTx and re-LTx, BMI, days on the waiting list, indication, FEV1%, FVC%, 6MWD, CMV and EBV status, HLA antibodies sensitization, PRA level >25%, or positive CDC-crossmatch (P>0.05, *Table 3*).

Among eight clamshell approach subgroup patients, four of them were converted from bilateral anterior thoracotomy intraoperatively for better exposure or bleeding control and four were performed directly by clamshell approach due to small chest, expected adhesions or hemodynamic instability. The operative time of patients undergoing a less invasive approach was significantly shorter than most of the patients with a more invasive approach (471.6±111.2 *vs.* 704.0±273.4 min, P=0.010). The incidence of PGD-3 at 72-h post-re-LTx was significantly lower in the off-pump clamshell-avoiding group (7.7% *vs.* 37.5%, P=0.038). In this group, the incidence of PGD-3 within 72-h post-re-LTx (34.6% *vs.* 68.8%), postoperative mechanical ventilation time (4.8±4.0 *vs.* 9.1±9.9 days), and ICU stay (14.7±20.8 *vs.* 27.1±33.8 days) were lower without statistical significance (P>0.05). There was also no statistical difference in postoperative hospital stay (38.7±27.8 *vs.* 46.4±35.9 days) and need for reoperation within 90 days (38.5% *vs.* 43.8%). The 1- and 5-year patient survival were similar (less *vs.* more invasive approach, 88.5% *vs.* 75.0% and 65.4% *vs.* 37.5%, respectively, P>0.05). Following re-LTx, DSA was found in 22.5% patients (9 of 40 tested) and 15 patients were diagnosed with CLAD (13 BOS and two RAS) after a mean time of 35 months. The detailed comparison

**Table 1** Comparison of perioperative characteristics in primary LTx

| Primary LTx recipient characteristics | Bilateral thoracotomy off-pump (n=26) | Bilateral thoracotomy (+) ECLS (n=8) | Clamshell thoracotomy (+/–) ECLS (n=8) | P |
|---|---|---|---|---|
| Indication | | | | 0.686 |
| Emphysema | 8 (30.8) | 2 (25.0) | 1 (12.5) | |
| Cystic fibrosis | 9 (34.6) | 5 (62.5) | 2 (25.0) | |
| Pulmonary fibrosis | 5 (19.2) | 0 | 5 (62.5) | |
| Pulmonary hypertension | 1 (3.8) | 0 | 0 | |
| Rare | 3 (11.5) | 1 (12.5) | 0 | |
| FEV1% | 35.1±21.8 | 28.6±8.9 | 31.9±13.1 | 0.341 |
| FVC% | 59.0±22.60 | 44.0±16.8 | 34.1±12.3 | 0.004 |
| 6MWD, m | 384.8±12.9 | 340.9±165.0 | 377.0±149.9 | 0.303 |
| Ambulatory | 23 (88.5) | 6 (75.0) | 7 (87.5) | 0.658 |
| Tx | | | | 0.289 |
| Single-lung Tx | 0 | 0 | 1 (12.5) | |
| Double-lung Tx | 24 (92.3) | 7 (87.5) | 7 (87.5) | |
| Heart-lung Tx | 2 (7.7) | 1 (12.5) | 0 | |
| Thoracotomy approach | | | | 0.463 |
| Bilateral off-pump | 16 (61.5) | 4 (50.0) | 4 (50.0) | |
| Bilateral (+) ECLS | 4 (15.4) | 1 (12.5) | 2 (25.0) | |
| Extended incision | 6 (23.1) | 3 (37.5) | 2 (25.0) | |
| Clamshell (+/–) ECLS | 4 | 3 | 2 | |
| Sternotomy (+/–) ECLS | 2 | 0 | 0 | |
| ECLS (+) | 10 (38.5) | 3 (37.5) | 2 (25.0) | 0.746 |
| VA-ECMO | | | | |
| Central | 5 | 1 | 2 | |
| Peripheral | 1[†] | 1[‡] | 0 | |
| VV-ECMO | | | | |
| Central | 0 | 0 | 0 | |
| Peripheral | 0 | 1[‡] | 0 | |
| CPB | | | | |
| Central | 1 | 1 | 0 | |
| Peripheral | 4[†] | 1[‡] | 0 | |
| Pre-LTx ECLS | 0 | 1 | 0 | |

