ELSEVIER

The Journal of
Heart and Lung
Transplantation

http://www.jhltonline.org

THEME: ADVANCED LUNG DISEASE

State of Art: Clinical ex vivo lung perfusion: Rationale, current status, and future directions

Pablo G. Sanchez, MD, PhD, Gregory J. Bittle, BSE, Lars Burdorf, MD, Richard N. Pierson, III, MD, and Bartley P. Griffith, MD

From the Division of Cardiac Surgery, University of Maryland School of Medicine, Baltimore, Maryland.

KEYWORDS:
isolated lung perfusion;
ex vivo lung perfusion;
lung mechanics;
lung metabolism;
lung transplantation

In recent years, ex vivo lung perfusion has emerged as an effective tool for increasing the number of available lungs accepted for transplant. As ex vivo lung perfusion use becomes more widespread, questions have arisen regarding the metabolic activity of the donor lung during ex vivo lung perfusion, optimal perfusion-ventilation strategy, and which parameters best define organ improvement or deterioration. Answers to many of these questions can be found in the published experience with the isolated perfused lung in the study of lung mechanics, pulmonary metabolism, and the effects of various interventions on lung quality. The purpose of this review is to summarize past and present evidence and to provide important background for clinicians and investigators using the ex vivo lung perfusion/isolated perfused lung system.

J Heart Lung Transplant 2012;31:339–48

Organ availability continues to be a major hurdle for lung transplantation. Although kidney and liver donors are relatively plentiful, only 15% to 25% of lungs from donors of at least one other organ are transplanted—the lowest graft acceptance rate of any solid organ.[1] Whether this rate of organ utilization and the associated acceptance standards are appropriate is unknown. A recent analysis found lungs classified as "marginal" based on an array of different criteria failed to identify any detrimental effect on clinical outcomes.[2]

The use of marginal lungs raises many difficult scientific, logistical, and ethical questions:

- What readily available, practical metrics, or innovative interventions can be applied to more accurately differentiate between "viable" grafts—lungs likely to perform as well as conventional criteria grafts—from those likely to fail?
- Which lungs can be better assessed by ex vivo perfusion after donation, and perhaps repaired by logical but as yet unproven interventions?

Ex vivo lung perfusion (EVLP) has been suggested as a novel method to differentiate between "good" and "bad" grafts in this sub-optimal population, because when these good grafts are transplanted, results are not different from standard criteria lungs.[3,4] But as the use of ex vivo evaluated lungs increases, new questions are emerging. Many of them have answers in the numerous reports that have used the isolated perfused lung (IPL) to study the diverse aspects of the physiology and pathology of the lung. In this review we will summarize the current knowledge regarding isolated lung perfusion, the state of the field of EVLP, and offer opinions and strategic options for going forward.

Fundamental components of IPL

Defining a perfusion-ventilation methodology

One of the most difficult tasks when establishing an IPL system is keeping it edema-free for extended periods of

Reprint requests: Bartley P. Griffith, MD, Thomas E. and Alice Marie Hales Distinguished Professor and Chief, Division of Cardiac Surgery, 22 S Greene St, Rm N4W96, Baltimore, MD 21201. Telephone: 410-328-3822. Fax: 410-706-0311.

E-mail address: bgriffith@smail.umaryland.edu

1053-2498/$ -see front matter
doi:10.1016/j.healun.2012.01.866

time. Some authors have proposed that isolated lung preparations are leaky per se,[5,6] but these observations seem to depend on the degree of vascular-alveolar recruitment, the length of perfusion, and the perfusate albumin concentration.[7]

An invariable finding across IPL literature is that a low flow, relative to normal cardiac output, more consistently provides an edema-free preparation. Fisher et al[8] reported that when rat lungs were perfused for 5 hours with high flows (25 ml/g lung/min; 100% pulmonary flow)[9] or low flows (12 ml/g lung/min), lungs in the low-flow group showed no signs of edema at the end of perfusion. Sasaki et al[10] demonstrated that this also occurs when using pulsatile flow, where flows of 0.1 ml/g animal weight/min led to 165 minutes perfusion and 0.03 ml/g animal weight/min afforded 4 hours. Recently, Cypel et al[11] reported extended perfusion times of 12 hours with low edema formation in a swine model of lung perfusion when using 40% of the animal cardiac output as the target flow.

