Ex Vivo Lung Perfusion

Subjects: Transplantation

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Compared to static cold storage (SCS), ex vivo lung perfusion (EVLP) offers clinicians unrivalled opportunity for rigorous objective assessment of donor lungs in conditions replicating normal physiology, thus allowing for better informed decision-making in suitability assessments. EVLP additionally offers a platform for the delivery of intravascular or intrabronchial therapies to metabolically active tissue aiming to treat existing lung injuries. In the future, EVLP may be employed to provide a pre-transplant environment optimized to prevent negative outcomes such as primary graft dysfunction (PGD) or rejection post-transplant.

ex vivo lung perfusion | lung transplantation | normothermic machine perfusion

1. Introduction

For many people with very advanced or terminal respiratory diseases, lung transplantation is the only therapeutic intervention which may prolong survival and improve quality of life. However, a significant and expanding mismatch between supply and demand for donor lungs means prolonged suffering and significant mortality of up to 30% on waitlists [1]. At present, transplantation activity is significantly restricted with only 20% of potential donor lungs being utilised, the rest being excluded due to an assessment of unsuitability, either true or perceived, with an estimated 40% of those declined being potentially suitable in retrospective analysis [2]. An ‘ideal’ donor has traditionally been considered as being less than 55, having a PaO 2/FiO 2 ratio > 300, having no smoking history , clear chest imaging and bronchoscopy and retrieved in the context of minimal ischaemic time [3]. Many potential donors do not fit these criteria or have demonstrated lung injury. Injury is common during the peri-mortem period and includes trauma, aspiration, infection, neurogenic oedema and barotrauma. However, lungs falling outside ‘ideal’ criteria restrictions may not necessarily be contraindicated for donation and injury may be reversible or inconsequential. Such organs are considered ‘marginal’ and expanded donor selection criteria have been implemented to encourage their use where appropriate. Whilst this initiative has been associated with increased primary graft dysfunction (PGD) and higher 30-day mortality, there seems to be no effect on survival found beyond this timeframe and this has profoundly expanded the pool of potential donors [4].

At present, most retrieved lungs are transported using static cold storage (SCS), which although remains an effective preservation tool, provides limited scope for in-depth assessment prior to implantation. Ex vivo lung perfusion (EVLP) is an organ preservation technique which provides a unique opportunity to thoroughly assess donor lungs in conditions aimed at imitating normal physiology, which may allow for the safe utilisation of more lungs for transplant, especially those considered to be ‘marginal’. EVLP may be particularly useful in the setting of lung donation after circulatory death and may increase clinician confidence in utilising organs from this pool in

particular by providing more detailed objective assessments [5]. Even further potential for EVLP lies in its scope as a platform for lung recovery via the administration of therapeutics to metabolically active and responsive cells, limiting or even reversing pre-existing lung injuries or those inherent to retrieval, fostering a lung environment best aligned with excellent outcome post-transplantation. This review first outlines the development of EVLP, its role as a lung assessment tool and the current evidence surrounding its use. It then focuses on its great potential as a therapeutic platform in the future.

2. Clinical Outcomes Associated with EVLP Use

Establishing at a minimum non-inferior safety of EVLP compared with SCS has been the first step to promulgating its use. Several systematic reviews and meta-analyses have collated the clinical efficacy results from EVLP trials reporting short-, mid- and long-term outcomes and adverse events. One such collation of 15 studies comparing 586 recipients of EVLP treated lungs with 1985 standard protocol lung transplant recipients reported comparable short-term outcomes with no statistically significant difference in 30-day survival (RR 1.69, 0.93–2.30 with 95% CI, p = 0.541), which was also true at 90 days and 1 year [6]. Interestingly, this study found a reduction in grade III PGD in EVLP treated lungs compared to standard protocol (RR 1.70, 0.64–4.53 with 95% CI, p = 0.003). The EXPAND trial which assessed clinical outcomes of EVLP treated extended criteria lungs showed 44% had grade III PGD at 72 h but despite this 99% went on to survive at 30 days [7]. Notably, this trial had a lung utilisation rate of 87%, far surpassing the utilisation rate found in current clinical practice. Other short-term outcomes explored by the aforementioned meta-analysis included no statistically significant difference in post-operative use of extracorporeal membrane oxygenation (ECMO), time to extubation, PaO2/FiO2 ratio, peak pulmonary function or hospital stay although there was higher intra-operative ECMO use and longer stays in intensive care units in the EVLP group [6]. With respect to longer term outcomes, a meta-analysis collating 13 trials comparing 407 recipients of EVLP treated lungs with 1765 standard protocol lung transplant recipients reported no statistically significant difference in mid- to long-term survival (HR 1.00, 95% CI 0.79 to 1.27, p = 0.981). Survival at 12, 24 and 36 months was 84%, 79% and 74% in the EVLP cohort and 85%, 79% and 73%, respectively, in the standard protocol group [8]. Importantly, a retrospective cohort study of 230 EVLP treated lung recipients with 706 standard protocol recipients showed no statistically significant difference in time to chronic lung allograft dysfunction (CLAD) (70% compared with 72% at 3 years; 56% compared with 56% at 5 years; and 53% compared with 36% at 9 years; log-rank p = 0.68) [9]. There is also no difference in measures of long term graft function including FEV 1 and 6 min walk test, in incidence of acute rejection episodes or in quality of life [10]. CLAD represents an Achille's heel to long term morbidity and mortality in lung transplantation and is a significant burden in both groups. It is possible that peri-operative events may establish a graft's steady march towards CLAD which EVLP-based interventions may provide an opportunity to ameliorate.

3. The Future Potential for EVLP

EVLP offers logistical advantages through the extension of preservation time without extending cold ischaemic time, meaning operations might be performed in normal working hours and transplantation surgeries can be

performed in series rather than parallel, the latter of which is only possible in select centres. Notably, one retrospective study noted there was no difference found in early outcomes comparing grafts with a preservation time > 12 h facilitated by EVLP with a group receiving grafts with a preservation time of <12 h [11].

Beyond transplantation, several innovation areas for EVLP have been suggested. First, EVLP provides an excellent and translatable platform for thoracic oncology drug trials [12]. EVLP could be coupled with autotransplantation for the administration of intolerably toxic chemotherapies [12] and antimicrobials [13] in the setting of otherwise incurable malignancies or multi-resistant lung infections. Finally, an area of great future potential lies in bioengineering of lungs, involving decellularization, seeding of the remaining tissue scaffold with multipotent progenitor cells of recipient origin and subsequent recellularization to produce a chimeric organ aimed at circumventing the issue of rejection. EVLP has already been shown to be an effective tool for decellularization and recellularization [14] and may provide a platform for assessment and safe use of bioengineered lungs in the future when this field progresses.

4. Conclusions

The potential for EVLP in clinical medicine and research is vast. In human lung transplantation it has been shown as a safe and effective tool for detailed lung assessment which can lift our lung utilisation rates from their current despairingly low levels. EVLP also provides a platform for the introduction of myriad therapies which may provide solutions to many of the issues encountered by patients who undergo lung transplantation and the clinicians who care for them.

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