Donor management and lung preservation for lung transplantation

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Although lung transplantation has become a life-saving option for patients with end-stage lung disease, this intervention is hampered by a shortage of lungs in view of the growing number of people on the waiting list. Lungs are retrieved from only a small percentage of multiorgan donors, and the transplantation and intensive-care communities have recognised the need to develop innovative methods to expand the donor pool. Advancements in lung-preservation techniques in the preretrieval and postretrieval periods have increased the pool of available donors, and novel research and discoveries in this area have steadily improved post-transplantation adverse events. This Review summarises current best practice and the latest research on intensive-care management of a potential lung donor. We also discuss lung-preservation techniques, including advancements in normothermic ex-vivo lung perfusion, and the potential for a personalised medicine approach to the organ.

Introduction

Lung transplantation is an effective, life-saving therapy for patients with end-stage lung disease. Over the past three decades, advancements in surgical technique, immunosuppression, and post-transplantation management have led to substantially improved outcomes and a proliferation of transplantation programmes around the world. The main limiting factor is a shortage of suitable donors. Meticulous management of potential lung donors and appropriate preservation and treatment of potentially transplantable lungs is at the crux of expanding the donor pool, in view of the growing number of people on the waiting list and a shortage of donors.

Donor management and lung preservation refers to the steps taken after determination of death to preserve lung quality and optimise function after transplantation. Novel methods of donor management, lung preservation, and ex-vivo therapeutics have focused on minimising the incidence and effect of primary graft dysfunction (PGD) after transplantation. PGD is a type of lung dysfunction characterised by hypoxia and impaired ventilation associated with transplantation-related lung injury. It is generally due to capillary leak of the pulmonary vasculature leading to non-cardiogenic pulmonary oedema. PGD can be associated with systemic inflammatory response syndrome (SIRS) leading to circulatory shock and, in its most severe form, multi-system organ failure. The incidence of PGD ranges from 10% to 30%, and it is the greatest contributor to early mortality after transplantation (panel 1).1

This Review focuses on the latest advancements and research into donor management in intensive-care units, and on a detailed approach to preservation of donor lungs, including preservation solutions, mode of transport, optimum temperature, optimum ischaemic times, and ex-vivo therapeutic options for injured donor lungs.

Donor lung preservation in the preretrieval phase

Donor selection

Factors that affect donor selection for lungs can be divided into chronic donor factors and acquired donor factors (induced by the cause of death and perimortem period). Acquired donor factors are potentially modifiable by the specific management interventions outlined below. With advancements in technology, surgical technique, and immunosuppression, the past few decades have seen a shift from using a very conservative set of donor criteria to extended, or marginal, donor criteria.

Panel 1: Primary graft dysfunction (PGD), as defined by the International Society for Heart and Lung Transplantation2

- Grading depends on the ratio of pulmonary arterial oxygen to fraction of inspired oxygen (PF ratio), and on postoperative chest radiograph
  - Grade 0 PGD = PF ratio higher than 300 mm Hg, normal chest radiograph
  - Grade 1 PGD = PF ratio higher than 300 mm Hg, diffuse pulmonary infiltrates involving lung allografts on chest radiograph
  - Grade 2 PGD = PF ratio 200–300 mm Hg, diffuse pulmonary infiltrates on chest radiograph
  - Grade 3 PGD = PF ratio lower than 200 mm Hg, diffuse pulmonary infiltrates on chest radiograph
- Secondary causes of graft dysfunction must be ruled out
  - Cardiogenic pulmonary oedema: defined as evidence of left ventricular systolic dysfunction on preoperative or postoperative echocardiogram and resolution of infiltrates with effective diuresis
  - Pathological evidence of rejection
  - Pneumonia (presence of fever, leucocytosis, purulent secretions, and positive culture on bronchoscopy)
  - Pulmonary venous outflow obstruction as shown on transoesophageal echocardiogram, surgical re-exploration, or post-mortem examination
- All patients on oxygen via nasal cannula with fraction of inspired oxygen less than 0·3 are grade 0 or 1 PGD, based on chest radiograph
- All patients on extracorporeal life support are grade 3 PGD
(panel 2). Although results have varied, outcomes of transplantation using extended-criteria donor lungs have generally been acceptable.8

Management of a brain-dead donor can be challenging for intensive-care physicians, since normal homeostatic balance is disrupted. Management should be directed towards maintaining the overall stability of the donor to maximise the transplantability of as many organs as possible.9 An added challenge is balancing the potentially competing needs of each organ group, such as maintaining sufficient fluid in the kidneys while minimising oedema in the lungs. It is estimated that lungs are retrieved from multiorgan donors in only 15–25% of cases.10,11 In brain-dead donors, lungs are especially fragile compared with other organs, because of the potential for direct injury due to aspiration, the resuscitation process, the systemic inflammatory response that ensues during and after brain death, and ventilator-associated lung injury (figure 1). Optimum ventilator management, haemodynamic support, and therapeutic interventions are reviewed below.

