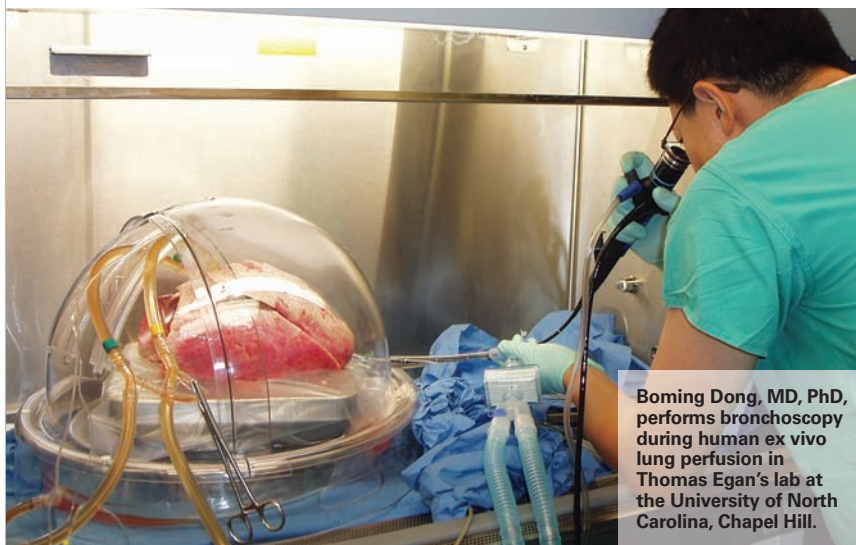


The AJT Report

News and issues that affect organ and tissue transplantation



Boming Dong, MD, PhD, performs bronchoscopy during human ex vivo lung perfusion in Thomas Egan's lab at the University of North Carolina, Chapel Hill.

Are Personalized Organs in Our Future?

Ex vivo lung perfusion may lead the way toward personalized organ repair

To date, the field of transplantation has focused on organ preservation via cold storage. Now, with experimental trials in the U.S. and approved usage in Canada, Europe and other world communities, ex vivo warm lung perfusion offers not only an opportunity for organ evaluation, but also the potential for personalized organ repair in lungs not otherwise suitable for transplantation. “These concepts might be applicable not only to lung transplantation but to all other organs,” says Thomas Egan, MD, a cardiothoracic surgeon at the University of North Carolina in Chapel Hill. “The future is very close.”

However, not all lungs are viable. “Currently, only about 17% of lungs in the U.S. are usable,” says R. Duane Davis, MD, director of transplantation for cardiothoracic surgery at Duke University in Durham, N.C. “That really should be closer to 50% to 60%. Right now there are 125,000 deaths from lung failure in the U.S., and 1,700 lung transplants. That’s a pretty wide gap. Ex vivo lung perfusion is potentially a way of solving this problem.”

Ex vivo lung perfusion has been shown in both animal and human models to allow donor lung evaluation in a nonhostile environment, outside the body and away from the inflammatory effects of brain death and/or problems associated with withdrawal of mechanical support. Additionally, researchers are investigating gene therapy and pharmaceutical interventions during ex vivo lung perfusion to improve the organ prior to transplantation.

Early Days

The first surgeon to successfully utilize human ex vivo perfusion for lung evaluation and modification was Stig Steen, MD, professor of cardiothoracic surgery at Lund University in Sweden.¹⁻³ As of December, his team had done eight transplants after ex vivo lung perfusion. His results have made him a firm believer that ex vivo perfusion offers a non-hostile environment for evaluation and lung reconditioning. “Gene therapy and different types of immunological modification of the donor lung are possibilities,” he says, adding that there could be treatment with surfactants or for issues such as hospital microorganisms resistant to high doses of chemotherapeutic drugs.