Data are presented as n (%), mean ± SD, and number. [†], a pulmonary hypertension patient was converted from CPB to VA-ECMO intraoperatively; [‡], in one single patient (Eisenmenger), CPB, VA- and VV-ECMO were used pre- and intraoperatively during his primary LTx. At the end of the procedure, the patient was weaned from ECLS. Tx, transplantation; LTx, lung Tx; ECLS, extracorporeal life support; FEV1%, the ratio of preoperative forced expiratory volume in 1 second/prediction; FVC%, the ratio of forced vital capacity/prediction; 6MWD, 6-minute walking distance; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VV-ECMO, veno-venous extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; SD, standard deviation.

**Table 2** Baseline differences of donor characteristics in re-LTx

| Re-LTx donor characteristics | Bilateral thoracotomy off-pump (n=26) | Bilateral thoracotomy (+) ECLS (n=8) | Clamshell thoracotomy (+/–) ECLS (n=8) | P |
|---|---|---|---|---|
| Donor type | | | | 0.127 |
| DBD | 19 (73.1) | 8 (100.0) | 6 (75.0) | |
| DCD-III | 6 (23.1) | 0 | 0 | |
| DCD-IV | 0 | 0 | 1 (12.5) | |
| DCD-V | 1 (3.8) | 0 | 1 (12.5) | |
| Donor age, years | 48.3 [18–68] | 43 [12–56] | 57.5 [17–66] | 0.660 |
| Male donor | 17 (65.4) | 2 (25.0) | 4 (50.0) | 0.113 |
| Donor cause of death | | | | 0.246 |
| Circulation | 1 (3.8) | 0 | 0 | |
| CVA | 13 (50.0) | 3 (37.5) | 5 (62.5) | |
| Euthanasia | 1 (3.8) | 0 | 1 (12.5) | |
| Hypoxemia | 0 | 2 (25.0) | 0 | |
| Not specified | 1 (3.8) | 0 | 0 | |
| Suicide | 7 (26.9) | 0 | 1 (12.5) | |
| Trauma | 3 (11.5) | 3 (37.5) | 1 (12.5) | |
| $PaO_2/FiO_2$ | 441.9±65.0 | 467.5±117.3 | 420.1±85.4 | 0.895 |

Data are presented as n (%), median [range], and mean ± SD. re-LTx, lung re-transplantation; ECLS, extracorporeal life support; DBD, donation after brain death; DCD, donation after circulatory death; CVA, cerebrovascular accident; $PaO_2$, partial pressure of oxygen; $FiO_2$, fraction of inspiratory oxygen; SD, standard deviation.

**Table 3** Baseline differences in recipient preoperative characteristics

| Re-LTx recipient characteristics | Bilateral thoracotomy off-pump (n=26) | Bilateral thoracotomy (+) ECLS (n=8) | Clamshell thoracotomy (+/–) ECLS (n=8) | P |
|---|---|---|---|---|
| Male recipients | 17 (65.4) | 1 (12.5) | 4 (50.0) | 0.055 |
| Re-LTx age, years | 41.2±11.9 | 33.8±16.9 | 44.9±9.9 | 0.657 |
| Year between 1st LTx and re-LTx | 6.3±1.6 | 2.8±2.2 | 6.4±3.4 | 0.133 |
| Recipient BMI, $kg/m^2$ | 20.1±3.3 | 18.9±2.9 | 20.1±1.6 | 0.580 |
| Indication of recipient | | | | 0.096 |
| BOS | 25 (96.2) | 6 (75.0) | 6 (75.0) | |
| RAS | 1 (3.8) | 1 (12.5) | 2 (25.0) | |
| POF | 0 | 1 (12.5) | 0 | |
| Recipient at listing, days | 120.5 [2–757] | 20.5 [1–336] | 53.5 [3–372] | 0.090 |
| Ambulatory | 20 (76.9) | 1 (12.5) | 3 (37.5) | 0.001 |
| FEV1% | 23.7±8.2 | 22.9±7.6 | 21.6±3.5 | 0.547 |
| FVC% | 47.5±14.8 | 40.9±9.7 | 46.0±29.1 | 0.497 |

