Update in lung transplantation: anesthetic considerations

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Abstract: The field of lung transplantation (LTx) has expanded rapidly since its inception in the early 1960s with the work of James Hardy and colleagues at the University of Mississippi from the work of local single specialty physicians into an international multidisciplinary specialty. Advancements throughout the next several decades have led to the completion of over 70,000 lung transplants worldwide. The unique challenges presented by patients with end-stage lung disease have both evolved and remained consistent since then, yet these challenges are being answered with major improvements and advancements in perioperative care in the 21st century. The current practice of LTx medicine is fundamentally multidisciplinary, and members of the LTx team includes surgeons, physicians, and allied health staff. The integration of anesthesiologists into the LTx team as well as the multidisciplinary nature of LTx necessitates anesthetic considerations to be closely incorporated into emerging surgical, medical, and systems techniques for patient care. This review discusses a host of emerging strategies across the spectrum of LTx, including efforts to expand the donor pool, utilization of perioperative extracorporeal life support, perioperative echocardiography, and anesthetic techniques to mitigate primary graft dysfunction that have all contributed to improved long term outcomes in LTx patients.

Keywords: Lung transplantation (LTx); thoracic surgery; cardiothoracic anesthesiology

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Introduction

In May of 1947, Vladimir Demikhov reported the first successful lung transplantation (LTx) in a dog (1,2). This landmark surgery brought about advancements in surgical technique, paving the way for the first human LTx reported by Dr. James Hardy and colleagues in 1963 (2). From 1963 to 1983, 40 LTxs were reported, with grim survival reported and only one patient surviving to 10 months (3). It wasn't until 1983 when Dr. Joel Cooper and colleagues at the Toronto Lung Transplant Group reported the first successful LTx with long-term survival of 7 years (4). The early indication for LTx was end-stage pulmonary fibrosis. Over time, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and cystic fibrosis were added as indications for LTx (3). These expanding indications and improving outcomes led to a significant evolution of the multidisciplinary field of LTx since the first successful human LTx.

A LTx is now the accepted definitive treatment for end-stage lung disease, with over 70,000 adult LTx procedures reported globally to date (5,6). Despite this growing number of LTxs performed worldwide, considerable challenges and barriers to achieving successful LTx outcomes persist. These challenges have resulted in a variety of advances in the 21st

century, including changes to the organ allocation systems, use of ex vivo lung perfusion (EVLP), and expanded donor criteria and donation after circulatory death (DCD) donors to improve the availability of suitable organs. Strategies employing extracorporeal life support have emerged as both an option to bridge to transplant, for intraoperative and post-operative support. Implementation of perioperative echocardiography and tailored anesthetic techniques aimed at preventing primary graft dysfunction (PGD) have also contributed to improved outcomes (7-9).

Donor pool expansion

Although the wait-list pre-transplant mortality rate has decreased (22.1 deaths per 100 waitlist years in 2014 to 16.1 in 2020), the number of patients added to the waitlist continues to rise (10). To meet this growing demand, transplant programs have reexamined their donor criteria. Centers throughout the world have explored the use of marginal or extended criteria donors (ECD), size mismatch allografts, and DCD donors (11,12). Donation after brain death (DBD) is most common whilst donations after circulatory death have largely been avoided due to the fear of warm ischemia time and associated allograft dysfunction (13). However, low metabolic demand and oxygen stored within alveoli provide some protection from ischemia. Restoration of ventilation in the absence of circulation can replenish alveolar oxygen supply and delay ischemic injury. Additionally, DCD donors experience less sympathetic storm, leukocyte influx, inflammatory changes and neurogenic pulmonary edema associated with brain death (11,12). One study estimated that utilization of optimal and suboptimal lungs from DCD donors could increase the lung donor pool by 50% (14). The first controlled DCD (cDCD) donor transplant was reported in 1995 (15). In the US, LTxs from DCD donors have increased from 3.1% [2015] to 7.4% [2020] of all LTxs (10). This trend is even more common in Europe where many countries report DCD Ltx rates greater than 20% of total LTxs (16).

