Ex vivo lung perfusion: Theme and variation

Jose P. Garcia, MD,^a and Keshava Rajagopal, MD, PhD^b

From the ^aDivision of Cardiac Surgery, Massachusetts General Hospital, Boston, Mass; and the ^bDepartment of Cardiovascular Surgery, Center for Advanced Heart Failure, Memorial Hermann Hospital/Texas Medical Center, Houston, Tex.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication June 18, 2015; accepted for publication June 23, 2015; available ahead of print July 28, 2015.

Address for reprints: Jose P. Garcia, MD, Division of Cardiac Surgery, Massachusetts General Hospital, 55 Fruit St, Cox Building 642, Boston, MA 02114 (E-mail: jgarcia@partners.org).

J Thorac Cardiovasc Surg 2016;151:576-7

0022-5223/\$36.00

Copyright © 2016 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2015.06.055>

Organ transplantation is challenged by an inadequate supply of donor organs to meet recipient needs. Several strategies have been developed and used to ameliorate the donor organ shortage, in the absence of durable artificial organ support or replacement, with varying degrees of success. Broadly, 4 strategies exist: (1) simply accept organs previously deemed unacceptable—redefining acceptability; (2) use tools to characterize organ acceptability more accurately and precisely—improving diagnostics for apparently marginal donor organs; (3) render unacceptable organs acceptable—therapeutic reconditioning; and (4) develop new sources for donor organs—xenografts and tissue-engineered organ constructs.

Organ perfusion systems are designed to perfuse allografts ex vivo under tightly controlled fluid dynamic conditions with specific choices of perfusates. With respect to lung transplantation, ex vivo lung perfusion (EVLP) with simultaneous controlled invasive mechanical ventilation permits rigorous allograft physiologic assessment. The goals of ex vivo organ perfusion, however, are not simply provision of improved diagnostics (strategy 2), but rather encompass rehabilitation of marginal donor organs (strategy 3). The pioneering work of Wierup and colleagues,¹ and subsequently the University of Toronto group,² has led to early enthusiasm for EVLP use for the purposes of lung reconditioning. Not only is it unclear whether EVLP as currently implemented provides a therapeutic benefit, however, but several core variables that comprise the “theme” of EVLP can influence allograft function—perfusate composition, fluid dynamic conditions, temperature, and mechanical ventilator settings. Moreover, adjunctive therapies provided during EVLP, such as pharmacologic or other therapies^{3,4} delivered either through the perfusion or ventilator circuits or “variations upon the theme,” may affect the possible therapeutic efficacy of EVLP.

In the current issue of the *Journal*, Nilsson and colleagues⁵ from Sahlgrenska Academy and Gothenburg University suggest potential benefits of hemofiltration during EVLP,

Jose P. Garcia, MD, and Keshava Rajagopal, MD, PhD

Central Message

Hemofiltration may be beneficial in ex vivo lung perfusion for lung reconditioning, and the results of this study should spur further investigation.

See Article page 570.

See Editorial page 315.

adding their variation on the central theme of EVLP. Nilsson and colleagues⁵ used a porcine model of high-pressure pulmonary edema produced by balloon-tipped catheter inflation in the left atrium. Lungs were then procured with relatively standard perfusion strategies and subjected to EVLP with or without hemofiltration. EVLP was conducted with a hemodiluted sanguineous perfusate, with pulmonary fluid flow titrated to achieve a mean pulmonary arterial pressure of 25 mm Hg, under nearly normothermic conditions, and with standard mechanical ventilation parameters. Antecedent pulmonary edema impaired lung mechanics and oxygenation as assessed during EVLP, as expected. Hemofiltration was associated with a relative improvement in lung mechanics but not oxygenation. Lung weight decreased, and perfusate oncotic pressure increased, in the setting of hemofiltration during EVLP.

Hemofiltration during EVLP is supported by sound physiological reasoning—the Le Chatelier principle and the Starling equation for transcapillary fluid flux both suggest that solvent (water) removal and concentration of the perfusate should cause edema fluid transport from the lung (both the alveolar and interstitial compartments) into the circuit. Improvements in edema during EVLP without hemofiltration have been described,⁶ and it seems reasonable that hemofiltration may result in even greater improvements. The current study, however, prompts several questions. First, the model used is

one of high-pressure pulmonary edema. Although this model can be tightly controlled, a more important and challenging model for marginal donor lungs is that of high-permeability pulmonary edema. Whereas high-pressure pulmonary edema is amenable to pharmacotherapy, high-permeability pulmonary edema is more difficult to manage; consequently, such lungs are generally deemed unsuitable for transplant.

Second, the model used produced deficits in oxygenation that were much more severe than those in lung compliance. The reasons for this are unclear, because animal studies⁷ and clinical experience suggest that interstitial edema precedes alveolar edema temporally and in severity. Also, the lack of improvement in oxygenation with hemofiltration may be due to the disproportionately impaired oxygenation induced in the model. Third, the outlet (left atrial) pressure can be controlled during EVLP. It is plausible that minimization of the outlet pressure would improve edema clearance; however, these data are not available. Fourth, particularly because cell membrane permeability is presumably relatively normal in the model system, it is possible that intentionally increasing the oncotic pressure of the perfusate by using a higher protein concentration would also improve edema clearance, lung compliance, and oxygenation.

Hemofiltration is one of many possibly beneficial EVLP adjuncts. This study of Nilsson and colleagues,⁵ demonstrating as it does promising initial results, should spur further investigation into the roles of hemofiltration and perfusate concentration in lung reconditioning during EVLP. More procedural and pharmacologic variations on the EVLP theme are expected in the future.

References

1. Wierup P, Haraldsson A, Nilsson F, Pierre L, Scherstén H, Silverborn M, et al. Ex vivo evaluation of nonacceptable donor lungs. *Ann Thorac Surg*. 2006;81:460-6.
2. Cypel M, Yeung JC, Hirayama S, Rubacha M, Fischer S, Anraku M, et al. Technique for prolonged normothermic ex vivo lung perfusion. *J Heart Lung Transplant*. 2008;27:1319-25.
3. Emaminia A, Lapar DJ, Zhao Y, Steidle JF, Harris DA, Laubach VE, et al. Adenosine A₂A agonist improves lung function during ex vivo lung perfusion. *Ann Thorac Surg*. 2011;92:1840-6.
4. Valenza F, Rosso L, Coppola S, Froio S, Colombo J, Dossi R, et al. β -adrenergic agonist infusion during extracorporeal lung perfusion: effects on glucose concentration in the perfusion fluid and lung function. *J Heart Lung Transplant*. 2012;31:524-30.
5. Nilsson T, Hansson C, Wallinder A, Malm C-J, Silverborn M, Ricksten S-E, Dellgren G. Hemofiltration in ex vivo lung perfusion—a study in experimentally induced pulmonary edema. *J Thorac Cardiovasc Surg*. 2016;151:570-5.
6. Cypel M, Rubacha M, Yeung J, Hirayama S, Torbicki K, Madonik M, et al. Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. *Am J Transplant*. 2009;9:2262-9.
7. Ware LB, Matthay MA. Clinical practice: acute pulmonary edema. *N Engl J Med*. 2005;353:2788-96.