Ventilation

In patients with brain injury, ventilation with higher tidal volumes has been associated with development of acute lung injury.12 Traditional recommendations for donor management were to ventilate the lungs with a tidal volume of 10–15 mL/kg; however, after the ARDSNet trial,13 which showed the injurious effect of higher tidal volumes in critical care, the transplantation community reassessed its practice. A 2010 trial by Mascia and colleagues14 investigated ventilation of brain-dead donors for 6 h with 6–8 mL/kg tidal volumes, higher positive end-expiratory pressure, and recruitment manoeuvres after any disconnection from the ventilator. They also performed the apnoea test on continuous positive airway pressure. After enrolling 118 patients, Mascia and colleagues14 showed an increase in donor eligibility using this protective strategy compared with the conventional strategy (95% vs 54%), and an increase in the number of lungs retrieved for transplantation (54% vs 27%). This was the first randomised trial to evaluate a lung-protective approach among lung donors, and its conclusions are important to the transplantation community.

More research into optimum ventilation of lung donors is needed to answer some key questions that arose as a result of Mascia and colleagues’ trial. Unfortunately, the trial was stopped early because of funding. The inclusion criteria used for the study were strict and many potential donors that would have been used in some centres were excluded; therefore, further research investigating the broader applicability of a lung-protective approach is needed, particularly among extended-criteria donors. Questions that remain include whether the protective strategy for ventilation translates into improved post-transplantation outcomes, such as reducing the incidence of PGD and early mortality, and whether one particular aspect of the intervention strategy had a stronger effect.

Haemodynamics, fluid, and vasopressors and inotropes

80% of brain-dead donors experience circulatory shock.15 The main cause of persistent shock after brain death is vasodilatory shock, hypovolaemia due to haemorrhage that is related to the cause of admission, hypovolaemia due to osmotic diuresis for cases with elevated intracerebral pressure, hypovolaemia due to diabetes insipidus, or capillary leak due to SIRS.16 Other potential causes of shock after brain death include vasodilatory shock from cortisol deficiency, cardiogenic shock from the cytokine storm related to brain injury, thyroid deficiency, or impaired chronotropy and inotropy from the lack of sympathetic flow that ensues. Maintaining haemodynamic stability is crucial to protect end-organ function. Haemodynamic assessment includes evaluating for any evidence of left ventricular dysfunction.

Panel 2: Standard criteria for lung donors8 and considerations regarding extended-criteria donors

- Age younger than 55 years
- Lungs from donors older than 55 years have been successfully transplanted
- Increased age is associated with borderline risk for increased 5-year mortality, increased 10-year mortality, and increased risk of bronchiolitis obliterans syndrome8
- Less than 20 pack-years smoking history
- No study has evaluated number of pack-years that would preclude lungs from being transplanted
- More than 20 pack-years is associated with longer time spent by recipient in intensive care, impaired early oxygenation and ventilation, but no difference in late outcomes8
- Recent study showed increased 3-year mortality associated with smoking donors compared with non-smoking donors, and an increased incidence of bronchiolitis obliterans syndrome8
- Crucial factor is assessment of lungs for evidence of emphysematous changes and malignancy
- Appropriate size matching with prospective recipient
- Oversized lungs can undergo lung-reduction surgery to prevent thoracic compartment syndrome
- Total donor lung capacity 75–125% of recipient capacity was not associated with clinical problems
- Ratio of pulmonary arterial oxygen to fraction of inspired oxygen (PF ratio) higher than 300 mm Hg*
- Consider ex-vivo lung perfusion in borderline grafts with PF ratios 300 mm Hg or lower
- No evidence of pulmonary infection, absence of purulent secretions on bronchoscopy, and absence of organisms on sputum Gram stain
- 50% of donors are colonised with organisms; however, this should not present as purulence
- Routine prophylaxis of every recipient with broad spectrum antimicrobials
- Blood-type compatibility, absence of chest trauma, no prior cardiopulmonary surgeries

*Fraction of inspired oxygen 1.00 and positive end-expiratory pressure 5.0 cm H2O are standard criteria.
using an echocardiogram, ruling out the presence of diabetes insipidus, and evaluating for vasodilatory shock. A large proportion of patients are volume depleted just before brain death, and this becomes exacerbated in a vasodilated state. A central venous or pulmonary artery catheter can be inserted to optimise haemodynamic management of a multiorgan donor. Once haemodynamic instability ensues, the patient should be assessed for diabetes insipidus and volume resuscitated to euvolaemia. If diabetes insipidus is present, treatment with vasopressin and desmopressin should be initiated. Optimum volume status is challenging to achieve and can be transplant-organ specific. In general, target endpoints to achieve include good perfusion pressure (mean arterial pressure >70 mm Hg), a euvolaemic state with a target urine output of 0.5 mL/kg/h, normal heart rate, decreasing lactate, and central venous blood gas higher than 70%.17