Dr. Steen is currently working on an ex vivo lung machine with pulsatile flow and iron-lung ventilation, which he says is a more physiological ventilation than intermittent positive pressure ventilation. In the near future, lungs may be treated ex vivo for days if needed. Then, due to the large number of noncontrolled organs donated after cardiac death, there will be no shortage of quality-tested donor lungs, he adds.

With more than 30 human lung transplants after extended ex vivo lung perfusion at body temperature, Shaf Keshavjee, MD, director of the Toronto Lung Transplant Program at the University of Toronto, Ontario, Canada, has done more post-ex vivo perfusion lung transplants than anyone else in the world.³⁻⁵ He’s taught his methods to teams from the U.S., Austria, Madrid, Germany and the U.K. While several of his European counterparts are performing transplants, surgeons in the U.S. are waiting for a Food and Drug Administration (FDA) investigational device exemption to move forward.

KEY POINTS

- Ex vivo warm lung perfusion offers an opportunity for organ evaluation and the potential for personalized organ repair.
- One goal of ex vivo lung perfusion is the ability to apply it to donation after cardiac death.

Dr. Keshavjee is currently working with gene therapy to repair injured lungs.⁵ Using an adenoviral vector encoding human interleukin-10 (IL-10), the team demonstrated a technique to use gene therapy to repair injured human donor lungs ex vivo before transplantation.⁵ In an editorial in the same issue of *Science Translational Medicine*, David S. Wilkes, MD, noted that the Keshavjee therapy resulted in “significant improvements in oxygenation and

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vascular resistance, diminished amounts of IL-1 β and IL-8, and evidence of recovered alveolar epithelial cell integrity 12 hours after initiation of the treatment.”⁶

The Keshavjee team is currently fine-tuning their gene therapy in the ex vivo circuit to avoid an inflammatory response to the vectors.

Global Technology

The new technologies in the field of ex vivo perfusion may give rise to a need for specialized solutions that differ from existing solutions, leading to opportunities for discovery. One company involved in the research is XVIVO Perfusion which, according to company product specialist Mary S. Pohl, holds approximately 90% of the world market for its product, Perfadex, which is used for the flushing of donor lungs prior to transplantation. To date, more than 60 ex vivo lung perfusions using products from the company have been performed globally. Additionally, the company distributes Steen Solution, which is used for normothermic evaluation and reconditioning of lungs outside the body and is approved for clinical use in Europe and Australia, but is not yet approved in Canada or the U.S.

More than 30 ex vivo lung evaluations have been performed by Toronto General Hospital, while Sweden, Spain, Austria and England combined have performed another 30-plus lung transplants using the XVIVO Perfusion products. Pohl says a multicenter clinical trial will start this year pending approval by the FDA for an investigational device exemption.

From Recent Cardiac Death to Successful Lung Transplant

Dr. Egan says his ultimate goal with ex vivo lung perfusion is to apply it to donation after cardiac death, “where you don’t have two or three days in the ICU on a ventilator with blood gases and serial chest x-rays to determine if those lungs are suitable for transplant.” He was awarded a \$1.47 million National Institutes of Health grant to perfuse lungs considered unusable and study their suitability for transplant. “What we’ve learned is that you can take lungs with pneumonia or a lot of pus in the airway, or lungs you wouldn’t normally transplant, perfuse them ex vivo and get pretty good gas exchange data,” he notes.

Dr. Egan has formed a for-profit company that will use his recent findings that blocking the innate immune system (the Toll 4 receptor, in particular) will prevent ischemia reperfusion injury. He plans to use this method in an ex vivo circuit to test the prevention of reperfusion injury before transplantation. However, he thinks the much larger opportunity is to go after the recently deceased, cardiac-death donor, noting that brain death is often accompanied by upregulated inflammation and neurogenic pulmonary edema.

