Introducing the concept of semielective lung transplantation through the use of ex vivo lung perfusion

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Lung preservation times redefined with ex vivo lung perfusion.

Central Message

With the advent of normothermic ex vivo lung perfusion, donor lungs are routinely preserved for more than 12 hours. Preservation times of 12 to 24 hours were recently shown to be clinically safe.

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Lung transplantation (LTx) has enjoyed remarkable successes during the past decade, and this is reflected in the significant increase in the number of procedures year to year.¹ Since the inception of successful clinical LTx by Cooper and colleagues in Toronto in 1983, however, donor lung preservation techniques have not significantly changed, and the practical intention continues to be to minimize preservation time. Although experimental work has shown that donor lungs can be reliably preserved for at least 12 hours of cold static preservation,² the usual acceptable time frame in the clinical setting has largely been limited to less than 8 hours of cold preservation. This is well documented by a recent United Network for Organ Sharing database analysis, which showed a mean cold preservation time of 5 hours in the United States.³ Clinically, the impact of cold preservation time remains unclear. Some studies have reported a deleterious effect of cold static preservation, whereas others have shown no significant impact, especially in high-volume specialized centers.³⁻⁵ A recent study, however, has actually shown worse outcomes for pediatric LTx when donor organs were preserved for less than 4 hours.⁶ This variability in results can be explained in part by the lack of standardization of organ procurement and preservation. Donor lung preservation is not a trivial process and includes donor management in the intensive care unit, proper organ handling after the chest is opened, proper lung ventilation and recruitment, quality of the cold flush, selection of the preservation solution and additives, degree of lung inflation for storage after explantation, and proper organ storage for transportation.⁷ All these steps can make a significant difference in the maintenance of organ quality during the preservation period.

Although cold preservation has several advantages in protecting the organ during preservation by slowing down cellular metabolism, this method of preservation is limited in its ability to assess organ function or to deliver treatment to the injured donor organ. Normothermic (EVLP) in the

contemporary experience was reintroduced by Steen and colleagues⁸ for short-term donor lung assessment. In Toronto, we extended the concept of normothermic EVLP not only for organ assessment but also for maintenance, extended preservation, and treatment. We subsequently translated this to routine clinical practice.^{2,8,9} This practice has been increasingly applied worldwide, including in the United States, Austria, France, and various European countries.¹⁰⁻¹⁵

In a recent study, we reported on our experience with the routine use of donor lungs with greater than 12 hours of preservation when normothermic EVLP was added to the lung preservation phase, leading to excellent recipient outcomes.¹⁶ The clinical application of EVLP continues to grow. Its principal use to date has been to test “questionable” donor organs before LTx. With EVLP, although significantly longer preservation times were observed, rates of primary graft dysfunction remained low.^{16,17} It is important to recognize that when using EVLP, total lung preservation time is now the sum of 4 intervals (Figure 1 and Table 1): (1) cold ischemic time 1 (CIT1, the period of cold static preservation from crossclamp and cold flush in the donor to the start of normothermic EVLP); (2) normothermic EVLP time; (3) cold ischemic time 2 (CIT2), the period of cold static preservation after EVLP and before placement in the recipient’s chest; and (4) implantation time, the time from placement in the chest to reperfusion, also known as *warm ischemic time*.

In our study, we demonstrated that patients receiving lungs exposed to 12 to 24 hours of total lung preservation time had early and late outcomes similar to those of patients receiving lungs with the standard 6 to 8 hours of lung preservation time. Of note, clinical EVLP time was fixed

FIGURE 1. Redefining lung preservation time. Total preservation time = cold ischemic time 1 (CIT1) + normothermic ex vivo lung perfusion time (EVLP) + cold ischemic time 2 (CIT2) + implantation time (IT).

at 4 to 6 hours, and thus the bulk of the preservation time was due to prolonged CIT1 and CIT2. This period of normothermic preservation with increased metabolic function may serve to interrupt cold preservation injury and clear away accumulated metabolic debts.

We therefore posed the question as to whether EVLP might interrupt inflammatory and ischemic injury and “restart the clock” after CIT1. A large animal model was used to study this, confirming that after a long CIT1 (10 hours) and 6 hours of EVLP, lungs could tolerate a CIT2 as long as 10 hours, for a total preservation time of 26 hours, without any measurable deleterious effect to the graft after LTx.¹⁸ Another study has demonstrated that a period of 4 hours of CIT1 was actually beneficial to lungs from donors after cardiac death relative to direct normothermic perfusion after organ retrieval.¹⁹

Clearly, more data are required for transplant centers at large to generalize these findings and safely adopt this concept. As we continue to confirm these results in subsequent clinical trials, however, LTx could conceivably be transformed into a more elective procedure. This will have a major impact on the current practice of LTx. For example, LTx could be delayed until the daytime hours with obvious advantages for surgical, anesthesia and operating room staff performing under optimal conditions. In addition, an elective delay of LTx could be used to address donor- or recipient-related logistic challenges. Indeed, although exact data are not available, logistics often plays a major role in declining organs for transplantation. Additional advantages of safe prolongation of donor lung preservation could include opportunities for expanding the geographic reach for donors, improving donor-recipient

immunologic matching,²⁰ avoiding the need to rush during difficult lung explantation procedures, and allowing patients to live several hours away from the transplant center as to avoid the adverse financial and social consequences of relocation. In addition, because 30% to 50% of donors after cardiac death do not have arrest after withdrawal of life support therapy in a suitable time for organ donation,²¹ it has been our practice not to admit a potential recipient to the hospital until full assessment of the retrieved lungs from a donor after cardiac death has been performed, and we then use the EVLP period to call in and prepare the recipient.

It is also evident as we enter the exciting era of biologic engineering that this added preservation time will provide the opportunity to repair donor lungs and create immunologically preprepared lungs that will be tolerated better by the recipient for superior long-term survival in times to come. This truly heralds the era of opportunity to create “super organs” provided in a fashion in which health care systems will be equipped to be able to deliver transplantation in far more effective and efficient manner.

In summary, combining properly performed cold static preservation and normothermic EVLP can substantially prolong donor lung preservation times without adverse effects to recipients. We are entering an era in which semiselective LTx is a reality, with several important potential advantages to LTx recipients.

Conflict of Interest Statement

M.C. and S.K. are cofounders of Perfusix Canada and XOR Labs Toronto, are consultants for Lung Bioengineering, and receive research support from Xvivo Perfusion. J.C.Y. has nothing to disclose with regard to commercial support.

TABLE 1. Definition of preservation times

Preservation times	Definition
Cold ischemic time 1	From cold flush in donor to initiation of EVLP perfusion
EVLP time	From normothermic EVLP initiation until EVLP termination at 10°C
Cold ischemic time 2	From EVLP termination at 10°C to insertion of graft in the chest cavity
Warm ischemic time	From graft insertion in chest cavity to opening of pulmonary artery clamp

EVLP, Ex vivo lung perfusion.

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