Commentary: INSPIRE results? A critical appraisal of study end points

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Central Message

Ex vivo lung perfusion was demonstrated to be safe in 2 randomized trials with standard criteria lungs; however, no clinically relevant benefits can be seen to justify its routine use in these donors.

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We read with great interest the article by Loo and colleagues¹ in this issue of the *Journal*, “Evaluation of the INSPIRE Trial and Its Implications for Lung Transplantation with Normothermic Portable Ex Vivo Lung Perfusion.” This expert opinion aimed to summarize results of the INSPIRE trial and discuss their implications for the clinical routine.²

The INSPIRE trial was a prospective, multicenter, randomized, controlled trial sponsored and designed by TransMedics, which aimed to compare preservation of standard donor lungs by the Organ Care System (OCS; TransMedics Inc, Andover, Mass) device to cold flush and static storage. The study reported comparable survivals, but with a lower incidence of primary graft dysfunction (PGD) within 72 hours in the OCS group, confirming results from a previously published randomized, controlled study by the Vienna group, which suggested the safety of ex vivo lung perfusion (EVLP) of standard lungs with a nonportable system.³ Both these trials, however, failed to show clinically relevant benefits to justify routine use of EVLP for lungs meeting standard criteria. In both studies, mechanical ventilation, intensive care unit stay, and hospital stay were similar between treatment and control arms, and short-term as well as long-term survivals were comparable. In fact, in the INSPIRE trial, 30-day survival was statically lower in the OCS arm (94.7%) than in the cold static preservation arm (100%); however, survivals at 1 year were exactly the same.

The results of the INSPIRE trial were controversially discussed in the community, mainly driven by weaknesses in the study protocol. A Food and Drug Administration executive summary published in May 2017 highlighted the most important confounders of the study.⁴ The main point of criticism was that the primary study end point had been changed during the study. Initially a composite primary end point of 30-day survival and PGD at 72 hours (t72) was defined. This was changed to 30-day survival and PGD within 72 hours (t0, t24, t48, or t72) at a time point

when 64% of the enrollment had already been completed. It is well described that only PGD grades at later time points (t48 and t72) correlate with survival. PGD grades at t0 hardly predict the further clinical course, and it is quite common that patients with mild bilateral infiltrations on arrival at the intensive care unit can be extubated within the next 2 days. In the INSPIRE trial, most of the differences in PGD were seen at t0 (21% in the OCS arm vs 13% in the cold static preservation arm). This difference nearly equaled out until t72 (5% in the OCS arm vs 3.9% in the cold static preservation arm).

In addition, chest x-ray evaluations and consequently PGD grades are highly susceptible to interobserver variability. We have previously shown that even trained thoracic radiologists only moderately agree in defining bilateral infiltrations in the modern era of lung transplantation, especially if radiographic changes are subtle.⁵ In case of a PO_2 less than 200 mm Hg, a chest x-ray diagnosis can make a difference between PGD grade 0 and PGD grade 3. We and others believe that alternative measurements—such as the ratio of PO_2 to inspired oxygen fraction, compliance, length of mechanical ventilation or best forced expiratory volume in 1 second—might be more useful as markers of lung quality and need to be provided in future studies evaluating the effects of organ preservation strategies on primary organ function.

The INSPIRE trial is an important study and represents one of the few prospective randomized trials in the field of lung transplantation. Although it did meet the intent of noninferiority, the results clearly demonstrate that similar clinical outcomes are achieved with current significantly “simpler” and “cheaper” cold static preservation.

In summary, cold static preservation continues to be the standard of care for preservation of donor lungs meeting standard criteria, whereas EVLP shows great promise for reevaluating and rehabilitating injured donor organs.⁶⁻⁸ We believe, however, that EVLP for *all* lungs may come into play when ex vivo therapies demonstrate efficacy in decreasing graft immunogenicity and thus improving short- and long-term outcomes of lung transplantation.^{9,10}

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