From a death outside the hospital, Dr. Egan believes doctors can obtain “fantastic” lungs to transplant. “But one of the issues

is addressing the role of emergency medical services, like Dr. Andres Varela has in Madrid,” he adds. In a 2007 paper, Dr. Varela and his team described his relationship with local advanced life-support units that agreed to start resuscitation within 15 minutes after receiving a call.⁷ Their efforts continue during transportation to the emergency department, where intensive care unit personnel certify death, and a request for organ donation is made. “With the ability to treat lungs in an ex vivo circuit, I think we can revolutionize lung transplantation,” says Dr. Egan.

Dr. Keshavjee agrees. “It’s a huge paradigm shift for transplantation,” he says. As the future unfolds, he predicts that while the lung is still in the donor, “we’ll take a biopsy so we can run it through our molecular diagnostics tests and know what’s wrong. Then, when we put it on the ex vivo circuit and bring it up to temperature, we can provide a specific, targeted treatment to fix it.”

References

1. Steen S, Sjoberg T, Pierre L, Liao Q, Ericksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. *Lancet* 2001; 357: 825-829.
2. Steen S, Ingemansson R, Ericksson L, et al. First human transplantation of a nonacceptable donor lung after reconditioning ex vivo. *Ann Thorac Surg* 2007; 83: 2194-2195.

Ex Vivo in Abdominal Organs

Several research groups are using animal models to investigate the potential of warm/normothermic perfusion in abdominal organs. Among these is James V. Guarrera, MD, surgical director of adult liver transplantation at Columbia University in New York. “I believe [that in] the future, ex vivo warm perfusion will be used in a clinical setting,” he says. “I think it will be a platform for dynamic interventions including gene therapy to ameliorate ischemia/reperfusion injury post transplant by reversing ischemic injuries and steatotic pathophysiology. In addition, warm perfusion may allow gene therapy for immunomodulation or to confer resistance to viral recurrence, which is an enormous problem for hepatitis C patients undergoing liver transplant.”

His team has performed ex vivo warm perfusion in discarded human livers and is currently working on molecular therapies for intervention in liver allografts to confer protection against ischemia/reperfusion injury, as well as viral resistance to hepatitis C recurrence.

3. Ingemansson R, Eyjolfsson A, Mared L, et al. Clinical transplantation of initially rejected donor lungs after reconditioning ex vivo. *Ann Thorac Surg* 2009; 87: 255-260.
4. Cypel M, Rubacha M, Yeung J, et al. Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. *Am J Transplant* 2009; 9: 2262-2269.
5. Cypel M, Liu M, Rubacha M, et al. Functional repair of human donor lungs by IL-10 gene therapy. *Sci Transl Med* 2009; 1: 4ra9.
6. Wilkes DS. A breath of fresh air for lung transplant recipients. *Sci Transl Med* 2009; 1: 4ps5.
7. de Antonio DG, Marcos R, Laporta R, et al. Results of clinical lung transplant from uncontrolled non-heart-beating donors. *J Heart Lung Transplant* 2007; 26: 529-534.

States Receive Medals for Donation

Donate Life America has presented its first awards to state teams in recognition of their achievements as part of the Donor Designation Collaborative, a national initiative to reach a 50% donor designation rate and 100 million designated donors. States receiving medals reached the top tier in at least three of five key categories: a 50% or greater donor designation rate; 50% or more of all state

residents age 18 and older registered as donors; and at least 40% of organ, eye and tissue donors authorized through state donor registries. Gold medals recognize achievement in five areas, silver in four and bronze in three for July 2009 through June 2010.

Gold medals went to Colorado, Louisiana, Ohio, Utah, Washington and Wyoming. Silver was awarded to Alaska,

Idaho, Illinois, Minnesota, North Carolina, Oregon and Virginia. Bronze went to Delaware, Georgia, Maryland, Missouri, Montana, North Dakota, Oklahoma, Pennsylvania and West Virginia. A third annual National Donor Designation Report Card prepared by Donate Life America shows that 86.3 million people were enrolled in state donor registries at the end of 2009. This represents an increase of 24.4% since 2007. **AJT**