Novel Technologies for Isolated Lung Perfusion
Beyond Lung Transplant

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KEYWORDS

• Lung perfusion • In vivo • Ex vivo • High-dose chemotherapy

KEY POINTS

- Strategies of isolated lung perfusion have been investigated for many years; however, significant progress has been made in recent years with lessons learned from lung transplantation and improvements in technology and lung perfusion solutions.
- EVLP has had a dramatic impact on clinical lung transplantation and a large body of research is being performed toward further technical optimizations and adjunct therapeutic strategies to repair donor organs.
- Advanced techniques of in vivo and ex vivo lung repair with gene and stem cell strategies using these perfusion technologies are now being investigated.

INTRODUCTION

Isolated lung perfusion (ILP) has been historically used as a method to study concepts of basic lung physiology using animal models. More recently, ILP has been further examined and developed in lung transplantation and thoracic oncology research. In lung transplantation, ILP has been used to assess physiologic integrity of donor lungs after removal from the donor. This procedure is called ex vivo lung perfusion (EVLP), and it has also been proposed as a method for active treatment and repair injured unsuitable donor organs ex vivo. Beyond lung transplantation, ILP has been primarily explored in thoracic oncology. ILP is attractive as a concept to potentially deliver high-dose chemotherapy to treat pulmonary metastatic disease. Because the lung vasculature is isolated in vivo, we refer to this technique as in vivo lung perfusion (IVLP). This article focuses on the rationale, technical aspects, and experimental and clinical experience of IVLP. A perspective on the future application of these techniques is described.

GENERAL CONCEPTS OF ISOLATED LUNG PERFUSION

Most of the knowledge in ILP has emerged from studies using organ perfusion ex vivo. EVLP simulates the in vivo scenario with ventilation and perfusion of the donor lung graft. In 1885, Max von Frey (1852–1932), while working at the Carl Ludwig Physiologic Institute in Leipzig, Germany, designed an apparatus that had criteria characteristic of a heart-lung machine. With this device, he perfused the entire lower extremity of dogs, and took measurements of oxygen consumption, and carbon dioxide and lactate production.[1] Originally proposed in 1938 by Carrel for organs in general[2] and then in 1970 by Jirsch and colleagues for the evaluation and preservation of lungs for distant

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procurement, attempts in those eras failed because of an inability to maintain the air-fluid barrier within the lung, leading to the development of edema and increased pulmonary vascular resistance in the donor lung during EVLP.[3] Driven by the objective to better evaluate lungs from donors after cardiocirculatory arrest, Steen and colleagues[4] in Lund, Sweden developed a modern ex vivo perfusion system with the intent of short-term evaluation of lung function of this population of lungs ex vivo. In doing so, they developed a buffered, extracellular solution with an optimal colloid osmotic pressure to act as the lung perfusate (Steen Solution, XVIVO Perfusion, Göteburg, Sweden). This solution helps hold fluid within the intravascular space during perfusion and provides some nutrients needed to maintain lung viability. The composition of Steen solution is a modification on the current clinically used preservation solution of low-potassium dextran glucose (Perfadex, XVIVO Perfusion) with human albumin as the major additional constituent. This protein is added primarily to maintain a higher oncotic pressure to reduce the development of pulmonary edema during perfusion. Steen and colleagues[4] used this solution mixed with red blood cells in combination with their circuit and were able to successfully perfuse and evaluate lungs in a large animal model for 1 hour without the development of pulmonary edema and subsequent successful transplantation. The ultimate goal of Steen's studies was to use EVLP as a method for short-term lung evaluation and thus the perfusion times were short. For the application of EVLP for extended preservation, improved evaluation, and the even loftier goals of lung recovery and repair, much more time is required.

We first described successful long-term (12 hour) EVLP using a lung-protective strategy for acellular normothermic perfusion and ventilation.[5] The strategies described next are relevant physiologic concepts for IVLP and EVLP. To achieve stable prolonged perfusion, several key lung protective strategies were used.[5] First, an acellular perfusate was used. Oxygen delivery to cells in the lung can occur via the airways (ventilator) and via the vasculature. This concept is also supported by previous studies where ventilation of a donor lung with room air at normothermia was demonstrated to preserve cell viability for many hours.[6,7] Acellular perfusion is logistically simpler for clinical use and also avoids the problem of limited lifespan of red blood cells in environment of the perfusion circuit.

Second, rather than subject the lungs to perfusion at 100% of cardiac output, maximal circuit flow was limited to 40%. This lower flow is protective in that it aids in the reduction of hydrostatic edema caused by perfusion and, despite lower flows to nondependent areas of the lung, histology and posttransplant function in EVLP lungs were shown to be normal. Third, we found that maintenance of a positive left atrial pressure of 3 to 5 mm Hg to be important for the success of long-term perfusion. This small, but positive left atrium (LA) pressure tents open the capillaries and postcapillary venules and prevents collapse of the microvessels from occurring during periods of increased in airway pressure and decreased flow that occur with alveolar distention during inspiration.[8] Absence of positive LA pressures can lead to unstable alveolar geometry and results in decreased lung compliance.[9]

Finally, we noted the importance of using a centrifugal pump. With ventilation, distention of the alveoli places pressure on the perialveolar vessels leading to cyclical increases in pulmonary vascular resistance with every breath. As a consequence of how a centrifugal pump functions, increased afterload to the pump results in decreased rotation and flow. Thus, the pump backs off during times of increased resistance rather than forcing fluid through, potentially causing injury or edema as a roller pump would do. During perfusion, oxygen is removed and carbon dioxide is added via a membrane oxygenator, essentially as a simulation of cellular metabolism. Removal of oxygen enables the measurement of lung function by taking the difference between postlung and prelung perfusate P_{O_2}. The addition of carbon dioxide helps maintain the homeostatic pH stability and acid-base balance of the perfusate. Carbon dioxide seems to be a contributor to endothelial protection during ILP. Using this strategy, reproducible, safe 12-hour normothermic ex vivo perfusion has been demonstrated in porcine and human lungs and this strategy of EVLP has been shown to interrupt ischemic injury related to prolonged static cold ischemia. This has been well validated in human lung transplantation.[5,10,11] The general components of a modern ILP circuit are shown in **Fig. 1**.

THE EVOLVING ROLE OF ISOLATED LUNG PERFUSION IN THORACIC ONCOLOGY

An attractive potential application of ILP is IVLP for the purpose of delivering high-dose chemotherapy or other anticancer agents to the lungs to treat cancer metastases without exposing the rest of the body to these agents and their associated side effects. The development of pulmonary metastases is a common occurrence in patients with advanced cancer. The most frequent