**Table 3** (*continued*)

**Table 3** (*continued*)

| Re-LTx recipient characteristics | Bilateral thoracotomy off-pump (n=26) | Bilateral thoracotomy (+) ECLS (n=8) | Clamshell thoracotomy (+/–) ECLS (n=8) | P |
|---|---|---|---|---|
| 6MWD, m | 357.1±186.1 | 321.3±124.5 | 343.9±247.9 | 0.704 |
| CMV (+) | 13 (50.0) | 2 (25.0) | 4 (50.0) | 0.530 |
| EBV (+) | 23 (88.5) | 7 (87.5) | 8 (100.0) | 1.000 |
| Pre-re-LTx* | | | | |
| HLA I (+) | 4 (16.0) | 1 (14.3) | 3 (37.5) | 0.444 |
| HLA II (+) | 11 (44.0) | 2 (28.6) | 3 (37.5) | 0.740 |
| Post-re-LTx | | | | |
| HLA I (+) | 2 (7.7) | 0 | 2 (25.0) | 0.628 |
| HLA II (+) | 7 (26.9) | 1 (12.5) | 5 (62.5) | 0.510 |
| Pre-re-LTx PRA >25%† | 6 (46.2) | 0 | 1 (20.0) | 0.165 |
| Pre-re-LTx CDC crossmatch (+) | 2 (7.7) | 2 (25.0) | 2 (25.0) | 0.180 |
| ECLS (+) | 0 | 8 (100.0) | 6 (75.0) | – |
| VA-ECMO | | | | |
| Central | | 2‡ | 5 | |
| Peripheral | | 0 | 0 | |
| VV-ECMO | | | | |
| Central | | 1‡ | 0 | |
| Peripheral | | 4 | 1 | |
| CPB | | | | |
| Central | | 2 | 0 | |
| Peripheral | | 0 | 0 | |
| Pre-re-LTx ECLS | | 1 | 1 | |

Data are presented as n (%), median [range], and mean ± SD. *, percentage in 40 patients with record in database [n=25 for bilateral thoracotomy off-pump group, n=7 for bilateral thoracotomy (+) ECLS group and n=8 for clamshell thoracotomy (+/–) ECLS group]; †, percentage in 22 tested patients [n=13 for bilateral thoracotomy off-pump group and n=5 for clamshell thoracotomy (+/–) ECLS group]; ‡, the patient was on VA- and VV-ECMO intraoperatively for primary organ failure 18 days after his primary LTx. re-LTx, lung re-transplantation; ECLS, extracorporeal life support; BMI, body mass index; BOS, bronchiolitis obliterans syndrome; RAS, restrictive allograft syndrome; POF, primary organ failure; FEV1%, the ratio of preoperative forced expiratory volume in 1 second/forced vital capacity; FVC%, the ratio of forced vital capacity/prediction; 6MWD, 6-minute walking distance; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; PRA, panel reactive antibody; CDC, complement-dependent cytotoxic; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VV-ECMO, veno-venous extracorporeal membrane oxygenation; CPB, cardiopulmonary bypass; SD, standard deviation.

of postoperative characteristics between the off-pump clamshell-avoiding group and the more invasive approach group is shown in *Table 4*.

One patient from the clamshell group without ECLS died at ICU on the 37th day after re-LTx due to circulatory arrest secondary to hypoxic respiratory failure. One patient was converted from veno-venous ECMO to VA-ECMO intraoperatively and remained on ECMO for 3 days after re-LTx. In one case from the thoracotomy group, intraoperative CPB was needed for making the left atrial anastomosis due to an inadequate patch. This patient died from post-operative bleeding 24 h after the re-LTx.

**Table 4** Comparison of short- and long-term outcomes between the thoracotomy and ECLS-avoiding and more invasive approach

