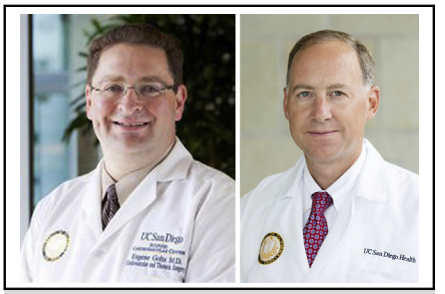
References

1. Cypel M, Yeung JC, Liu M, Anraku M, Chen F, Karolak W, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. *N Engl J Med*. 2011;364:1431-40.
2. Machuca TN, Cypel M. Ex vivo lung perfusion. *J Thorac Dis*. 2014;6:1054-62.
3. Boffini M, Ricci D, Barbero C, Bonato R, Ribezzo M, Mancuso E, et al. Ex vivo lung perfusion increases the pool of lung grafts: analysis of its potential and real impact on a lung transplant program. *Transplant Proc*. 2013;45:2624-6.
4. Iskender I, Arni S, Maeyashiki T, Citak N, Sauer M, Caviezel A, et al. Perfusate-adsorption during ex vivo lung perfusion improves early post-transplant lung function. *J Thorac Cardiovasc Surg*. 2021;161:e109-21.
5. Machuca TN, Cypel M, Yeung JC, Bonato R, Zamel R, Chen M, et al. Protein expression profiling predicts graft performance in clinical ex vivo lung perfusion. *Ann Surg*. 2015;261:591-7.

See Article page e109.

Commentary: Ischemia reperfusion—Looking ahead

Eugene Golts, MD, and Mark Onaitis, MD



Eugene Golts, MD, and Mark Onaitis, MD

CENTRAL MESSAGE

Optimizing lung transplant organ outcomes via absorption of inflammatory mediators causing ischemia-reperfusion injury is an exciting possibility.

The number of lung transplantations has increased steadily over the past 2 decades. The experience gained over this time period has allowed physicians to accept higher-risk patients for transplantation and to expand the donor pool regarding both the quality of the organs and the ischemic time associated with travel for procurement. Travel times will most likely continue to increase if the hard borders for lung allocation are removed, as has been proposed recently.[1]

The cost of longer ischemic time is the development of more severe ischemia-reperfusion (IR) injury. IR injury has been defined as acute sterile inflammation after ischemic insult to the donor lungs and reestablishment of pulmonary blood flow in the recipient body.[2]

Clinical strategies to ameliorate the effects of IR injury are limited and focused on shortening the duration of ischemia, as well as on performing controlled reperfusion of the lungs. More recently, experimental approaches including the removal of free radicals and addition of anti-inflammatory substances have been described.

An extension of these approaches is described by Iskender and colleagues[3] in this issue of the *Journal*, demonstrating that perfusate adsorption during ex vivo lung perfusion ameliorates the effects of IR injury to porcine allografts. The authors report this method to be largely effective, as demonstrated by a significant decrease in the concentration of interleukin (IL)-1ra in the plasma of transplanted animals after reperfusion, as well as statistically significant decreases in the concentrations of IL-1ra, IL-6, and IL-8 in the bronchial wash fluid at 4 hours after lung implantation.

Furthermore, the authors demonstrate significantly higher dynamic compliance in the transplanted lungs, accompanied by improvement of gas exchange in the treated lungs that closely approaches the threshold of statistical significance. Although these findings are very impressive and potentially clinically useful, a histological analysis of transplanted lungs performed by 2 independent pathologists failed to demonstrate a decrease in the level of neutrophil recruitment into the lungs or of vascular endothelial cellular activation in the treatment group compared with controls.

From the Division of Cardiothoracic Surgery, Department of Surgery, University of California San Diego, La Jolla, Calif.

Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Dec 10, 2019; accepted for publication Dec 10, 2019; available ahead of print Dec 20, 2020.

Address for reprints: Mark Onaitis, MD, 9300 Campus Point Drive, 7892, La Jolla, CA 92037 (E-mail: monaitis@health.ucsd.edu).

J Thorac Cardiovasc Surg 2021;161:e124-5
0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.12.010

Our understanding of the IR injury processes in the transplanted lungs is rather limited. This important basic science article provides another glimpse into the mechanism of the problem and offers a practical solution involving the nonselective removal of several molecular mediators of inflammation. Decreases in the concentrations of the various acute-phase reactants resulted in improved allograft function. Further studies will undoubtedly focused on more selective removal of proinflammatory mediators during the reconditioning of the lungs before implantation.

It is the hope of everyone in the field of lung transplantation that clinically important methods for reducing IR injury will be introduced into clinical practice as the severity of IR injury continues to increase, reflecting the current practice trends in the field of lung transplantation.

References

1. U.S. Department of Health & Human Services. Organ Procurement and Transplant Network. Modifications to the distribution of deceased donor lungs. Available at: https://optn.transplant.hrsa.gov/. Accessed February 18, 2020.
2. Laubach VE, Sharma AK. Mechanisms of lung ischemia-reperfusion injury. *Curr Opin Organ Transplant*. 2016;21:246-52.
3. Iskender I, Arni S, Maeyashiki T, Citak N, Sauer M, Caviezel A, et al. Perfusate adsorption during ex vivo lung perfusion improves early post-transplant lung function. *J Thorac Cardiovasc Surg*. 2021;161:e109-21.

THOR

See Article page e109.

Check for updates

Commentary: Double, double, toil, and trouble: Removing evil humours during ex vivo lung perfusion

Daniel Rodriguez, BS, and
Jonathan D'Cunha, MD, PhD

Removal of inflammatory mediators during EVLP may aid in preventing primary graft dysfunction.

The increasing number of patients diagnosed with end-stage respiratory failure has made the discrepancy between availability and demand more prominent despite the overall increasing number of donor lungs. Currently, the roadblock for those patients awaiting lung transplantation is organ utilization. The estimated rate of donor lung utilization is only roughly 20% both in the United States and the United Kingdom.[1] In response to this disparity, efforts have been made to determine ways to improve the utilization of donor lungs. Ex vivo lung perfusion (EVLP) has given hope to the field of lung transplantation with the potential to increase the number of available suitable donor lungs. To date, the clinical focus of EVLP has centered around its use as an organ assessment tool that has become widely available to transplantation centers. The future of the technology is the hope that lungs can be "resurrected" or improved to be suitable for transplantation.

CENTRAL MESSAGE

We comment on the promising work addressing the removal of inflammatory mediators from the perfusate during EVLP in a porcine model as a means of preventing primary graft dysfunction.

To address this hope, several groups are currently investigating how lungs can be manipulated on the circuit with the goal of improving quality or converting them to usable organs for transplantation. One of the issues critical to EVLP is its potential for promoting the ischemia and

From the Department of Cardiothoracic Surgery, Mayo Clinic Arizona, Phoenix, Ariz.

Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Dec 6, 2019; accepted for publication Dec 8, 2019; available ahead of print Dec 20, 2020.

Address for reprints: Jonathan D'Cunha, MD, PhD, Department of Cardiothoracic Surgery, Mayo Clinic Arizona, 5777 E Mayo Blvd, Phoenix, AZ 85054 (E-mail: DCunha.Jonathan@mayo.edu).

J Thorac Cardiovasc Surg 2021;161:e125-6
0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.12.011