“Ex” becomes “in”: A new direction for ex vivo lung perfusion?

John H. Dark, FRCS

From the Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Sept 19, 2017; accepted for publication Sept 22, 2017; available ahead of print Oct 28, 2017.

Address for reprints: John H. Dark, FRCS, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne NE2 4HH, United Kingdom (E-mail: john.dark@ncl.ac.uk).

J Thorac Cardiovasc Surg 2018;155:438-9
0022-5223/\$36.00

Copyright © 2017 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2017.09.101>

John H. Dark, FRCS

Central Message

Can the technology of ex vivo lung perfusion be applied to the in situ lung? There are potential lessons from management of lung donor injury for a much wider population.

See Article page 440.

As a successful clinical technology, ex vivo lung perfusion has been with us for more than a decade and a half.¹ A range of interventions, both clinical (eg, antibiotics reducing microbial load²) and experimental, have been shown to improve the donor lung. The latter range from simple molecular agents (β -2-adrenergic receptor and adenosine receptor antagonists), through added gases (notably hydrogen), even to mesenchymal stem cells to both repair injury and manipulate immune response.³ The technology is promising potent approaches to repair the donor lung way beyond the simply marginal.

We have a technique that can safely perfuse a lung for many hours, gives the opportunity for delivery of a number of agents, and potentially manipulate a range of pathways. Might this next extend to other areas of lung disease? In particular, can it be used beyond the setting in which the lungs are outside the body—ex-vivo—which is peculiar and almost specific to transplantation?

One obvious approach is to use ex vivo lung perfusion techniques for delivery of chemotherapeutic agents in primary or metastatic lung cancer. This is being explored by a number of teams.⁴

Another potential, and exciting application is for the treatment of adult respiratory distress syndrome, detailed in a potentially landmark article from Mehaffey and colleagues⁵ in this issue of the *Journal*. The experiments were technically complex but conceptually simple. A standard lipopolysaccharide-induced lung injury resulted in a predicted severe hypoxia and poor compliance in pigs. All animals were then placed on central extracorporeal membrane oxygenation (ECMO) support through the open chest. The left lung was additionally cannulated such that it could be perfused entirely independently of the systemic circulation. This continued for 4 hours, then both lungs were reperfused. The left lungs had less edema, lower expression of pro-inflammatory markers, and better oxygenation than the right lungs when the animals (6 of 8) were weaned from ECMO.

These studies were necessarily initial and exploratory and are open to a number of criticisms. Most importantly,

there was no true control group—no animals received the insult alone, and none had ECMO alone. And although Mehaffey and colleagues⁵ would point out that the animals served as their own controls, the right and left lungs had very different treatment. A stretch of imagination is required to believe that improved compliance, necessarily of both lungs, between the beginning and end of the ECMO run is a true indicator of less injury in the left lung. It is also difficult to see how “oxygenation,” the difference in pulmonary artery and pulmonary vein partial pressures, can be assessed when one lung is effectively bypassed with central ECMO and the other is perfused at only 20% of predicted cardiac output.

The overall concept, however, that of isolated treatment of the injured lung within the body, is sound. When techniques for ECMO have become routine, safe, and widely practiced, the additional intervention is very attractive. As a timely review article⁶ describes, there have been no real advances in the treatment of adult respiratory distress syndrome since the introduction of lung protective ventilation. A range of therapies have been well tested, in good trials, and found wanting. This new innovation, driven by surgeons with a deep understanding of both the technologies available and the biology of lung injury, is very exciting. The next, key step is to see whether this can be achieved for both lungs, and percutaneously!

References

1. Steen S, Sjöberg T, Pierre L, Liao Q, Eriksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. *Lancet*. 2001;357:825-9.
2. Andreasson A, Karamanou DM, Perry JD, Perry A, Özalp F, Butt T, et al. The effect of ex vivo lung perfusion on microbial load in human donor lungs. *J Heart Lung Transplant*. 2014;33:910-6.
3. Van Raemdonck D, Neyrinck A, Rega F, Devos T, Pirenne J. Machine perfusion in organ transplantation: a tool for ex-vivo graft conditioning with mesenchymal stem cells? *Curr Opin Organ Transplant*. 2013;18:24-33.
4. dos Santos PR, Iskender I, Machuca T, Hwang D, dePerrot M, Liu M, et al. Modified in vivo lung perfusion allows for prolonged perfusion without acute lung injury. *J Thorac Cardiovasc Surg*. 2014;147:774-81; discussion 781-2.
5. Mehaffey JH, Charles EJ, Schubert S, Salmon M, Sharma AK, Money D, et al. In vivo lung perfusion rehabilitates sepsis-induced lung injury. *J Thorac Cardiovasc Surg*. 2018;155:440-8.
6. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *N Engl J Med*. 2017;377:562-72.