Previous studies have shown that a central venous pressure (CVP) of 4–6 mm Hg is optimum for lung preservation. A CVP of 8–10 mm Hg resulted in an increase in the alveolar–arterial oxygen gradient, leading some groups to recommend maintaining a CVP of 10–12 mm Hg if only abdominal organs are being retrieved, lower than 8 mm Hg for potential lung donors, and 8–10 mm Hg if abdominal organs and lungs are being donated.18,19 A study from Spain20 assessed the safety of using a restrictive fluid balance to increase lung procurement; the investigators noted that a negative or euvolaemic fluid balance with a CVP target of lower than 6 mm Hg did not have a deleterious effect on graft survival of the kidney or on development of delayed graft function. In view of the limitations associated with measurement of CVP and pulmonary capillary wedge pressure, novel methods to evaluate volume status are being studied, including pulse-pressure variation and extravascular lung water (table 1).

There is no evidence of any difference in post-transplantation outcomes with use of crystalloid versus colloid solutions for resuscitation in lung-transplant donors. From a physiological perspective, colloid would be expected to best minimise pulmonary oedema, but this has not been validated in any clinical trials.21 Hydroxyethyl starches should be avoided since they could induce renal tubular injury and early renal graft dysfunction.22

A state of vasopressin deficiency is common after brain death and is often a cause of shock. It has been shown that brain-dead patients with autonomic failure are hypersensitive to the vasoconstrictor effects of vasopressin.23 Because of its lack of direct stimulation of alpha-1 and beta-1 receptors, and its dual effect in the presence of diabetes insipidus, vasopressin is the initial vasopressor of choice after euvolaemia has been achieved.24 Recommended second-line therapy for haemodynamic instability includes use of alpha-1 agonists, such as norepinephrine, epinephrine, or phenylephrine. A concern with the use of alpha agonists is the potential to induce vasoconstriction in vascular beds of organs, inducing ischaemia. A study of 60 patients assessed potential lung donors exposed to exogenous catecholamines compared with those who were not.25 The study showed a drop in PF ratio in the first 6 h after transplantation among recipients of lungs exposed to exogenous catecholamines; however, this did not translate to prolonged duration of mechanical ventilation and no further endpoints, such as PGD, were assessed.25 This result cannot be attributed solely to the action of catecholamines, since patients who needed catecholamines probably had a higher degree of systemic inflammatory response, which possibly leads to a greater risk of capillary leak and PGD at the time of transplantation. Further research is needed to elucidate the effect of catecholamines on donor lungs.

The best inotropic supportive agent has not been extensively studied in the brain-death setting. Dopamine is often the inotrope of choice, but it is recommended with caution in potential heart-transplant donors, because of the possible downregulation of beta-1 receptors. If high levels of inotropic agents are needed along with vasopressors, and there is evidence of impaired ejection fraction, placement of a pulmonary artery catheter could be considered to more accurately guide therapy for multifactorial shock. In the era of novel haemodynamic monitors, including pulse-pressure variability, stroke-volume variability, and echocardiography, non-invasive methods of assessment might replace the use of pulmonary artery catheters.

**Hormone therapy**
Brain death results in dysfunction of the hypothalamic–pituitary axis, leading to a deficiency in key hormones.
and subsequent diabetes insipidus, adrenal insufficiency, and hypothyroidism. These conditions can exacerbate shock. There has been substantial debate over whether hormone dysfunction actually occurs in brain death, the extent to which it occurs, its effect on haemodynamics, and whether exogenous replacement can lead to improved outcomes in terms of lung function after transplantation.26–29 Further study is needed in this area.

Diabetes insipidus ensues as a result of inadequate antidiuretic hormone production within hours of brain death, leading to high-volume diuresis of hypotonic urine. If left untreated, diuresis could result in profound hypovolaemia and hypernatraemia. Although volume repletion is recommended, maintaining an appropriate urine output is much more easily achieved with vasopressin (100–200 mL/h), and with desmopressin if there is persistent evidence of ongoing diabetes insipidus despite vasopressin use.35

Glucocorticoids enhance vascular tone in the setting of cortisol deficiency, and have also been suggested to optimise donor lung function through blunting the inflammatory response associated with brain death.30–32 Use of methylprednisolone has been shown to improve donor oxygenation and lung utilisation, and is standard practice.33 One study investigating the use of methylprednisolone alone, methylprednisolone with tri-iodothyronine, tri-iodothyronine alone, or placebo showed attenuation in the accumulation of extravascular lung water in the methylprednisolone-alone group only;34 however, this did not translate to improvement in PF ratios among those donors. Post-transplant outcomes were not assessed. Limitations of the study were that it was underpowered and there was a delay in the administration of the steroids (12–5 h after brain death); therefore, further research is needed to assess the effect of steroids in lung transplantation. Currently, it is recommended that early methylprednisolone (15 mg/kg) be used in potential lung-transplant donors, for haemodynamic and lung-protective effects.

