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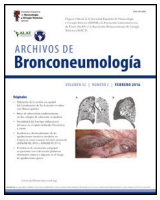

Editorial

Overcoming the Limits of Lung Transplantation: 10 °C Static Cold Preservation

One of the key factors of successful lung transplantation (LTx) is the optimal preservation of donor lungs during retrieval process and the 'out of body' storage period. There are numerous variables that play a critical role in preservation procedures. As suggested by various preclinical and clinical studies, optimal lung preservation entails the use of low-potassium dextran based solutions[1] developed especially for lung preservation; antegrade perfusion using 50–60 ml/kg of volume,[2] followed by retrograde perfusion[3,4]; lung grafts ventilated at 30–50% of their total lung capacity[5] and with a fraction of inspired oxygen (FiO2) of 50%[6]; use of prostaglandin E1[7]; storage of the lungs in an ice cooler at 4 °C; and, finally, a cold ischemia time (CIT) ideally no longer than 8 h due to the association with primary graft dysfunction (PGD) and an increase in early mortality after prolonged preservation times.[8] Great effort has been made to refine each of these parameters, resulting in the above recommendations. For instance, a pig model of extended CIT up to 12 h has been published describing the same inflammatory profile when compared to a 6 h of standard ice cold storage.[9] On the other hand, suboptimal preservation of the lungs during the retrieval process can lead to the decline of the organ. In addition, although CIT can usually be estimated before accepting the donor, some grafts may be rejected if CIT ends up being too long.

Yet, what if changes to the preservation strategy could push current limits of CIT? What if a simple measure such as optimizing storage temperature of donor lungs has the potential to change the current concept of lung preservation? The Toronto Lung Transplant Group (TLTG) recently published 2 key studies combining the outcomes of an animal model and its translation into a clinical setting.[10,11]

In the early years of LTx, several studies were published which evaluated the optimal storage temperature.[12–14] In fact, 10 °C was found to be the ideal temperature for preservation, however, it was not implemented in clinical practice for two reasons. Firstly, because of the lack of mechanistic data explaining why a temperature of 10 °C was better than storing a lung at 4 °C. Secondly, it was thought that a margin of safety was needed to ensure lung tissue viability and 10 °C stored lungs could easily warm up.

The Toronto study revisited the concept of optimal temperature in 2021 and delved into the mechanistic insights at the level of the mitochondria and its metabolism. The group compared performance of pig lungs in the ex vivo lung perfusion (EVLP) platform after 36 h of 4 °C versus 10 °C static cold storage. The functional evaluation showed favorable outcomes when the grafts were stored at 10 °C (less peak and plateau airway pressure, better dynamic and static compliance, better ratio of oxygen partial pressure to fraction of inspired oxygen (P/F ratio), and fewer changes in lung weight). Furthermore, mitochondrial metabolites showed a protective profile at 10 °C, with greater concentrations of itaconate, N-acetylglutamine and glutamate, all linked to a better response to ischemia reperfusion injury (IRI). The study could also show that that the function of Na+/K+ ATPase is critical in maintaining mitochondrial metabolism and cell healthiness during cold storage. This preclinical study paved the way for a proof-of-concept trial with the first five patients included in the publication. 10 °C as the target temperature for lung preservation was used to intentionally prolong CIT, allowing LTx procedure to become a semi-elective procedure. The median total preservation time for the first lung was around 10 h and for the second lung 12 h (in some cases even as long as 16 h). None of the patients developed PGD grade 3 at 72 h and all were discharged from hospital and alive at the time of publication. This study served as the basis for a multicenter clinical trial in which CIT was intentionally prolonged in order to avoid nighttime LTx (ClinicalTrials.gov identifier: NCT04616365). Seventy patients were included and compared to matched 1:2 controls. Although not yet published, the main results were communicated in the plenary session of the annual meeting of the AATS Meeting in 2022 (Boston, MA). A significantly longer total preservation times with comparable early postoperative outcomes was reported in the 10 °C study arm.

The role of 10 °C cold storage has already been subject to further exploration. In a porcine lung injury model using gastric fluid, lung grafts were randomly assigned to 12-h cold storage preservation at either 4 °C or 10 °C,[11] followed by left graft transplantation and functional and metabolomic evaluation within the following 4 h. Similar to previous studies, 10 °C preservation led to superior functional outcomes. Even more intriguing was the fact that 10 °C storage for 12 h lead to better outcomes compared to minimal CIT, highlighting that 10 °C may induce some reparative processes during preservation.

All above mentioned studies deepen our knowledge of the underlying mechanisms that can explain the effects of using a temperature of 10 °C in the preservation of lung grafts. Its full-scale clinical implementation, however, has the potential to become nothing less than a game changer. It could mean reducing geographical boundaries and enabling long-distance transportation of lung, which could lead to an improved organ sharing between distant regions. It could facilitate better immunological matching especially in pre-sensitized recipients. Storage of donor lungs at

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10 °C would also allow specific pre-surgical preparation for recipients, i.e. immunoadsorption, antagonization of OAKs/NOAKs, etc. It could mean accepting two or more donors at the same time and delaying one of the transplants in order to spread the workload of transplant teams. And it could mean being able to 'adjust' the start time of transplant operations, moving nighttime transplants to during the day or moving transplant surgery to the evening after scheduled elective cases have been finished. With regard to the latter, it has been reported that nighttime transplant surgeries may lead to either greater early mortality[15] and lower mid- and long-term survival rate.[16]

Meanwhile, another important step in this direction has been made. Ali et al. recently published an animal study in which a preservation strategy, combining a temperature of 10 °C for 3 cycles of 20 h plus 2 cycles of 4 h of normothermic EVLP, was tested.[17] This concept resulted in total preservation times of 3 days. Afterwards, the left lung was transplanted showing excellent functional results, and encouraging histological and metabolic data. Therefore, the combination of two preservation strategies may enhance the beneficial effects. However, further studies are needed to expand this idea, but the door of organ banking and ex vivo lung repair beyond several hours has been opened.

In summary, donor lung preservation methods are moving forward at a continuous and exciting pace, which will significantly change the entire field of lung transplantation. However, much effort is still needed to better understand the biological behavior of lung tissue during preservation. For now, the aforementioned studies suggest that the ideal temperature for static cold storage is 10 °C, allowing longer and safer lung preservation, overcoming little by little the limits of lung transplantation.

Conflict of Interests

The authors state that they have no conflict of interests.

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