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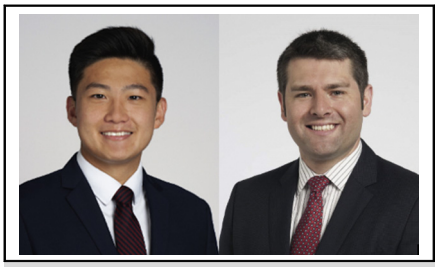
Commentary: Back(ward) to the future—novel technique of inverted left lung–right chest lung transplant in rats

Lin Chen, BA,[a] and Alejandro C. Bribriesco, MD[a,b,c,d]



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CENTRAL MESSAGE

A novel technique of "inverted" rat lung transplant with left donor lung rotated 180° and implanted to recipient contralateral/right chest provides a promising model for future experiments.

Animal models have been a cornerstone in the development of lung transplantation. The first long-term clinical successes with heart–lung transplant at Stanford in 1981 and isolated lung transplantation by the Toronto group in 1983 were built on preceding decades of animal model research.[1,2]

Early animal experiments were aimed at developing surgical techniques, such as en bloc double-lung transplantation in canine models.[3] Presently, more cost-effective and reproducible rodent models are the predominant platform for mechanistic experiments in exploring critical items such as primary graft dysfunction, acute rejection, and chronic lung allograft dysfunction. Compared with other lung transplant models such as hilar occlusion or tracheal transplant, orthotopic left lung transplantation (OLLT) is a robust and versatile experimental technique that most closely simulates the human situation.[4-6] However, there are notable limitations to the OLLT model. Anatomically, the rodent left lung consists of only 1 lobe compared with the 5 lobes of the right such that the contribution from the transplanted left lung can be completely masked by the native right lung. This negates the important experimental end point of animal survival as a marker of allograft status. Orthotopic right lung transplant has been described but is technically more challenging, thereby hindering widespread adoption.[7] To date, orthotopic bilateral lung transplant (either en bloc or sequential) in the rodent has not been achieved.

In this issue of *JTCVS Open*, Huang and colleagues[8] turn the tables of the animal model-to-human paradigm with a technical report of a novel "inverted" rat single-lung transplant procedure inspired by the Kyoto group's successful human lobar lung transplantation of a right lower lobe implanted into the left chest.[9] Elegantly described and depicted in the accompanying video, a rat donor left lung is rotated 180° and transplanted to the recipient's right chest using a standard 3-cuff anastomotic technique (inverted left-right transplant, IL-RT). This innovative model leverages the anatomic size discrepancy between the smaller left lung versus larger right chest cavity, allowing for a technically simpler and reproducible procedure compared with other techniques of right lung transplant.

In 10 IL-RT procedures, the authors report 100% intraoperative technical success with 90% survival to the planned end point of 7 days. Total procedure time was comparable between IL-RT and 10 standard/control OLLT animals (58.2 vs 56.6 minutes, P = not significant). Important experimental details to note were the differences in cold and warm ischemic times between the IL-RT and OLLT

From the [a]Case Western Reserve University School of Medicine; [b]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University School of Medicine; [c]Section of Cardiothoracic Surgery, Surgical Services, Louis Stokes Veteran Affairs Medical Center; and [d]Section of Thoracic Surgery, Department of Thoracic and Cardiovascular Surgery, Heart Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio.

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Address for reprints: Alejandro C. Bribriesco, MD, Section of Thoracic Surgery, Department of Thoracic and Cardiovascular Surgery, Heart, Vascular and Thoracic Institute, Cleveland Clinic, 9500 Euclid Ave, Mailstop J4-1, Cleveland, OH 44195 (E-mail: bribria@ccf.org).

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groups. When compared with the OLLT, the IL-RT group had shorter cold ischemia time (14 minutes vs 25.5 minutes, $P < .001$) but longer warm ischemia time (19.8 vs 13.7 minutes, $P < .001$). It is unclear whether these small absolute differences in ischemic times will have meaningful biologic effect, but these and other facets of the IL-RT model will likely be explored and potentially gainfully used in forthcoming experiments.

The authors are to be commended for their impressive technical achievement. As with all animal models, there are limitations to be addressed but, overall, this innovative procedure represents an exciting new tool for future research in lung transplantation.

References

1. Venuta F, Van Raemdonck D. History of lung transplantation. *J Thorac Dis*. 2017;9:5458-71.
2. Bribriesco AC, Li W, Nava RG, Spahn JH, Kreisel D. Experimental models of lung transplantation. *Front Biosci (Elite Ed)*. 2013;5:266-72.
3. Dark JH, Patterson GA, Al-Jilaihawi AN, Hsu H, Egan T, Cooper JD. Experimental en bloc double-lung transplantation. *Ann Thorac Surg*. 1986;42:394-8.
4. Lama VN, Belperio JA, Christie JD, El-Chemaly S, Fishbein MC, Gelman AE, et al. Models of lung transplant research: a consensus statement from the National Heart, Lung, and Blood Institute workshop. *JCI Insight*. 2017;2:e93121.
5. Okazaki M, Krupnick AS, Kornfeld CG, Lai JM, Ritter JH, Richardson SB, et al. A mouse model of orthotopic vascularized aerated lung transplantation. *Am J Transplant*. 2007;7:1672-9.
6. Lin X, Li W, Lai J, Okazaki M, Sugimoto S, Yamamoto S, et al. Five-year update on the mouse model of orthotopic lung transplantation: scientific uses, tricks of the trade, and tips for success. *J Thorac Dis*. 2012;4:247-58.
7. Li W, Sugimoto S, Lai J, Patterson GA, Gelman AE, Krupnick AS, et al. Orthotopic vascularized right lung transplantation in the mouse. *J Thorac Cardiovasc Surg*. 2010;139:1637-43.
8. Huang H, Yan H-J, Zheng X-Y, Wang JJ, Tang HT, Li CH, et al. Right lung transplantation with a left-to-right inverted anastomosis in a rat model. *J Thorac Cardiovasc Surg Open*. 2022;10:429-39.
9. Chen F, Miyamoto E, Takemoto M, Minakata K, Yamada T, Sato M, et al. Right and left inverted lobar lung transplantation. *Am J Transplant*. 2015;15:1716-21.