The presence of hypothyroidism in brain-dead donors remains controversial. Although many studies have documented a reduction in free plasma tri-iodothyronine (T3) concentrations, not all have shown changes in thyroid stimulating hormone or tetra-iodothyronine (T4). This raises the question as to whether a state of sick-euthyroid syndrome is created, which does not warrant therapy, or whether true hypothyroidism exists. A true hypothyroid state can lead to ATP depletion and mitochondrial dysfunction, followed by impaired cardiac inotropic and chronotropic function. Thyroid replacement with thyroid hormone (T4) is associated with an increase in the number of organs retrieved and an improvement in left ventricular dysfunction, but thyroid replacement has not been shown to specifically improve lungs.38–42 A recent systematic review and meta-analysis43 assessed the effect of thyroid hormone administration to potential donors who were brain dead. The findings did not support routine administration of thyroid hormone, because it did not lead to a significant effect on donor cardiac output. However, only a small number of donors were haemodynamically unstable, so it is difficult to conclude that this subgroup would not benefit from thyroid hormone.43

There is little evidence to guide appropriate timing of hormone therapy initiation (except in the case of vasopressin given for shock or evidence of diabetes insipidus). Some guidelines recommend initiating hormone resuscitation in the setting of haemodynamic instability, other groups advocate initiation when left ventricular ejection fraction is below 45%, and yet others recommend broad empirical use in all donors.44,45

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### Table 1: Ongoing studies of organ management in potential donors

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<thead>
<tr>
<th>Study description</th>
<th>Sponsor; location</th>
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<tr>
<td><strong>Lung specific</strong></td>
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<tr>
<td>Novel lung trial: normothermic ex-vivo lung perfusion (EVLP) as an assessment of extended/marginal donor lungs (NCT01365429)</td>
<td>A prospective, non-randomised, multicentre trial investigating use of EVLP using Steen solution</td>
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<tr>
<td>International randomised study of the TransMedics Organ Care System (OCS) for lung preservation and transplantation (INSPIRE; NCT01650434)</td>
<td>A prospective, international, multicentre, randomised controlled trial comparing preservation of donor lungs by use of normothermic preservation with the OCS lung device versus cold flush and storage</td>
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<tr>
<td><strong>All organs</strong></td>
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<tr>
<td>Remote ischaemic preconditioning in neurological death organ donors (RIPNOD; NCT01515072)</td>
<td>A prospective, randomised, open-label trial to determine whether lower limb ischaemic preconditioning after brain death and incision for organ recovery improves donor stability, organ quality, organ yield, and early post-transplantation outcomes</td>
</tr>
<tr>
<td>Monitoring organ donors to increase transplantation results (MONITOR; NCT00987714)</td>
<td>A prospective, open-label, randomised trial to determine whether protocol-guided resuscitation of brain-dead organ donors using pulse-pressure variability can increase the number of organs transplanted per donor</td>
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Additional interventions

Animal studies and ex-vivo models have shown that the use of beta agonists can enhance the clearance of pulmonary oedema.48,49 However, a recent randomised controlled trial assessed the use of nebulised albuterol versus placebo in 500 organ donors, and did not show improved donor oxygenation or lung utilisation in the group that received a beta adrenergic agonist.48

Donor management protocols

Standardisation of donor management protocols has led to promising results with regard to increasing the donor pool, particularly in lung transplantation. A 2010 study by Franklin and colleagues40 assessed the establishment of donor management goals for intensive care in 805 donors. Goals were set for mean arterial pressure, pH, partial pressure of oxygen in blood, sodium, glucose, single vasopressor use, urine output, and central venous pressure. Achievement of these goals correlated with a significant increase in the organs transplanted per donor. Goals that had the greatest effect included minimisation of vasopressor use and of partial pressure of oxygen. Thoracic organs had the greatest increase in use when donor management goals were established and adhered to.46 Optimum timing of organ retrieval during the donor management phase has also been assessed.47 By contrast with the investigators’ initial hypothesis, donor management that lasted longer than 20 h increased organ yield and successful transplant rates, particularly for lungs, compared with management for less than 20 h. This study suggests that organs retrieved during the systemic inflammatory response have the potential for ongoing capillary leak, increased vasopressor requirements, and further impairment in oxygenation. Allowing the inflammatory response to settle could lead to amelioration of SIRS and better organ function (figures 1 and 2). Therefore, spending time to stabilise and treat multimorbid donors can increase the yield of successfully transplantable organs (panel 3).