| Re-LTx recipient characteristics | Bilateral thoracotomy off-pump (n=26) | Bilateral thoracotomy (+) ECLS (n=8) | Clamshell thoracotomy (+/–) ECLS (n=8) | P |
|---|---|---|---|---|
| Operative time, min | 471.6±111.2 | 814.0±135.9 | 594.0±131.9 | 0.010 |
| PGD-3 at 72 h | 2 (7.7) | 4 (50.0) | 2 (25.0) | 0.038 |
| PGD-3 in 72 h | 9 (34.6) | 6 (75.0) | 5 (62.5) | 0.055 |
| Mechanical ventilation, days | 4.8±4.0 | 5.4±7.6 | 12.9±11.7 | 0.148 |
| ICU stay, days | 14.7±20.8 | 25.5±46.3 | 28.6±21.7 | 0.158 |
| Hospital stay, days | 38.7±27.8 | 47.6±48.2 | 45.3±20.9 | 0.436 |
| Hospital mortality | 0 | 1 (12.5) | 1 (12.5) | – |
| Reoperation in 90-day | 10 (38.5) | 1 (12.5) | 6 (75.0) | 0.757 |
| 1-year surviving patients | 23 (88.5) | 5 (62.5) | 7 (87.5) | 0.397 |
| 5-year surviving patients | 17 (65.4) | 2 (25.0) | 4 (50.0) | 0.078 |
| Post-re-LTx DSA (+)[†] | 8 (32.0) | 1 (14.3) | 0 | 0.117 |
| Pre-existing | 6 | 0 | 0 | |
| *De novo* | 2 | 1 | 0 | |
| CLAD after re-LTx[‡] | 11 (45.8) | 1 (16.7) | 3 (42.9) | 0.317 |
| CLAD-free time, months | 41.1±17.7 | 12 | 21.7±15.5 | – |
| BOS | 10 | 1 | 2 | |
| RAS | 1 | 0 | 1 | |

Data are presented as n (%) and mean ± SD. [†], percentage of 40 available patients [n=25 for bilateral thoracotomy off-pump group and n=7 for bilateral thoracotomy (+) ECLS group]; [‡], patients died in the first postoperative 6-month were excluded. ECLS, extracorporeal life support; re-LTx, lung re-transplantation; PGD-3, grade 3 primary graft dysfunction; ICU, intensive care unit; DSA, donor-specific antibodies; CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome; RAS, restrictive allograft syndrome; SD, standard deviation.

## Discussion

In this retrospective analysis, we observed that in selected cases bilateral re-LTx can be safely performed in a less invasive way by bilateral anterior thoracotomy avoiding both clamshell and use of ECLS. Previous LTx increases the surgical complexity during re-LTx due to adhesions, fibrothorax and limited exposure (12). In these cases, a clamshell approach is generally considered to gain better exposure that allows better vascular control, resulting in reduced anastomotic times (10,12-15). However, a multi-center, retrospective analysis from the LTx working group of the European Society of Thoracic Surgeons analysed 2,690 LTx patients between 2005 and 2020, of which 26 had a previous history of anatomical lung resection by open approach. Survival of these patients seemed comparable to conventional LTx patients, thereby indicating that a history of previous thoracic surgery is not an absolute contraindication (16). In this study, we did not find that the use of clamshell or ECLS during the primary LTx is a prerequisite to use the same approach in re-LTx. Since almost half of the patients who had such invasive approaches in their primary LTx were still able to adopt a less invasive approach in their re-LTx. Therefore, based on our experience, re-LTx can be started through a bilateral anterior thoracotomy.

However, the need for ECLS in (re-)LTx remains a matter of debate. Some centers have shown that routine use of ECLS can result in improved short-term outcome by decreasing the PGD-3 rate at 72 h (17-19). On the other hand, it has also been described that ECLS might result in some vascular and coagulopathy complications such as bleeding and thrombosis (20-23). In our series, we found that re-LTx without ECLS resulted in a PGD-3 rate at 72 h of 7.7% only. In the same cohort, we did not observe much difficulty in weaning from mechanical ventilation

and the need for reoperation within 90 days in contrast to the ECLS group. It has previously been described that re-LTx with ECLS resulted in a longer ICU stay and lower overall survival than primary LTx or re-LTx without ECLS (24-26). In our study, patients with ECLS had longer operative time and higher incidence of PGD-3. However, this can be attributed to the fact that ECLS was needed in more complex cases or patients with surgical complications like intraoperative bleeding. Therefore, these two groups cannot be compared head-to-head and the implementation of ECLS in re-LTx should be considered on a case-by-case basis.