The inability to randomize donors and recipients limits the evidence about DCD LTx. However, in the recent study of 105 LTx with robust donor data, DCD donation was associated with increased need for postoperative extracorporal membrane oxygenation (ECMO) (32.0% *vs.* 7.5%) and the difference remained considerable after adjustment for the pre- and intraoperative covariates {risk ratio (RR) =4.11 [95% confidence interval (CI): 0.95–17.7], P=0.058} (17). Furthermore, authors reported an increased incidence of delayed chest closure and postoperative chest drainage after DCD donation (17). Verzelloni Sef *et al.* reviewed 95 lung transplant recipients (DCD n=17, DBD n=78) and analyzed the incidence of acute kidney injury (AKI) and renal replacement therapy (RRT) at 7 and 30 days postoperatively (18). Data suggest that DCD donors were associated with twice higher risk of AKI and RRT (18). However, other reports suggest there is likely no difference in 1-year mortality, PGD or acute rejection between DCD and DBD donors (19-22). Overall, the current evidence suggests that cDCD donors are a viable and safe source with equivalent short term and potentially, long term outcomes.

In contrast to cDCD donors, the evidence supporting Maastricht Category I and II uncontrolled DCD (uDCD) donors is not as robust. An initial series of 29 transplants from 2002-2009 found acceptable mid- and long-term survival rates; however, there was a high rate of PGD (23). The same group compared outcomes from 38 uDCD and 292 DBD donor transplants and found similar rates of PGD3 and freedom from CLAD. However, there was a significantly decreased rate of overall survival in the uDCD group at 1, 5 and 10 years and increased rate of PGD when grades 2 and 3 were combined (24). Recently, Campo-Cañaveral de la Cruz *et al.* reviewed all LTxs from 2013–2019 (239 DBD, 29 cDCD and 14 uDCD donors) (25) and found no difference in outcomes amongst the three groups including 30-day, 90-day, 1- and 3-year survival, PGD at 3 and 72 hours, chronic lung allograft dysfunction (CLAD) incidence, airway complications, need for ECMO, or hospital or intensive care unit (ICU) length of stay (25). uDCD donors can be a feasible and safe organ source, especially with advancements in lung protective ventilation, topical cooling and EVLP.

In addition to expanding the donor pool, another method of increasing organ supply is by increasing the number of acceptable donor lungs for utilization (26). EVLP is a promising platform that allows for allograft assessment in a normothermic controlled environment, outside of the donor body with active ventilation and perfusion (27). EVLP significantly extends the safe organ preservation time to up to 12 hours (28,29). Increased preservation time allows for assessment and optimization of the allograft, especially in marginal donors. It also allows transplant teams to overcome logistical constraints (30). EVLP may directly increase LTx volume by recuperating organs that initially did not meet donation criteria into acceptable organs for transplant (31). Many centers with active EVLP programs report increases up to 70% in transplant volume

and utilization because of EVLP (26,27,32-35).

The first LTx with application of EVLP took place in 2001 by Steen *et al.* in Lund, Sweden (36). Since then, EVLP use has steadily increased. Van Raemdonck *et al.* show EVLP was used in 15% of 1,090 DCD donors, and de la Cruz *et al.* show EVLP was employed in 28% of uDCD donors (25,37). The results from two prospective randomized controlled trials (RCTs) demonstrated comparable or non-inferior short term outcomes in standard criteria lungs transplanted with and without EVLP (29,38). The EXPAND trial used the OCS Lung system specifically in extended criteria donors and reported an 87% utilization rate of DCD organs and excellent 30-day, 6-month and 1-year survival rates of 99%, 93% and 91%, respectively (39). A meta-analysis of 8 studies (Toronto and Lund protocols) comparing outcomes of marginal donor LTxs with (n=186) and without EVLP (n=1,005) found no difference in length of intubation, postop ECMO need, length of ICU or hospital stay, and most importantly PGD 3 at 72 hours, 30 day or 1 year survival (40). This was in spite of the EVLP group having significantly higher rates of abnormal lung radiographs, smoking history rate, and lower donor PaO_2/FiO_2 ratios (40).

EVLP systems facilitate gross examination and biopsy of the allograft, laboratory monitoring, imaging, and bronchoscopy (26,28). Many centers are also investigating using EVLP for advanced molecular diagnostics, targeted genetic, anti-inflammatory and anti-microbial therapies and specialized treatments such as thrombolysis, leukoreduction and ultraviolet therapy to optimize and repair allograft function (26,31,41). Leveraging the benefits of EVLP to improve allograft utilization rates in marginal, DCD and especially, uDCD donors, may significantly expand the donor pool. However, Vilavicencio *et al.* recently demonstrated that EVLP when used in DCD LTx can be associated with more pulmonary edema on chest X-ray in the immediate postoperative period and longer mean time to extubation (42). The full potential of EVLP is yet to be discovered; however, it is clearly an encouraging technology that may not only increase organ availability, but also improve organ quality and transplant outcomes.