Donation after cardiac death

Donation after cardiac death (DCD) is a method by which patients who do not fulfil the criteria for brain death can donate organs after elective withdrawal of life-sustaining therapies. Uncontrolled DCD occurs when the donor is either dead on arrival to the hospital or has died after unsuccessful resuscitation. Controlled DCD can occur from patients awaiting cardiac arrest or after cardiac arrest in brain-dead donors (figure 3). DCD has increased the number of organs available for transplantation. The largest increase in multiorgan donors in recent years has been in the DCD category, and this type of donation will have a substantial effect on organ utilisation in the future.

Currently, DCDs account for about 20% of all deceased organ donors. Compared with grafts from brain-dead donors, those from DCDs have shown equivalent rates of PGD and bronchiolitis obliterans syndrome, and 1-year, 3-year, and 5-year patient survival rates after lung transplantation are also similar.45 In many centres, the cutoff for lung retrieval is death within 1 h of withdrawal of life-sustaining therapy; however, in the era of ex-vivo lung perfusion (EVLP), our centre will wait up to 2 h to retrieve lungs. The lungs are further assessed on an ex-vivo circuit before deciding on transplantation. Strategies to maintain the integrity of the graft after withdrawal and before death are key to effective graft function. The shorter the timeframe, thus a shorter warm ischaemic time, the better the outcome.49 A range of prediction tools to determine death within 60 min or 120 min in potential DCD candidates have been assessed.46 However, broad application of these methods has not shown consistent results between time predicted and actual time of death. More research is needed to identify which variables can better predict accurate time to death.

Donor lung preservation at retrieval and during transportation

Preservation

Vigilant preservation helps protect against PGD and improves long-term graft function. Maintaining viability of the lungs depends on several preservation factors, including type of preservation solution and method of administration, storage temperature, lung inflation volume and pressure, mode of transportation, pharmacological agents, and ischaemic times.

At the start of organ recovery, the lungs are flushed with a preservation solution in an anterograde and
A perfusion volume of 60 mL/kg is used by airway pressures, and more effective removal of improved oxygenation, pulmonary compliance, lower models, retrograde flushing showed an association with bronchopulmonary circulation. In animal and human vasoconstriction. Furthermore, retrograde flushing via the pulmonary veins probably allows additional access to bronchopulmonary circulation. In animal and human models, retrograde flushing showed an association with improved oxygenation, pulmonary compliance, lower airway pressures, and more effective removal of thrombus. A perfusion volume of 60 mL/kg is used by most centres, after a study by Haverich and colleagues showed that a high volume and high flow rate improved postoperative lung function and achieved better lung cooling than a lower volume at a lower flow rate. Although 150 mL/kg has also been used in some centres, it has not been found to be better than 60 mL/kg with regard to post-transplantation outcomes. Perfusion pressure of the solution is also an area of controversy, since a balance must be achieved between too high a pressure, which can damage the pulmonary vasculature, and too low a pressure, which can result in inhomogeneous distribution of preservation fluid. In a rabbit model investigating flushing pressures from 5 to 25 mm Hg, the most effective flushing pressure was 10–15 mm Hg. Uniform and complete flushing was not achieved with the higher and lower pressures. Preserves of 20 mmHg or higher were associated with a decrease in endogenous nitric oxide production, raising concern about precipitation of vasoconstriction of the vasculature and a detrimental effect on the lungs after reperfusion.

Early organ preservation solutions, which were high-potassium, low-sodium intracellular solutions, led to development of oedema and vasoconstriction, limiting the ability to achieve a uniform flush. An ideal solution prevents the development of oedema, facilitates aerobic metabolism, and prevents pulmonary vasoconstriction, thus facilitating an evenly distributed flush. In the 1980s, Fujimura and colleagues created an extracellular solution that was better than existing intracellular options with respect to preservation of pulmonary function. Keshavjee and colleagues showed that better lung function was achieved with low-potassium dextran solution (LPD) than with the traditional intracellular Euro-Collins solution, in a canine model. Addition of glucose potassium prevents vasoconstriction, and dextran is an oncotic force that minimises oedema, has better rheological properties than traditional high-potassium, low-sodium intracellular preservation solutions, and prevents endothelial adhesion and cellular clumping in the microvasculature. Glucose is a metabolic substrate that allows for sustained aerobic metabolism and maintenance of cellular integrity. Several extracellular organ preservation solutions have since been created (eg, Perfadex, Papworth, Cambridge, and Celsior) and show superiority in terms of
over all lung function over the earlier intracellular versions. Perfadex is used by most centres and is based on the original low-potassium, dextran-40, and glucose (LPD) solution that was developed specifically for lung transplantation. Many studies have shown the benefit of the LPD solution over the intracellular version, including better early graft function, decreased incidence of primary graft dysfunction, and lower 30-day mortality.64–65