Important to stress is that safe clamping of the pulmonary artery is required. Intrapleural dissection of the artery is often difficult and dangerous because of dense adhesions with the bronchial anastomosis and/or its peribronchial fat pad. Therefore, in primary LTx, we suggest not opening the pericardium and performing the anastomosis in the intrapleural space. In re-LTx, we recommend immediately opening the pericardium anterior to the phrenic nerve to encircle the main pulmonary artery intrapericardially between the ascending aorta and the superior cava vein on the right side and medial to the Botalli ligament on the left side. In this sense, during re-LTx, there will be fewer adhesions in the pericardial space where it is easier to clamp the pulmonary artery. If needed, conversion into a clamshell approach with the use of ECLS is always possible. We found that all our RAS patients [and one patient with primary organ failure (POF)] underwent re-LTx with an invasive approach. RAS as a known independent negative prognostic factor is defined by declining pulmonary function and restrictive pulmonary defect without evidence of obstruction following LTx, accounting for 25–35% of all CLAD indications (27-29). In these patients, anatomical changes such as traction bronchiectasis, architectural deformation, volume loss, pleural adhesions and hilar retraction can be observed, which increase surgical complexity (30,31). Furthermore, RAS patients have a higher oxygen requirement and lung allocation score than BOS patients, often resulting in a more urgent Tx (32-35). Therefore, we do not recommend adopting the minimally invasive approach during re-LTx on RAS patients for possible needs of an extended surgical approach and intraoperative ECLS.

We observed that the off-pump clamshell-avoiding group tended to have more male patients. What role gender difference in donor and recipient exerts in LTx and re-LTx is still not well known. Anatomically, the lung capacity and physical reserve in women are usually lower than in men. Gender mismatch could result in organ-chest cavity size mismatch and could be a disadvantage in LTx and re-LTx (36). The female chest cavity is smaller, so a clamshell incision would improve exposure. Moreover, female patients are at higher risk for RAS development, possibly due to more prevalent HLA sensitization in females, which influences re-LTx prognosis as mentioned above (35). However, there are also studies questioning the relationship between gender and (re-)LTx prognosis. Saito *et al.* (37) did not find any difference in outcomes among BOS- *vs.* RAS-matched cohorts. Kilic *et al.* even found male donor to be a risk factor in re-LTx (38). Further research on this gender topic is required in the field of re-LTx.

Recognizing risk factors is crucial when evaluating and selecting the surgical protocol, especially in re-LTx cases. Among re-LTx patients, risk factors include female donor, non-BOS indication (RAS, POF, and others), the time interval between primary and re-LTx <2 years, low BMI, hospitalization before surgery, older age, 6MWD <400 ft, etc. (38-44). We found a similar trend in our study that patients in the less invasive group tended to include more ambulatory status, more BOS indication, fewer female donors, and more days on the waiting list than patients needing a more invasive approach, although some differences were not significant.

Our study suffers from some limitations. The sample size is small due to the rarity of the indication with only 5% being re-LTx in our institution. Moreover, there may have been a selection bias in those patients requiring ECLS and clamshell incision. A multi-center analysis should be conducted on this topic.

## Conclusions

In conclusion, our experience showed that off-pump ECLS-avoiding re-LTx is possible and safe in the majority of selected patients and could be considered as a first step during re-LTx.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee UZ/KU Leuven (No. S51577). There is no experiment in this paper as it is a retrospective study of clinical strategies, therefore informed consent is not required.



## References

1. Verleden SE, Todd JL, Sato M, et al. Impact of CLAD Phenotype on Survival After Lung Retransplantation: A Multicenter Study. Am J Transplant 2015;15:2223-30.
2. Chambers DC, Perch M, Zuckermann A, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult lung transplantation report - 2021; Focus on recipient characteristics. J Heart Lung Transplant 2021;40:1060-72.
3. Bos S, Vos R, Van Raemdonck DE, et al. Survival in adult lung transplantation: where are we in 2020? Curr Opin Organ Transplant 2020;25:268-73.
4. 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;38:1042-55.
5. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report--2014; focus theme: retransplantation. J Heart Lung Transplant 2014;33:1009-24.
6. Inci I, Ehrsam JP, Van Raemdonck D, et al. Extracorporeal life support as a bridge to pulmonary retransplantation: prognostic factors for survival in a multicentre cohort analysis. Eur J Cardiothorac Surg 2022;61:405-12.
7. Hayanga JW, Aboagye JK, Hayanga HK, et al. Extracorporeal membrane oxygenation as a bridge to lung re-transplantation: Is there a role? J Heart Lung Transplant 2016;35:901-5.
8. Mody GN, Coppolino A, Singh SK, et al. Sternotomy versus thoracotomy lung transplantation: key tips and contemporary results. Ann Cardiothorac Surg 2020;9:60-4.
9. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2021;40:1349-79.
10. Vandervelde CM, Vos R, Vanluyten C, et al. Impact of anastomosis time during lung transplantation on primary graft dysfunction. Am J Transplant 2022;22:1418-29.
11. Orlitová M, Goos W, Van Slambrouck J, et al. Complications related to extracorporeal life support in lung transplantation: single-center analysis. J Thorac Dis 2023. [Epub ahead of print]. doi: 10.21037/jtd-23-443.