Evolving role of extracorporal life support (ECLS)

Guidelines on the indications and practice of ECMO are published by Extracorporal Life Support Organization (ELSO) (43). ECMO is a viable and lifesaving option for patients with acute exacerbations of end-stage pulmonary disease when used as a bridge to LTx (44-46). ECMO provides critically ill patients valuable oxygenation and ventilation support with veno-venous (VV) ECMO as well as additional circulatory support with veno-arterial (VA) ECMO if needed (47). Furthermore, it may provide the advantage of weaning patients off positive pressure mechanical ventilation and engaging in physical therapy while already having needed intra-operative ECLS strategy (48,49).

Even though there is no dedicated ECMO variable in current LTx allocation scoring, a higher urgency is proxied into the scoring system and may be calculated separately (50,51). Overall, ECLS use in this context has increased dramatically (52), yet less than 7% of patients undergoing transplantation are currently bridged with ECMO (10). Although, generally associated with greater perioperative risk and poorer long-term survival, in experienced centers, the one-year survival after LTx of these high-risk patients bridged with ECMO has been reported to be 69–88% (53-56). This is similar to overall survival rates reported by the ISHLT registry (6). The average duration of ECMO was between 6–29 days (depending on the study), half of patients supported with a VV configuration and numerous patients were ambulatory and awake until transplantation (53-56).

Reported prognostic factors associated with favorable outcomes in ECMO when used as bridge to transplant include age <50, normal bilirubin, <14-day ECMO support, and sequential organ failure assessment (SOFA) score <6 (45). Additionally, being awake and able to participate in physical therapy with ambulatory ECMO appears to be the most predictive of favorable post-transplant survival (53). ECMO as a bridge to LTx is an attractive therapy with promising perioperative and early survival transplant outcomes. Adequate patient selection and early use rather than emergent salvage therapy in experienced centers is imperative for successful patient outcomes (57).

There is a wide practice variability both in LTx surgical approaches as well as in the types of ECLS employed for support; these include cardiopulmonary bypass (CPB), peripheral or central ECMO with VA or VV strategies. Because of improvements in single-lung ventilation technique and effective vasoactive management, only 30–50% of LTxs end up requiring intra-operative ECLS either as a planned part of the procedure or on an emergent backup basis (58,59). Patients most likely to need ECLS are those who would not be able to sustain single lung ventilation because of lung fibrosis, those with pulmonary hypertension [mean pulmonary arterial pressure (mPAP) >25 mmHg] and right ventricular (RV) dysfunction (58,60-62).

Historically ECLS has been in the form of CPB, with one stage or bicaval cannulation done prior to lung resection (61). The benefits of CPB include excellent oxygenation and ventilation in patients who would not easily tolerate single lung ventilation, controlled re-perfusion, and added hemodynamic support particularly to those susceptible to acute RV dysfunction (58). The use of CPB leads to coagulopathy, neutrophil and complement activation which is associated with end-organ injury (58,61). Furthermore, systemic inflammation and reports of early graft dysfunction have been associated with the use of CPB (58,61).

It is not surprising therefore, that there is a recent trend toward utilizing ECMO support instead of CPB, especially in light of observational studies showing increase levels of (PGD) in those undergoing CPB (1,59,63-65). Intra-operative ECMO has become the preferred method of ECLS in many experienced centers (66-69). Benefits of intra-operative ECMO over CPB include full respiratory (VV ECMO) and possibly hemodynamic support (VA ECMO) with less heparinization, and elimination of the cycling of blood through suction devices, use of a reservoirs with a liquid air interface that would result in added inflammation and coagulopathy. Hoetcher *et al.* outlines evidence for ECMO use as the preferred ECLS option during LTx through retrospective data and propensity score matching from a single high-volume center. The authors showed an increased 1-, 3-, 5-year survival in the ECMO group compared to the non-ECLS group (89%, 85%, and 85% *vs.* 85%, 79%, and 77%, respectively), with a trend towards less early PGD presumably from attenuation of the ischemic-reperfusion injury as cardiac output is diverted away from the grafts in the ECMO group (67).