Lung inflation and the administration of oxygen are thought to protect donor lungs through three mechanisms: preservation of pulmonary surfactant, preservation of epithelial fluid transport, and maintenance of aerobic metabolism. Optimum lung inflation pressure is unknown. Inflated donor lungs are considered to be better than collapsed lungs, which tolerate ischaemia poorly; an atelectatic lung has lower alveolar fluid clearance, higher pulmonary vascular resistance, and diminished distribution of preservation solution.62–64 However, the amount of inflation is crucial, since hyperinflation can also have a detrimental effect on the lungs due to barotrauma and reperfusion oedema. Furthermore, if donor lungs are transported by air, the degree of inflation must take into account possible additional expansion, which can occur even in pressurised cabins where barometric pressure might not exactly match ground pressure. DeCampos and colleagues61 investigated optimum inflation volume by comparing rat lung blocks stored atelectatically and at 25%, 50%, 75%, and 100% of total lung capacity. They found that the optimum inflation level for lung preservation (in terms of haemodynamics and gas exchange) was 50% of total lung capacity.

Inflation is done with an inspired oxygen tension of 30–50%. While the lung remains ischaemic, the oxygen facilitates a metabolically active environment in the setting of glucose-enriched preservation solution. Thus, aerobic metabolism can continue, albeit at a reduced rate due to hypothermia; this can delay cell death and prevent the accumulation of cellular metabolites. Although the optimum oxygenation threshold is unclear, high oxygen concentrations might induce the production of oxygen free radicals, increasing the risk of PGD during reperfusion.66 Thus, most groups inflate lungs with a fraction of inspired oxygen of 50% before retrieval and transportation.

Most centres cool lungs to 4–8°C. A study by Kayano and colleagues,69 using a rat model, reported an optimum storage temperature of 10°C. However, concern that any incremental increase above this threshold could have a detrimental effect on the lungs has led to a lower target of 4–8°C, to retain a clinical margin of safety.66

Prostaglandin E1 has been broadly used in the pre-treatment phase before lung procurement. Prostaglandin E1 was originally administered before lungs were flushed with preservation solution, because of its ability to induce pulmonary vasodilatation and offset the vasoconstricting effects of the cold solution. Additionally, it has been found to be an effective anti-inflammatory agent that can further reduce PGD,68 and is therefore used in the flush preservation solution and as a continuous intravenous infusion to treat severe post-transplantation PGD.

Heparin is administered to minimise the risk of thrombus formation. In the setting of DCD, administration of heparin before circulatory arrest might be viewed as unethical, since its sole purpose is for organ preservation. Therefore, heparin could be administered into the pulmonary artery after cardiac arrest and distributed by a few beats induced by cardiac massage. A study by Erasmus and colleagues69 reported excellent outcomes of lung graft function in pigs using DCD lungs without the use of heparin before cardiac arrest.

Other experimental interventions for donor-lung preservation that are still being assessed include the use of pulmonary surfactant, complement inhibition, inhaled hydrogen sulphide, nitrites, and inhaled nitric oxide. A large registry evaluating more than 5000 lung transplants showed a higher 30-day mortality with cold ischaemic times longer than 8 h; however, with improved lung-preservation techniques, ischaemic times of up to 10–12 hours have been safely reported (panel 4).70–72

Normothermic EVLP

The process of death renders lungs vulnerable to injury, leading to low retrieval rates from multiorgan donors. Unfortunately, this is a significant limitation to expanding the donor pool for lung-transplant recipients, since roughly 80% of available lungs worldwide are rejected.8 Transplant surgeons who assess the lungs at the time of death necessarily take a conservative approach and often reject lungs that appear marginal, because of the morbidity and mortality associated with PGD.71

Often, damage to the lungs caused by the inflammatory cascade associated with death has not had time to recover at the time the lungs are assessed. Preserving the lungs in a hypothermic environment does not allow for rapid recovery from cellular injury, or for further assessment of lung function. Thus, cellular injury can manifest itself in the post-transplantation phase, often in the form of graft dysfunction.

Panel 4: Lung-preservation techniques

- Extracellular solution consisting of dextran-40, glucose, and low potassium; anterograde and retrograde flushing at 60 mL/kg and 30 cm height
- Storage temperature 4–8°C
- Inflation to 50% of total lung capacity, fraction of inspired oxygen 50%
- Pharmacological additives: prostaglandin E1, heparin, glucocorticoids
- Cold ischaemic times generally less than 8 h
- Normothermic ex-vivo lung perfusion based on lung assessment and therapeutics
EVLP attempts to simulate the in-vivo environment of a donor lung, using ventilation and perfusion (figures 4 and 5). EVLP allows for further assessment and potential repair of injured lungs. The concept of normothermic EVLP was introduced in the 1970s, and it was first used in practice by Steen and colleagues in the early 2000s, for short-term assessment of lungs after DCD. The first clinical trial and largest clinical experience of normothermic EVLP so far is by the Toronto group, who modified the technique from the model used by Steen and colleagues. The concept is to use normothermia to assess and treat or repair the lungs, using hypothermia when necessary to protect the lungs (eg, immediately after extraction from the donor or during the implantation procedure).