 

12. Elhenawy AM, Lien DC, Khani-Hanjani A, et al. Redo Heart Double-Lung Transplant in a Previous Double-Lung Transplant Recipient With Pneumonectomy: A Case Report. Transplant Proc 2021;53:2616-8.
13. Jochmans I, Fieuws S, Tieken I, et al. The Impact of Implantation Time During Liver Transplantation on Outcome: A Eurotransplant Cohort Study. Transplant Direct 2018;4:e356.
14. Heylen L, Pirenne J, Naesens M, et al. "Time is tissue"-A minireview on the importance of donor nephrectomy, donor hepatectomy, and implantation times in kidney and liver transplantation. Am J Transplant 2021;21:2653-61.
15. Puri V, Patterson GA. Adult lung transplantation: technical considerations. Semin Thorac Cardiovasc Surg 2008;20:152-64.
16. Iskender I, Pecoraro Y, Moreno Casado P, et al. Lung transplantation in patients with a history of anatomical native lung resection. Interact Cardiovasc Thorac Surg 2022;35:ivac256.
17. Hoetzenecker K, Donahoe L, Yeung JC, et al. Extracorporeal life support as a bridge to lung transplantation-experience of a high-volume transplant center. J Thorac Cardiovasc Surg 2018;155:1316-1328.e1.
18. Hoetzenecker K, Benazzo A, Stork T, et al. Bilateral lung transplantation on intraoperative extracorporeal membrane oxygenator: An observational study. J Thorac Cardiovasc Surg 2020;160:320-27.e1.
19. Cypel M, Keshavjee S. Extracorporeal life support as a bridge to lung transplantation. Clin Chest Med 2011;32:245-51.
20. Dalton HJ, Garcia-Filion P, Holubkov R, et al. Association of bleeding and thrombosis with outcome in extracorporeal life support. Pediatr Crit Care Med 2015;16:167-74.
21. Chandler WL. Platelet, Red Cell, and Endothelial Activation and Injury During Extracorporeal Membrane Oxygenation. ASAIO J 2021;67:935-42.
22. Mazzeffi M, Greenwood J, Tanaka K, et al. Bleeding, Transfusion, and Mortality on Extracorporeal Life Support: ECLS Working Group on Thrombosis and Hemostasis. Ann Thorac Surg 2016;101:682-9.
23. Loor G, Huddleston S, Hartwig M, et al. Effect of mode of intraoperative support on primary graft dysfunction after lung transplant. J Thorac Cardiovasc Surg 2022;164:1351-61.e4.
24. Abdelnour-Berchtold E, Wurlod DA, Ris HB, et al. 125 Outcome of patients with lung re-transplantation requiring preoperative extracorporeal membrane oxygenation. Chest 2017;151:A22.
25. Pereira ROL, Rodrigues ES, Martin AK, et al. Outcomes After Lung Retransplantation: A Single-Center Retrospective Cohort Study. J Cardiothorac Vasc Anesth 2022;36:1366-72.
26. Sommer W, Ius F, Kühn C, et al. Technique and Outcomes of Less Invasive Lung Retransplantation. Transplantation 2018;102:530-7.
27. Brun AL, Chabi ML, Picard C, et al. Lung Transplantation: CT Assessment of Chronic Lung Allograft Dysfunction (CLAD). Diagnostics (Basel) 2021;11:817.
28. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant 2019;38:493-503.
29. Verleden SE, Ruttens D, Vandermeulen E, et al. Elevated bronchoalveolar lavage eosinophilia correlates with poor outcome after lung transplantation. Transplantation 2014;97:83-9.
30. Suh J, Son N, Lee J, et al. The Effect of Disease Type on Changes in Total Lung Volume after Lung Transplantation Measured by Three-Dimensional (3D) CT Reconstruction. J Heart Lung Transplant 2021;40:S357-8.
31. Verleden SE, de Jong PA, Ruttens D, et al. Functional and computed tomographic evolution and survival of restrictive allograft syndrome after lung transplantation. J Heart Lung Transplant 2014;33:270-7.
32. Charoenpong P, Adedeji A, Daoud N, et al. Clinical Characteristics of Patients with Chronic Lung Allograft Dysfunction Listed for Lung Re-Transplant. J Heart Lung Transplant 2021;40:S304.
33. Charoenpong P, Song D, Ford D, et al. Outcome of Lung Re-Transplant in Chronic Lung Allograft Dysfunction. J Heart Lung Transplant 2021;40:S303-4.
34. Halloran K, Aversa M, Tinckam K, et al. Comprehensive outcomes after lung retransplantation: A single-center review. Clin Transplant 2018;32:e13281.
35. Verleden GM, Vos R, Vanaudenaerde B, et al. Current views on chronic rejection after lung transplantation. Transpl Int 2015;28:1131-9.
36. International Society of Heart and Lung Transplantation Registry; Sato M, Gutierrez C, et al. The effect of gender combinations on outcome in human lung transplantation: the International Society of Heart and Lung Transplantation Registry experience. J Heart Lung Transplant 2006;25:634-7.
37. Saito T, Liu M, Binnie M, et al. Distinct expression