The ECMO practice has evolved to be able to tailor to more unique and challenging circumstances such as cerebral hypoperfusion, left ventricular (LV) dilation, pulmonary hypertension (PH), and RV dysfunction. These are "alternative ECMO techniques" and include the use of additional ECMO cannulas, non ECMO mechanical support devices and atrial septostomy procedures for LV venting (69,70). Martin *et al.* outlines how a hybrid-ECMO-CPB circuit facilitates conversion from ECMO to CPB by excluding the CPB reservoir through clamping the inflow canula and utilizing the system as ECMO (71). In the event conversion to CPB is needed, the reservoir is simply added to the system by unclamping the inflow. The routine use of ECMO support following LTx has become a more standard practice in patients deemed high risk for development of acute PGD such as those with preexisting PH (72,73).

Although guidelines vary among institutions, avoiding aggressive ventilator settings known to predispose patients to acute PGD and supporting the RV in those with primary or secondary PH is imperative for successful outcomes (74). Prophylactic ECLS with VA ECMO following transplantation in patients with severe PH portrays favorable survival rates through controlled postoperative graft reperfusion strategy, lung protective ventilation, and improvement in hemodynamics with RV unloading while optimizing volume status (73,75).

Perioperative echocardiography

In the early era of LTx, advanced hemodynamic monitoring was limited to arterial blood pressure and pulmonary arterial catheters. Gradually, transesophageal echocardiography (TEE) has become integral in cardiac surgical patients and its role in LTx has also grown (59,73). Although TEE is utilized almost ubiquitously by transplant anesthesiologists, it remains only a Class IIb indication for intraoperative monitoring (76-78). This is likely because no LTx specific guidelines nor quantitative cutoffs exist for abnormal findings (79).

Pre-operative or pre-transplant TEE (post-induction of anesthesia) is crucial in establishing the current status of the patient (80). In a study of patients with PH waiting for transplant, pre-operative TEE findings altered the surgical plan in 25% of cases (81). Induction of anesthesia can be high risk, with acute changes in systemic (SVR) and pulmonary (PVR) vascular resistance, loss of muscular tone and positive pressure ventilation. Many patients have PH associated right ventricle dysfunction, RV outflow tract obstruction, and/or tricuspid valve (TV) insufficiency placing them at risk for acute right-sided heart failure and cardiogenic shock (80,82-84). TEE allows for rapid diagnosis of shock etiology, and unusual, undiagnosed pathology (85,86). Importantly, TEE can determine the ability of the RV to tolerate increased PVR secondary to one lung ventilation and pulmonary artery (PA) clamping. During PA clamping, TEE allows for live assessment of RV dilation and dysfunction, TV dysfunction and interventricular septal shift as well as titration and response to preload, inotropes and pulmonary vasodilators to determine need for ECMO or CPB (80,82-84). If cannulation is necessary, TEE is vital in guiding aortic and venous cannulation (87). Intracardiac shunts should be identified as shifts in right atrial (RA) and left atrial (LA) pressure can cause shunt reversal and hypoxia (80,84,88). Of

note, Subramaniam found that 12.7% respondents in their survey always closed a patent foramen ovale (PFO), while 24.9% did not and the majority intervened on a case-by-case basis (89).

After allograft implantation, TEE allows for monitoring during reperfusion and assessment of pulmonary arterial and venous cuff anastomoses. Reperfusion injury or inadequate de-airing and gaseous coronary emboli can cause transient ventricular dysfunction (80,82-84). TEE uniquely allows for continuous and immediate morphological and functional assessment of ventricular and valvular function, guidance of therapy and assessment of recovery. Reported incidences of airway anastomotic complications range from 2% to 33%, although most centers have rates in the range of 7% to 18% (90,91). Anastomotic complications are associated with increased morbidity and mortality; therefore, early identification can allow for early intervention and resolution (87,92,93). TEE is valuable for interrogation of the anastomoses, specifically shape and size, kinks and stenosis, thrombus, flow velocities and laminar *vs.* turbulent flow (84). Ideally, baseline pulmonary vein (PV) and pulmonary artery (PA) assessment should routinely be performed allowing for comparison post-reperfusion. PA anastomotic stenosis or obstruction can lead to acute PH, RV failure, hypotension, hypoxemia, PGD, allograft failure and death (79,80,87,92,94). PV or atrial cuff dysfunction will cause allograft venous congestion and pulmonary edema resulting in similar complications with high risk for PGD and mortality (87,92,94,95). PV anastomotic failure can occur due to stenosis or thrombus, kinking of the cuff from torsion, size mismatch, or external compression (87,92).

