Lung transplantation
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Purpose of review
To describe recent advances in lung transplantation relevant to anesthesiologists.

Recent findings
There is recent literature describing medical, surgical, anesthetic and critical care of lung transplant recipients.

Summary
There have been substantial changes in preoperative selection and preparation of lung transplant recipients; these include donation after cardiac death, and improved lung-preservation solutions. Newer immunosuppression regimens have been successfully evaluated in clinical trials. Particular advances in anesthesia include endorsement of fluid restriction in thoracic surgery, greater use of transesophageal echocardiography, and postoperative extracorporeal membrane oxygenation.

Keywords
anesthesia, gene transfection, reperfusion injury, transesophageal echocardiography

Introduction
Lung transplantation was first performed successfully in 1983, and has evolved and been refined to now represent a viable therapy for end-stage lung and pulmonary vascular diseases, such that around 20000 human lung transplantations have now been performed [1\textsuperscript{**}].

Historically, the biggest limitations to the growth and success of lung transplantation have been the lack of a supply of transplantable organs, difficulties with early graft dysfunction in the intensive care unit (ICU) and the late development of chronic rejection due to bronchiolitis obliterans syndrome (BOS). Pleasingly, in recent years, there have been significant advances in most of these areas.

The challenges faced by anesthesiologists caring for lung transplantation recipients extend beyond the provision of stable anesthesia to include specific skills in endobronchial intubation and lung isolation, optimization of gas exchange during one-lung ventilation, transesophageal echocardiography (TEE), and management of right and left ventricular impairment [2]. Hemodynamic disturbances are commonly precipitated by induction of anesthesia and institution of positive pressure ventilation, as well as thoracic epidural block, blood loss, surgical retraction, pulmonary artery clamping, and lung allograft reperfusion [2]. Intraoperative and early postoperative care may require advanced supportive therapies that can include inhaled nitric oxide (iNO), right ventricular assist device support and extracorporeal membrane oxygenation (ECMO).

Extending the pool of donor lungs
Lungs used for human lung transplantation have traditionally been derived from brain-dead cadaveric donors with preserved lung function. It has become evident that lung allografts do not need to be pristine to be successfully transplanted and ‘extended’ donor criteria are being adopted [3]. Extended donor age (beyond 60 years), those with an asthma or smoking history, chest radiographic infiltrates and airway secretions, are now routinely considered as viable donors by experienced lung transplantation units [4]. There is still debate whether such organs confer quite as good long-term outcomes but early and mid-term results are comparable with those seen when using traditional criteria [5]. Using a sophisticated normothermic extracorporeal perfusion circuit, Swedish investigators are pioneering lung transplantation after reperfusion and...
resuscitation of initially rejected poorly performing donor lungs [6].

As an alternative organ source, living-related lobar transplants have been performed in some centers, and in Japan represent the bulk of lung transplantation performed [7]. This ethically challenging procedure essentially involves elective donor lower lobectomies from two adults, with bilateral transplantation into a smaller recipient. Long-term results, including those with pediatric recipients, are excellent [7].

Donation after cardiac death has further extended the donor pool [8]. There are four different clinical scenarios from which such organs arise — the so-called Maastricht Criteria — with the most common situations being out-of-hospital cardiac arrest or withdrawal of futile therapy in an ICU setting. Postimplantation lung allograft function is surprisingly good, tolerating an hour of unsupported warm ischemia [8]. It is likely this represents a major area of expansion for lung transplantation. Early results are promising but long-term function is as yet uncertain.

**Donor lung preservation and protection from ischemia–reperfusion injury**

The transplanted lung is at risk of ischemia–reperfusion injury, an inflammatory syndrome that leads to poor postoperative performance known as primary graft dysfunction (PGD) [9]. PGD is one of the most frequent causes of early morbidity and death after lung transplantation. Tracheal extubation is delayed and ICU stay is prolonged [10,11]. A recent study found that ICU mortality was increased five-fold (odds ratio (OR) 4.8, 95% confidence interval (CI): 1.1–22) in patients with PGD [10*].

Guillen et al. [11] did a retrospective study of 9 years of experience (n = 190) in the management of PGD in the early postoperative period after lung transplantation. Lung allograft dysfunction occurred in 37% of patients, but only in 12% was it severe; most (62%) patients were extubated within 5 days. The variables associated with a significantly increased PGD included bilateral lung transplantation, and a requirement for cardiopulmonary bypass (CPB).

A number of recent trials [12,13] have demonstrated improved early graft function using a low molecular weight dextran solution, Perfadex (Vitrolife, Gothenberg, Sweden), for lung preservation during procurement. This is now used in the majority of units worldwide [9,14*].