Cyipel and colleagues recently reported on 50 lung transplants that met criteria for EVLP and ultimately went on to transplantation. These lungs were from DCD donors or were lungs from brain dead donors with borderline compliance and PF ratios that would have otherwise disqualified them for transplantation. The lungs underwent 4–6 h of EVLP, during which PF ratio, pulmonary arterial pressure, compliance, and peak airway pressure were documented every hour. Bronchoscopic exams and radiographic images were done at 1 h and 3 h. During EVLP assessment, stability or improvement in these parameters, along with a PF ratio higher than 350 mmHg, qualified the lungs to be transplanted. Incidence of grade 3 PGD at day 3 (PF ratio <200 mm Hg, with evidence of bilateral airspace disease), the need for mechanical ventilation, extracorporeal life support after transplantation, bronchiolar complications, duration of mechanical ventilation, and 30-day, 1-year, and 3-year mortalities were similar in the EVLP group and control group, who received lung transplants not treated with EVLP. There was a lower incidence of grade 3 PGD at 72 h in the EVLP group compared with the control group (2% vs 8.5%), suggesting that the additional time for cellular recovery and repair in a normothermic environment can have a favourable effect on post-transplantation outcomes. A larger trial is needed to further investigate this theory. With the use of EVLP, the Toronto group has increased lung transplantations by 15–20% in the past few years. Ongoing studies investigating which physiological and biological markers during EVLP are the most reliable predictors of function and lung injury are underway. In the future, we predict that biomarkers will be used for accurate diagnostic assessment of every lung before transplantation, not just in the setting of EVLP.

Three EVLP systems are currently being tested in clinical trials (the Toronto technique, Vivoline, and the Organ Care System [OCS]); table 2 outlines the differences between these systems. The main difference between the Toronto technique and the others is use of an acellular perfusion solution, a closed circuit with a positive left-atrial pressure, and lower perfusion flows. The potential for the EVLP technique extends beyond a normothermic environment allowing for assessment, diagnosis, and organ repair (figure 6); the Toronto group reported a median preservation time with EVLP of more than 10 h, demonstrating the safety of an extended preservation period. Thus, EVLP can be a medium for lung resuscitation and therapeutics that require increased time. Use of EVLP as a platform for administration of antimicrobial therapy can reduce the burden of bacterial load in lungs that would be rejected for infectious reasons. EVLP as a platform to deliver thrombolytics in the setting of pulmonary emboli can potentially increase the pool of donors and improve graft function in lungs with pulmonary embolism at the time of retrieval. Gene therapy with an adenoviral vector encoding human interleukin 10, an anti-inflammatory cytokine, has been administered using EVLP technology to attenuate inflammation in injured human donor lungs.

Figure 4: Methods of lung preservation
(A) Cold static preservation: advantages include convenient, fast, and cost-effective method of transport; disadvantages include inhibition of cellular metabolism and possible manifestation of cellular injury post-transplantation. (B) Normothermic ex-vivo lung perfusion: advantages include ongoing cellular metabolism and allowance for organ repair, and continuous functional evaluation of potential lungs post-retrieval; disadvantages include cost and the expertise needed for its use.

Figure 5: Pulmonary oedema before and after 3 h of ex-vivo lung perfusion
This series of x-ray images shows donor lungs before EVLP (demonstrating pulmonary oedema), donor lungs while on the EVLP circuit after 1 h and 3 h, and the transplanted lungs in the recipient with less pulmonary oedema and improved PF ratio. PF ratio = ratio of arterial oxygen concentration to the fraction of inspired oxygen. EVLP = ex-vivo lung perfusion.
Resuscitation

Treatment

lungs. These lungs showed improved lung function after 12 h of EVLP. The use of mesenchymal stem cells to reduce extravascular lung water is also in experimental stages, but could have a profound effect on minimizing neurogenic pulmonary oedema in the setting of neurological death. Not every lung transplantation centre has the capabilities and expertise for EVLP; however, a recent clinical trial reported successful remote EVLP to assess and improve function, transportation, and transplantation of donor lungs, demonstrating the concept of an organ repair centre. In view of the benefit of assessment of donor lungs, and the potential therapies that can be applied with EVLP, centre-based or centralised organ-repair models are an attractive proposal (figure 6).