The right PA can easily be visualized in the upper esophageal ascending aorta short-axis view after slight rotation to the right. The left PA may be difficult to visualize due to dropout from the left main bronchus; however, surface ultrasound can be used to assess the left PA anastomosis (96). Assessment of the PA involves confirmation of laminar flow and lack of stenosis (vessel diameter at anastomosis and/or pressure gradient), obstruction or thrombus. Some studies recommend the PA of the donor lung should be at least 75% of the proximal PA of the recipient (80,97,98). Signs of stenosis can be narrowing of the anastomotic site, turbulent flow, significant gradient, blunted PV flows on ipsilateral side, or increased PV flows on contralateral side. In one case, Abrams *et al.* described a prominent hilar lymph node causing external compression and stenosis of the right PA anastomosis (87).

Ideally, all PVs should be identified pre-transplant and interrogated after reperfusion. Like the left PA, contact ultrasound can help visualize difficult to see PVs (96). Assessment of PVs involves measurement of diameter (ideally greater than >5 mm, <2.5 mm has been associated with graft failure and thrombosis), evidence of obstruction, kinking or thrombus, color flow doppler for laminar flow, and spectral doppler for PV flow velocities (PVFV) and triphasic flow pattern (80,84,87). PVFV are highly affected by cardiac output, volume status, ECMO, and left atrial pressure (shunt, mitral regurgitation, diastolic dysfunction, etc.). In single LTx, flow velocities may be elevated due to preferential flow to the transplanted lung with a low pulmonary vascular resistance. In bilateral orthotopic LTx, PVFV should be measured after both lungs are implanted as PA clamp during second lung implantation will artificially increase PVFV in the newly implanted lung. Elevated PVFVs can also result from contralateral PA stenosis and left to right shunt (80,87,99,100). Lastly, external compression or torsion can occur after chest closure, so PVFV should be re-measured (84,87). No established cutoff exists for elevated PVFV; however peak systolic flow velocities <1 m/s are acceptable and suspicion of obstruction should increase when velocities are >1 m/s. Obstruction is even more likely when velocities are >1.6 m/s (93,94,101,102). Elevated PVFVs should be taken into consideration with the clinical status of the patient and other TEE findings such as flow turbulence, PV diameter or kinking. Other spectral doppler findings, such as loss of triphasic flow pattern, blunting of the S wave, an elevated baseline, or a multidirectional tracing further endorse an issue (87,93,94,101). Kumar *et al.* reported the overall rate of pulmonary cuff dysfunction to be 4% (1.4% PV stenosis and 2.5% PV thrombus), while patients with cuff dysfunction had mean peak PVFV 1.59±0.66 m/s and mean PV diameter 0.48±0.2 cm. PVFV were significantly higher in patients with stenosis over thrombus (102). TEE assessment of the pulmonary vein cuff is essential as patients with cuff dysfunction were found to have a 32% mortality rate (45% PV stenosis, 24% PV thrombus) (102).

In the perioperative period, TEE allows for rapid, bedside diagnosis in the setting of graft dysfunction or hemodynamic instability (85). TEE can rule out anastomotic issues or intracardiac shunt in the setting of hypoxia and tamponade, pleural effusion, ventricular dysfunction, and volume status during hemodynamic instability (87). Kumar *et al.* found that the majority of pulmonary cuff dysfunction diagnoses were made in the early postoperative period, usually due to clinical deterioration (102). However, Abrams and others argue that intraoperative diagnosis could allow

for early, curative intervention (87,92).

The role of a perioperative TEE service is vital in the care of LTx recipients. TEE is a quick and feasible bedside exam that provides immediate diagnostic information allowing for guided therapeutic intervention (88). Although anesthesiologists are already using TEE for most LTxs, further evidence is needed from large, multicenter studies to better establish quantifiable echocardiographic parameters for normal and abnormal findings. This will likely also increase the level of evidence and indication for TEE in LTx.

Conclusions

The beginning of the 21st century has brought many new developments in LTx. Advancements in donor allocation systems, perioperative echocardiography, and mitigation of PGD have all contributed to improved long-term outcomes. Implementation of extracorporeal life support institutional protocols and bridging strategies have been instrumental in improving outcomes and expanding access to patients with end-stage lung disease (103). Although the scarcity of suitable donors continues to present considerable challenges, the utilization of DCD donors has expanded the number of available allografts. Additionally, the evolution of EVLP has provided an avenue to preserve donor lungs that would have otherwise been deemed unsuitable. Though further investigation is warranted as concerns remain regarding an increased incidence of lung edema postoperatively and increased time to extubation in EVLP donor lungs. The continued developments and advancements in LTx anesthesiology and perioperative medicine throughout the 21st century will have significant impact on defining the future of multidisciplinary LTx care.

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