Although there are a number of demographic and disease-related factors that are associated with PGD, donor pulmonary emboli have recently been identified as one probable cause [15]. Donor emboli are unexpectedly common (37% in one series) when diagnosed by pulmonary venous retrograde flush maneuvers at the time of implantation [15]. In fact, the retrograde flush is now commonly used as a technique to enhance traditional antegrade allograft flush preservation [16]. Graduated initial reperfusion of the graft at the time of implantation has also been shown to limit endothelial damage and minimize PGD [17].

Study has shown that PGD is one of the most critical determinants of early morbidity and mortality following lung transplantation [9,14*]. An international consensus definition has assisted the study of this entity [9,14*]. It is now recognized that the recipient PaO2/FiO2 ratio and chest radiograph findings can be combined as early as 6 h post-lung transplantation to predict future lung function [18]. This provides an important potential therapeutic interventional window, given that the nadir of PGD occurs at 12–24 h after surgery [18].

Preliminary evidence supports a possible beneficial role of aprotinin in preventing PGD. Bittner et al. [19] compared an historical cohort of 112 lung transplantation patients before 2000, and compared these with a subsequent cohort of 59 recipients in the next 5 years who had routinely received aprotinin. Despite longer ischemic times and older donors in the aprotinin group, the incidence of acute post-transplant lung injury was more than halved (from 18% to 7%). Thus, in addition to its antifibrinolytic effect of reducing blood loss and transfusion requirements [20], aprotinin may decrease the incidence of transplant ischemia–reperfusion injury significantly.

There has been some recent interest in using iNO to reduce ischemia–reperfusion injury in lung transplantation. Perrin et al. [21] did a randomized clinical trial in 30 bilateral lung transplantation recipients, comparing 20 ppm iNO at the time of reperfusion with a no-treatment control group. They could not, however, identify any reduction in extravascular lung water (P = 0.61) or improvement in gas exchange (P = 0.61). Thus, unlike previous nonrandomized studies, it appears that prophylactic iNO administration has no effect on surrogate markers of PGD following lung transplantation.

Gene therapy is also being investigated. Both early and chronic allograft failure after lung transplantation are believed to be immune-mediated, and the lung provides simple access to local gene delivery via the airway. A number of issues first need to be considered, however, before its use in lung transplantation [22]. In an ongoing series of elegant experiments, Canadian investigators have shown that donor-lung biopsy cytokine profile assessment can identify those organs at risk of PGD.
The evolution of lung transplantation recipient selection and operative techniques

Acceptability criteria for potential lung transplantation recipients have been recently summarized in an international consensus statement [24]. This statement notes that the aim of lung transplantation should be to successfully transplant as many individuals as possible, recognizing the need to respect the altruistic gift of organ donation and the current scarcity of donor organs. It follows that transplantation should not therefore be offered to individuals who manifest behavioral traits (i.e. poor compliance), or become so ill (i.e. deconditioned and immediately preterminal) that long-term success is unlikely.

Notwithstanding, there has been a steady expansion in the breadth of acceptable patients. With aggressive preoperative and intraoperative interventions, many traditional medical [i.e. significant coronary artery disease (CAD)] and surgical (i.e. pleurectomy) absolute contraindications have now been downgraded to relative contraindications [24].

Although right heart catheterization and transthoracic echocardiography are part of the routine work-up for lung transplantation candidates, the need for the former has been questioned because of its inherent risks, cost and inconvenience. Ben-Dor et al. [25] examined the correlation between pulmonary pressures estimated by echocardiography and right heart catheterization among lung transplantation candidates, as well as with their correlation with measurements done intraoperatively during lung transplantation. They had echocardiographic data for 79 of 106 (75%) recipients, with modest correlation ($r = 0.80$) between echocardiographic and catheterization estimations at the pretransplant work-up. In 14 (18%) patients, the difference between the two methods was more than 20 mmHg. Importantly, the correlation between these earlier measurements and those done during lung transplantation was even weaker: right heart catheterization $r = 0.50$, echocardiography $r = 0.31$. The poor agreement between the two assessment periods may reflect the significant time interval between both, but in any case this suggests that the need for right heart catheterization in lung transplantation work-up should be questioned.

A review of 268 adult patients who underwent lung transplantation, of which 210 had coronary angiography preoperatively, found none with severe CAD, but 33 patients had mild or moderate disease [25]. There was no significant difference in early postoperative complications, including hospital or late mortality, between recipients with or without CAD. In fact, the patients with mild or moderate CAD had no hospital mortality and no late cardiac mortality. Three recipients with moderate CAD developed late ischemic cardiac events, however, two of whom later underwent revascularization [26].