In a recent pilot study of the OCS system, Warnecke and colleagues investigated the use of a normothermic EVLP system for lung assessment and as a technique for normothermic organ transport. 12 patients received lung transplants at two centres, using standard-criteria donor lungs transported via the OCS lung-transport device. This device allows for immediate connection to a normothermic EVLP system as opposed to cold preservation. The pilot study established that the device can be used safely on standard-criteria donor lungs. All patients survived at least 30 days and were discharged from the hospital. A large, multicentre, prospective, randomised trial (INSPIRE) is currently underway to elucidate the safety and benefit of OCS, and to help determine whether normothermic storage after organ retrieval is better than cold static preservation. A cost-benefit analysis of the effect of the OCS lung transport device is an important aspect of this trial, since it is investigating use of OCS in standard lungs, which generally have better outcomes with cold preservation than lungs from high-risk donors.

Conclusions

Transplanted lungs are subjected to injuries ranging from the event causing death of the donor, to the inflammatory cascade in brain death. Further injuries are related to resuscitation of the donor and management in the intensive-care unit and on ventilation. Injury related to organ extraction, preservation, transport, and implantation then follows. Once implanted in the recipient, ischaemia-reperfusion injury is followed by immunological attack of the foreign organ by the recipient host. For optimum short-term and long-term results, we need to understand and ameliorate each of these injuries along the trajectory of the transplanted organ.

Organ preservation thus begins in the donor. A carefully orchestrated management plan involving several teams—including the donor-management intensivist, the organ-retrieval team, the EVLP team, and the transplant surgeons—are paramount to preserving and evaluating lung function. Novel techniques and potential therapeutics in the area of EVLP are exciting and will provide the means to increase the donor pool, making lung transplantation a reality for more people.

Search strategy and selection criteria

We searched PubMed and Medline with the key terms “lung transplant”, “preservation”, and “donor management”. The search was restricted to studies published in English, and the final search was done in October, 2012. We screened 277 references and included 75 in this Review. We examined the reference lists of selected publications for any additional original research, systematic reviews, or published abstracts of interest that did not come up in the original search.

Table 2: Ex-vivo lung perfusion protocols

<table>
<thead>
<tr>
<th></th>
<th>Toronto</th>
<th>Lund (Vivoline)</th>
<th>Organ Care System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target total</td>
<td>40% cardiac output (1 h)</td>
<td>100% cardiac output (1 h)</td>
<td>2.5 L (15–30 min)</td>
</tr>
<tr>
<td>Start rate</td>
<td>150 mL/min</td>
<td>100 mL/min</td>
<td>200 mL/min</td>
</tr>
<tr>
<td>Pulmonary arterial pressure</td>
<td>&lt;15 mm Hg*</td>
<td>&lt;20 mm Hg*</td>
<td>&lt;20 mm Hg*</td>
</tr>
<tr>
<td>Left atrial pressure</td>
<td>3–5 mm Hg</td>
<td>0 mm Hg</td>
<td>0 mm Hg</td>
</tr>
<tr>
<td>Pump</td>
<td>Centrifugal</td>
<td>Roller</td>
<td>Pulsatile</td>
</tr>
<tr>
<td>Perfusate</td>
<td>2 L Steen solution</td>
<td>2 L Steen solution plus red</td>
<td>1.5 L Steen solution plus red blood cells (haematocrit 10%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blood cells (haematocrit 10%)</td>
<td>(haematocrit 20%)</td>
</tr>
<tr>
<td><strong>Ventilation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start ventilation</td>
<td>32°C</td>
<td>32°C</td>
<td>32°C</td>
</tr>
<tr>
<td>Start perfusion</td>
<td>25°C</td>
<td>25°C</td>
<td>32°C</td>
</tr>
<tr>
<td>Start evaluation</td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
</tr>
<tr>
<td>Perfusion time</td>
<td>12 h</td>
<td>2 h</td>
<td>Duration of transport†</td>
</tr>
</tbody>
</table>

*Pulmonary arterial pressure of <15 mm Hg used in pigs. †Mean time of 5 h in pilot study (range 3–10)."
Contributors
LM did the literature review, outline, primary drafts, and created the panels, tables, and figures. MC reviewed all drafts and suggested modifications, additional insight and references, and assisted with the creation of the panels, tables, and figures. SK reviewed the final drafts and added additional insight and suggestions. All authors approved the final version.

Conflicts of interest
SK and MC were principal investigators for the Toronto Ex-Vivo Lung Perfusion Trial sponsored by Vitrolife, a company that makes sterile solutions for organ preservation.

References
40 Ware L. A randomized trial of nebulized albuterol to enhance resolution of pulmonary edema in 506 brain dead organ donors. J Heart Lung Transplant 2012; 31 (suppl 4): 116.