 

patterns of alveolar "alarmins" in subtypes of chronic lung allograft dysfunction. Am J Transplant 2014;14:1425-32.
38. Kilic A, Beaty CA, Merlo CA, et al. Functional status is highly predictive of outcomes after redo lung transplantation: an analysis of 390 cases in the modern era. Ann Thorac Surg 2013;96:1804-11; discussion 1811.
39. Kawut SM, Lederer DJ, Keshavjee S, et al. Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 2008;177:114-20.
40. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015;34:1-15.
41. Hall DJ, Belli EV, Gregg JA, et al. Two Decades of Lung Retransplantation: A Single-Center Experience. Ann Thorac Surg 2017;103:1076-83.
42. Hayanga J, Plets M, Woodwyk A, et al. A global analysis of contemporary trends in lung re-transplantation: a question of selection. Interact Cardiovasc Thorac Surg 2014;19:S73.
43. Ren D, Kaleekal TS, Graviss EA, et al. Retransplantation Outcomes at a Large Lung Transplantation Program. Transplant Direct 2018;4:e404.
44. Harhay MO, Cherikh WS, Toll AE, et al. Epidemiology, risk factors, and outcomes of lung retransplantation: An analysis of the International Society for Heart and Lung Transplantation Thoracic Transplant Registry. J Heart Lung Transplant 2022;41:1478-86.

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## Supplementary

**Table S1** Criteria for Re-LTx Referring to the Consensus Statement of Selecting LTx Candidates by ISHLT in 2021 (9)

| Indication | Absolute contraindication |
|---|---|
| Meeting all the following general criteria: | 1. Lack of patient willingness or acceptance of transplant |
| 1. High (>50%) risk of death from lung disease within 2 years if re-LTx is not performed | 2. Malignancy with high risk of recurrence or death related to cancer |
| 2. High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function | 3. Acute coronary syndrome or myocardial infarction within 30 days |
| 3. BODE score 7–10 | 4. Acute liver or renal failure |
| And meeting any of the following general criteria: | 5. Liver cirrhosis with portal hypertension or synthetic dysfunction |
| 1. Presence of moderate to severe pulmonary hypertension | 6. Stroke within 30 days |
| 2. FEV1 <25% predicted | 7. Septic shock |
| 3. Rapid decline in lung function or progressive symptoms despite appropriate treatment | 8. Active extrapulmonary or disseminated infection |
| 4. Hospitalization because of respiratory decline or acute exacerbation requiring persistent mechanical ventilatory support and /or ECLS without expectation of clinical recovery and with evidence of irreversible lung destruction | 9. Active tuberculosis infection |
| | 10. HIV infection with detectable viral load |
| | 11. Limited functional status (e.g., non-ambulatory) with poor potential for post-transplant rehabilitation |
| | 12. Progressive cognitive impairment |
| | 13. Active substance use or dependence including current tobacco use, vaping, marijuana smoking, or IV drug use |
| | 14. Other severe uncontrolled medical conditions expected to limit survival after transplant |


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