The same group identified 35 of 700 lung transplantation recipients who had undergone concomitant cardiac-lung transplantation surgery [27] between 1988 and 2003. The most common procedures were repair of patent foramen ovale and other septal defects (PFO 18, ASD 9, VSD 2); coronary artery surgery ($n = 4$) and other procedures ($n = 2$) were rare. They found that although duration of mechanical ventilation and ICU stay were longer with combined cardiac and lung transplant surgery, this had no effect on operative morbidity or mortality when compared with their other lung transplantation recipients. They concluded that lung transplantation can be offered to patients with cardiac disease, provided they have normal ventricular function and require limited cardiac surgery [27].

There is interest in developing less invasive bridge to transplant devices to support those with terminal ventilatory failure without the need for ECMO. Fischer et al. [28] have developed a pumpless lung-assist device (‘NovaLung’) in patients with severe respiratory failure refractory to conventional mechanical ventilatory support. In their experience of 176 lung transplantation patients in the period 2003–2005, 12 had severe ventilation-refractory hypercapnia and respiratory acidosis. These patients were connected to the NovaLung for bridge to lung transplantation. The mean (range) duration of NovaLung support was 15 (4–32) days. NovaLung implantation substantially improved carbon dioxide excretion, with mean (SD) PaCO2 levels dropping from 128 (42) mmHg to 52 (5) mmHg ($P < 0.05$). Ten of 12 patients were successfully bridged to lung transplantation; 1-year survival was 80%.

Matching strategies vary around the world depending on local ethical, political and financial structures. In the US, the United Network for Organ Sharing (UNOS) has recently revised its matching process [29]. Having previously been simply based on time accrued on the waiting list, this system now utilizes a number of disease-specific clinical parameters and sophisticated modeling to base lung allocation according to who will get the best predicted improvement in survival. Irrespective of transplant endpoints, much will be learnt from the systematic collection of data on terminal lung disease over coming years.

The type of transplant being performed also depends on a number of local factors, but there has been a worldwide trend to bilateral lung transplantation [1**]. This is based on a perception of superior long-term results and ease of
management of early post-lung transplantation complications [1**,26]. The use of cut-down organs, both as anatomical lobar resections or nonanatomical ‘lung-shaving’, is also allowing greater surgical flexibility without compromising results [7,30]. This may become an increasing consideration in pediatric lung transplantation where the majority of donor organs come from adults [31].

Most previous studies report CPB increases complications after lung transplantation [2]. In one of the largest studies to date, Dalibon et al. [32]* reviewed their experience of 140 lung transplantations, in which 23 (16%) were performed with CPB. They confirm previous studies [2,11], finding that CPB was associated with a longer period of postoperative mechanical ventilation, more pulmonary edema, more blood transfusion requirement, and increased early mortality in those requiring CPB [32]*.

If poor allograft function and/or right heart dysfunction occur immediately after implantation, chest closure can result in severe deterioration. Delayed chest closure is sometimes used. A small study suggests that despite a greater need for tracheostomy and delayed hospital discharge, 30-day survival was unaffected if chest closure was delayed for up to a week [33]. This group opted for this approach in 7 of their 28 (25%) lung transplantation procedures. All of those requiring delayed chest closure were alive at 30 days. There were no wound infections.

**Anesthesia**

The restriction on anesthetic drug administration, because of severe hypotension, makes awareness a possibility [34,35]. Myles et al. [35] conducted a large randomized trial of bispectral index (BSI) monitoring in patients at increased risk of awareness. This included 735 patients undergoing high-risk cardiothoracic surgery and 103 with severe end-stage lung disease, 10 of whom underwent lung transplantation. There were 13 cases of awareness; two patients with awareness had undergone lung transplantation. Intraoperative BSI monitoring was associated with a five-fold reduction in the risk of awareness [relative risk (RR) 0.18, 95% CI: 0.02–0.83; \( P = 0.022 \)].

As the lung allograft is very sensitive to pulmonary edema, fluid restriction and protective lung ventilation strategies should be implemented [36]. These include use of a smaller tidal volume, at 6–8 ml/kg, use of low FiO\(_2\) compatible with adequate oxygenation, and PEEP 5–15 cmH\(_2\)O [36]. Optimal fluid management can be guided by judicious fluid replacement aiming for a central venous pressure of less than 7 cmH\(_2\)O, with systemic perfusion supported by vasoactive infusion [37].

