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INVITED COMMENTARY

Increasing pre-transplant confidence and safety for use of questionable donor lungs with *ex-situ* assessment and reconditioning

Dirk Van Raemdonck[1,2] & Arne Neyrinck[3,4]

1 Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium
2 Department of Chronic Diseases, Metabolism and Ageing, KU Leuven University, Leuven, Belgium
3 Department of Anaesthesiology, University Hospitals Leuven, Leuven, Belgium
4 Department of Cardiovascular Sciences, KU Leuven University, Leuven, Belgium

Correspondence
Prof. Dr. Dirk Van Raemdonck MD, PhD, Department of Thoracic Surgery, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.
Tel.: ++32 16 34 68 23;
fax: ++32 16 34 68 24;
e-mail:
dirk.vanraemdonck@uzleuven.be

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Since its successful kick-off in the early eighties, lung transplantation has evolved as a life-saving treatment for selected patients with end-stage lung disease [1]. As for all types of solid organ transplantation, the practice of lung transplantation is limited by the number of available donors and their percentage of good quality pulmonary grafts [2]. Strict donor criteria as set by experts in the early days of lung transplantation were not derived from high quality scientific studies [3]. Many good, but not perfect donor lungs in that era may not have been used because of the fear, not to function immediately to support the breathing and thus the life of the recipient. Over the years, it became clear that many of the individual donor criteria like young age, absence of smoking history, excellent oxygenation, clear chest X-ray and negative bronchoscopic findings were not evidence-based and could be further relaxed with equally good recipient outcome after lung transplantation [4,5]. In addition, donor information provided by the organ allocation organization does not always match with the real clinical situation when donor lungs are assessed *in situ* by the retrieval team. Continuation of donor management, bronchoscopic suctioning of airway secretions and full recruitment of both donor lungs in the chest might dramatically improve lung function and change their status to 'acceptable'. The most important lesson, therefore, is to travel to the donor hospital whenever possible to verify

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the quality of donor lungs in the chest [6]. Another strategy could be to retrieve donor lungs for further evaluation *ex situ* and resuscitation over time using normothermic perfusion prior to accepting these pulmonary allografts for transplantation. In a retrospective donor database analysis from our center, we estimated that about 20% of declined donor lungs could potentially become transplantable with this technique [7].

In the article by Schiavon *et al.* [8] from the University of Padua, Italy, in this issue of the journal, the authors reported on their initial experience with *ex-situ* lung perfusion to assess and recondition extended criteria donor lungs using the portable platform Organ Care System (OCS™ Lung, Transmedics, Andover, MA, USA). The safety and efficacy of this device for standard lung preservation was recently demonstrated in a randomized trial (Inspire) comparing standard cold storage (SCS) versus normothermic portable machine perfusion. Importantly, the incidence of PGD grade 3 within 72 h after transplantation was significantly lower ($P = 0.015$) in the OCS group compared to the SCS group [9]. In this study from Padua, from January 2014 to October 2016, out of 86 lungs that were evaluated on site in the donor hospital, eight were identified as potentially treatable with this technique. Physiological parameters of these donor lungs improved during normothermic perfusion, in particular oxygenation with an increase in PaO_2/FiO_2 ratio from 340 mmHg in donor to 537 mmHg on OCS™ Lung, leading to successful lung transplantation in all cases. The authors of this single institutional study have followed the same donor lung inclusion criteria used in a larger international, multicenter study evaluating the Safety and Effectiveness of The Portable Organ Care System (OCS™) Lung For Recruiting, Preserving and Assessing Expanded Criteria Donor Lungs for Transplantation (Expand trial): (i) donor PaO2/FiO2 ≤ 300 mmHg; or (ii) expected ischemic time >6 h; or (iii) donor after circulatory death (DCD donor); or (iv) donor age ≥55 years [10]. In addition, the investigators in Padua included donor lungs (3 out of 8 in total) with presumed reversible pulmonary edema. The findings of the Expand trial have already been presented at the 2018 annual meeting and scientific sessions of the International Society for Heart and Lung Transplantation [11]. The publication of the final analysis, however, is still awaited. The Expand study found promising results with 87% utilization rate of OCS assessed donor lungs similar to the reported 86% in the HELP trial in Canada [12–14], but much higher when compared to the lung yield in other trials investigating the value of *ex-situ* lung perfusion to assess and recruit extended criteria lungs: 54% in the Novel trial in the USA [15,16] and 34% in the DEVELOP trial in the UK [17,18].

Multi-organ retrieval is often a very hectic procedure with many teams involved not leaving much time to properly assess donor organs in the body, especially when the donor becomes unstable or when the retrieval team arrives too late in the donor operating room. Compared to *in-situ* assessment of donor lungs, *ex-situ* evaluation during portable normothermic perfusion can be done in a more relaxed way during transport or after arrival in the donor hospital. The decision to transplant the donor lungs can be made by the most experienced member of the team. Physiological parameters such as pulmonary vascular resistance, airway pressure, compliance, and oxygenation can be observed over time to evaluate the performance of the functioning pulmonary allograft. Additional evaluation with X-ray can be helpful [19]. *Ex-situ* bronchoscopy permits to evaluate the amount and nature of airway secretions and to take samples for further microbiological and immunological testing. In addition, machine perfusion helps with the logistics of the transplant procedure as lungs can be safely preserved on the device for a longer period while the recipient is being prepared [20]. In addition to an optimized and in-depth evaluation setting for extended donors, other biological mechanisms might explain the high reported acceptance rate of these organs. Indeed, activation of intrinsic repair mechanisms during a metabolic active (normothermic) interval might help to restore the alveolo-capillary membrane, ventilation, perfusion and finally gas exchange.

Several teams have reported good posttransplant outcome with standard cold preservation for extended criteria lungs from older donors [21], from DCDs [22], and after long cold ischemic intervals [23]. Further experience with *ex-situ* machine assessment and preservation is needed to demonstrate its true benefit in increasing organ availability and in improving early and late recipient outcome [24]. Future will tell whether the additional costs of this technique outweigh the benefit for both the patient and the transplant community.

Conflicts of interest

Dirk Van Raemdonck was a principal investigator for both the Inspire and Expand trials sponsored by Transmedics Inc, Andover, MA, USA. He received reimbursement of travel expenses to attend advisory board meetings.

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