It seems counterintuitive that ex vivo lungs perform better at lower flows than those encountered in vivo, but they do exhibit the expected increase in edema development with increasing pulmonary vascular pressure. Petak et al[12] when studying the effects of different left atrial pressures (P_{LA}), pulmonary artery pressures (P_{PA}), and flows (Q_{PA}) on the mechanical properties of the IPL in a rat model reported that changes in lung mechanics began when the pulmonary microvascular pressure rose above 20 mm Hg, and increases in lung weight were observed with pressures above 25 mm Hg. Another relevant finding was that significant perturbations of P_{LA}, either lower or higher than the normal range, led to alterations in lung mechanics. The maintenance of a physiologic P_{LA} (6 mm Hg) favors pulmonary vasculature recruitment, mitigating the development of ventilator induced lung injury during isolated perfusion compared with a low P_{LA} (1 mm Hg).[13] The deleterious effect of a low P_{LA} could be attributed to repetitive vascular collapse and an increased pulmonary vascular resistance (PVR) by compression of the microcirculation during ventilation.[14]

Gravity has an effect on the pulmonary hydrostatic pressures; therefore, one must consider these effects on the position of the lung during isolated perfusion.[15] Because most ex vivo systems work with lungs in the supine position, west zone 2 conditions on the upper region and zone 3 conditions on the lower region are favored. As a consequence, the lower region (dependent zone) will be under greater microvascular pressure, with higher capillary filtration coefficients that will lead to very different alveolocapillary micromechanics (Figure 1A-B).[16,17]

Variation in transpulmonary pressures further influence the microvascular environment, thereby rendering the selected ventilatory strategy of fundamental importance in maintaining a viable IPL/EVLP.[18] Fu et al[19] reported capillary failure with edema formation when transpulmonary pressures increased from 5 to 20 cm H_2O, and Parker et al[20] described an increase in the capillary filtration coefficient in a dose-dependent manner when peak airway pressures rose above 20 cm H_2O. Conversely, low alveolar pressures seem to favor clearance of the perialveolar liquid. Bhattacharya et al[21] reported that low alveolar pressures (7 vs 15–23 cm H_2O) are fundamental in maintaining perialveolar liquid clearance because ventilation acts as a pump to the lung interstitium, favoring lymph fluid transit from the peri-microvascular space to the larger lymphatics vessels[22] (Figure 1C).

In clinical EVPL, low volume ventilation (6–8 ml/kg) has been suggested as a protective strategy in maintaining lungs perfused ex vivo for extended periods of time because low airway pressures are required to achieve these tidal volumes.[11] Because this method requires periodical maneuvers to reclaim collapsed alveoli, a phenomenon manifested by a decrease in lung compliance over time, care should be taken when performing alveolar recruitments because they have been associated with the development of lung edema in IPL[23] by stress failure of the pulmonary capillaries.[19]

Perfusate composition

Perfusate composition is of central importance in maintaining a stable perfusion preparation. The ideal perfusate should have osmotic and oncotic pressures similar to normal blood and must also provide an energy source and an electrolyte milieu consistent with extracellular fluid[24] so that normal cellular processes might be preserved.[25] It is unclear, however, whether enhanced oxygen-carrying capacity, although a fundamental function of human blood, is of any value in the ex vivo system because of the large lung oxygen reserve.[26]

The effects of colloid concentration have been studied, with a particular focus on albumin. Chang et al[27] demonstrated that 5 g/dl albumin in the perfusate provided a significant degree of protection against edema formation under low and high capillary filtration coefficients (P_{LA} 0 vs 10 mm Hg). Experiments with low albumin concentrations (0.1 g/dl) were only stable when P_{LA} was 0 mm Hg, but failed under higher P_{LA}, demonstrating that perfusates with low albumin concentration render sub-optimal results unless a low capillary filtration coefficient is maintained by decreasing P_{LA}.[27] The addition of albumin to the perfusate seems to provide more than just an adequate oncotic-osmotic environment,[7] with positive effects attributed to albumin's carrier properties involved in delivering nutrients and removing toxins from the cells during perfusion.[28]

Some groups have emphasized the use of blood over acellular colloid-buffered perfusates,[29,30] whereas others have observed spontaneous lung injury when using whole blood (edema and hypertension).[31] These effects were mitigated when using leukopenic and thrombocytopenic homologous blood with impaired platelet thromboxane release.[32] Clinically, the addition of leukocyte-reduced blood to a colloid-buffered solution has been proposed to improve tissue oxygenation during EVLP,[33] although no studies have been published demonstrating the superiority of either perfusate strategy (blood + buffered solution, or buffered solution + colloid).