Excessive bleeding and a need for blood transfusion may also threaten the new lung allograft. There is some evidence that blood transfusion may increase the risk of infection and other complications [38], and so cell salvage and antifibrinolytic drug therapy are often used [39]. Although aprotinin clearly reduces the need for blood transfusion [20*], however, there is some recent evidence linking aprotinin with renal failure [40,41]. It is unclear whether the lysine analogs, epsilon aminoacproic acid and tranexamic acid, have similar adverse effects.

Adequate postoperative analgesia is essential, and epidural regimens have been a standard of care for most lung transplantations. A recent systematic review and meta-analysis found that paravertebral block had a lower rate of postoperative respiratory complications, and fewer side effects (hypotension, urinary retention, and nausea and vomiting) when compared with epidural block for thoracic surgery [42]. This has particular relevance for lung transplantation because hypotension increases the need for vasoconstrictor therapy and this typically delays tracheal extubation. Paravertebral block is probably unsuitable for bilateral lung transplantation because of the high volume of local anesthetic required, but would be ideal for most single lung transplant recipients.

**Thromboembolic complications and transesophageal echocardiography**

In a review of 70 lung transplantation procedures [43], thromboembolic complications developed in 6 of the 70 patients (8.6%) at 4–24 months after transplantation: deep vein thrombosis (DVT) in two patients, pulmonary embolism in one patient, both DVT and pulmonary embolism in one patient, and retinal vein thrombosis in two patients. All patients experiencing thromboembolic complications demonstrated abnormalities on coagulation testing: raised fibrinogen \( (n=6) \) or factor VIII, IX, and/or XI levels \( (n=5) \), and prothrombotic mutations (e.g. factor V-Leiden) in five patients.

TEE has become more widely used in lung transplantation [44,45*,46*]. The multiple benefits are seen in other types of cardiothoracic surgery: assessment of left and right ventricular function, intravascular filling, and detection of unexpected abnormalities, but there are additional benefits. TEE allows visualization of adequate flow into the left atrium from the pulmonary veins after completion of the anastomoses [44], as well as identifying any thrombus that may have formed intraoperatively [45*,46*].

**Intensive care unit management**

Although ECMO has become a widely used therapy for severe lung allograft failure [47], the merits of extended ECMO continue to be debated. The Cleveland Clinic group evaluated their lung transplantation experience, for
Late outcomes from lung transplantation
In 2006, a 90% 1-year, 65% 5-year and 40% 10-year survival is to be expected in experienced units [49]. By comparison with results a decade ago, these results predominantly reflect improvements in early post-lung transplantation care. Unfortunately, we are yet to see a clear-cut decline in the subsequent rate of chronic graft failure (BOS) beyond the first year. Once BOS has been initiated, typically manifesting as an irreversible fall (>20%) in forced expiratory volume in 1 s, there is an ensuing 50% 3-year survival overall [11*]. A number of effective therapies have been recently identified in clinical trials to prevent and treat BOS. These include inhaled cyclosporine [50**], everolimus [51], and mycophenolate [52].

Conclusion
The complexities of lung transplantation, which include management of the patient's condition and its interactions with anesthesia and surgery, as well as other aspects of perioperative care, surgical requirements, and pathophysiological perturbations during and after surgery, demand a lot from the anesthesiologist. Advances in each of these areas have occurred over the past few years, but there are few large randomized trials to identify the most effective interventions. Future research should aim to identify the optimal lung-preservation solution, and address the potential benefits of iNO, aprotinin, and gene therapy.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 83 – 84).

The up-to-date and definitive review of lung transplantation.


A report of their initial experience of 5 cases of LTx from donors after cardiac death, with excellent results.


An expert summary of current evidence.


A retrospective analysis of 60 LTx procedures identifying factors associated with reperfusion injury.


Using a pig model, Perfadex solution provided lung preservation for 27 h of cold ischemia; retrograde application was superior to antegrade perfusion.


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When compared with an historical control group, the introduction of aprotinin in LTx had beneficial effects on patient outcomes and ischemia-reperfusion injury.


A meta-analysis of randomized trials could not identify superior blood conservation with aprotinin when compared to the lysine analogs.


26 Thoracic anaesthesia


33 A large case series from an experienced unit found CPB was associated with poorer outcome after LTx.


46 The first report of pulmonary vein thrombosis detected by intraoperative TEE.


48 A series of 3 cases of pulmonary vein/left atrial thrombosis in LT


53 An excellent clinical trial showing that inhaled cyclosporine did not improve acute rejection, but did extend chronic rejection-free survival and improve overall survival.
