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INVITED COMMENTARY

Measuring physiological shunt fraction during normothermic *ex-vivo* lung perfusion to assess transplantability of questionable donor lungs

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Lung transplantation as a live-saving treatment for selected patients with end-stage lung disease still suffers from a shortage of suitable lung donors [1]. The process of accepting donor lungs is often based on a subjective decision following a short-term macroscopic evaluation of the pulmonary graft by bronchoscopy, palpation, and inspection inside the donors' chest at the time of multi-organ retrieval [2]. P/F ratio defined as partial pressure of oxygen measured in a systemic artery (PaO_2)/fraction of inspired oxygen (FiO_2) is the historic clinical gold standard to assess gas exchange of donor lungs *in vivo* as an estimate of post-transplant pulmonary function. A value for PaO_2/FiO_2 (P/F) of >300 mmHg or >40 kPa is widely used as the cut-off for acceptance [3]. However, P/F may turn out to be falsely low in donors whose lungs are hypo-ventilated and not well-recruited because of a high body mass index, atelectasis from retained airway secretions, or acquired lung injury when ventilated in the intensive care unit for several days. Differential pulmonary vein gas sampling after bronchoscopic suctioning and maximum ventilatory recruitment of lung parenchyma with the chest open may help to better evaluate the real oxygenation capacity of the pulmonary allograft prior to procurement [4,5]. Moreover, P/F ratio's may be largely influenced by multiple factors including FiO_2, peak inspiratory pressure (PIP), positive end-expiratory pressure, ventilator mode and pulmonary blood flow.

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Normothermic ex-vivo lung perfusion (EVLP) has become a reliable and powerful tool that is increasingly adopted to re-evaluate and recondition questionable donor lungs prior to transplantation [6–8]. Beside the trends in pulmonary vascular resistance (PVR) and dynamic lung compliance (Cdyn), the change in *ex vivo* P/F ratio during EVLP is considered a major physiologic parameter to determine lung graft transplantability [9–11]. However, P/F ratio is not the most sensitive parameter to reflect presence of lung oedema when compared with Cdyn and PIP showing earlier deterioration during EVLP [12,13]. Another parameter of oxygenation capacity frequently analysed during EVLP is delta (Δ) PO_2 measuring the difference in PO_2 between the inflowing (deoxygenated) and outflowing (oxygenated) perfusate. A ΔPO_2 of at least 350 mmHg between the left atrium and pulmonary artery is generaly considered an acceptable value for donor lung acceptance [12].

In the article by Niikawa *et al.* [14] from the Cleveland Clinic, Cleveland, OH, USA, in this issue of the journal, a new parameter, named P/F difference (PFD) was introduced as an estimator of physiologic shunt fraction and a reliable tool to predict transplantability of questionable donor lungs. The same authors previously reported that P/F varies with different levels of FiO_2. In a porcine model they found that, when P/F at FiO_2 0.21 ($P/F_{0.21}$) was lower than P/F at FiO_2 1.0 ($P/F_{1.0}$), this correlated with higher pulmonary compliance and lower shunt fraction when compared with $P/F_{0.21}$ being higher than $P/F_{1.0}$ [15]. In the present EVLP study with rejected human and porcine donor lungs, the most prominent finding using ROC curve analysis was that $PFD_{1.0–0.4}$ showed the highest sensitivity to identify suitable lungs for transplantation based on current standard criteria (PVR, Cdyn) in cellular EVLP. In addition $PFD_{1.0–0.4}$ on regression analysis showed a significant correlation with lung weight ratio as a surrogate marker of lung oedema at 2 h of EVLP. $PFD_{1.0–0.4}$ also correlated with pathological findings and inflammatory cytokines in lung tissue. Finally, $PFD_{1.0–0.4}$ showed potential as a valid parameter for assessment of each lobe in a donor lung with regional differences related to parenchymal abnormalities. PFD measurement from pulmonary vein gas analysis, therefore, can help to select suitable lobes for lobar transplantation from taller donors into smaller sized recipients or to select a single lung for a patient with emphysema of pulmonary fibrosis listed for unilateral transplantation. The real value of $PFD_{1.0–0.4}$ as a new additional predictor of pulmonary function during cellular EVLP, however, still needs validation in a transplantation model.

A sound understanding of the underlying physiology is critical to rely on appropriate parameters to assess transplantability of donor lungs with EVLP. When measuring gas exchange several phenomena may play a role such as shunting, ventilation/perfusion mismatch, perfusion flow and hypoxic vasoconstriction. As discussed in the paper, the main causes of physiological shunt are atelectasis and alveolar filling resulting from oedema, pneumonia, or aspiration. It is expected that macroscopic atelectatic areas in the lung can be recruited during EVLP, thereby decreasing shunt fraction and increasing PFD. In contrast, lungs with alveolar oedema showing a lower PFD with persistent shunting will need longer time to recover during EVLP. Lung weight ratio rather than ventilator mechanics such as PIP, plateau pressure and Cdyn demonstrated better correlation with PFD. Yeung and colleagues in a porcine lung injury EVLP model with acellular perfusate previously reported that PO_2 taken alone is not a reliable parameter in assessing the *ex vivo* lung [10]. Areas of shunt will affect PO_2 less during acellular perfusion. Evaluation of other physiologic parameters takes on greater importance. An important aspect of pulmonary physiology in relation to gas exchange is the impact and pattern of pulmonary flow. Lower flows (especially nonpulsatile) during EVLP might result in lower vascular recruitment and simply exclude perfusion of injured regions, thereby falsely increasing P/F ratios [16,17]. Our group recently demonstrated that also the impact of flow distribution during EVLP by prone positioning might affect physiological parameters and extravascular lung water content [18].

The team at the Cleveland Clinic should be congratulated with their study introducing the concept of measuring PFD during EVLP. Further studies assessing lungs with low *in vivo* PaO_2 at the time of organ recovery are needed to demonstrate the real benefit of *ex vivo* PFD as a new and reliable parameter to assess pulmonary graft viability during EVLP. This may help to further increase our donor lung acceptance rate with a higher level of confidence in the future.

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Conflict of interest

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