With the recent decision by the Centers for Medicare & Medicaid Services and other payers to cover the costs of lung cancer screening, the implementation in the United States is marching forward. European authorities, in contrast, have largely chosen to await the results of the NELSON trial. In centers where screening is performed, the results of the DLCST should be used as an opportunity to recognize the importance of strategies that result in careful patient selection to minimize any potential harms. The DLCST investigators are to be congratulated for including pulmonary function in their trial, which confirms the importance of COPD in identifying those at greatest risk for lung cancer.

Although more work is needed to identify the best methods for identifying populations that will benefit from screening, one recent advance is the development of PLCO_{m2012}, a logistic model incorporating four smoking variables and seven other variables, including COPD, to estimate lung cancer risk (16). A 6-year risk greater than 0.015% using this model identifies patients most likely to benefit from screening and, importantly, was more efficient than the currently recommended NLST criteria using only age and smoking history. Better selection of patients for screening, using model based tools such as PLCO_{m2012}, will likely result in greater benefits and fewer harms from screening and warrants further evaluation. ■

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References

1. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
2. Moyer VA; U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160:330–338.
3. Becker N, Motsch E, Gross ML, Eigentopf A, Heussel CP, Dienemann H, Schnabel PA, Eichinger M, Optazait DE, Puderbach M, *et al*. Randomized study on early detection of lung cancer with MSCT in Germany: results of the first 3 years of follow-up after randomization. *J Thorac Oncol* 2015;10:890–896.
4. Horeweg N, Scholten ET, de Jong PA, van der Aalst CM, Weenink C, Lammers JW, Nackaerts K, Vliegenthart R, ten Haaf K, Yousaf-Khan UA, *et al*. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. *Lancet Oncol* 2014;15:1342–1350.
5. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, Brambilla G, Angeli E, Aranzulla G, Chiti A, *et al*; DANTE Study Group. Long-term follow-up results of the DANTE Trial, a randomized study of lung cancer screening with spiral computed tomography. *Am J Respir Crit Care Med* 2015;191:1166–1175.
6. Pastorino U, Rossi M, Rosato V, Marchianò A, Sverzellati N, Morosi C, Fabbri A, Galeone C, Negri E, Sozzi G, *et al*. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev* 2012;21:308–315.
7. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, Døssing M, Hansen H, Kofoed KF, Larsen KR, *et al*. CT screening for lung cancer brings forward early disease: the randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax* 2012;67:296–301.
8. Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, Clementsen PF, Hansen H, Larsen KR, Mortensen J, *et al*. Results of the randomized Danish Lung Cancer Screening Trial with focus on high-risk profiling. *Am J Respir Crit Care Med* 2016;193:542–551.
9. Kovalchik SA, Tammemägi M, Berg CD, Caporaso NE, Riley TL, Korch M, Silvestri GA, Chaturvedi AK, Katki HA. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med* 2013;369:245–254.
10. Tammemägi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, Chaturvedi AK, Silvestri GA, Riley TL, Commins J, *et al*. Selection criteria for lung-cancer screening. *N Engl J Med* 2013;368:728–736.
11. de-Torres JP, Wilson DO, Sanchez-Salcedo P, Weissfeld JL, Berto J, Campo A, Alcaide AB, García-Granero M, Celli BR, Zulueta JJ. Lung cancer in patients with chronic obstructive pulmonary disease. Development and validation of the COPD Lung Cancer Screening Score. *Am J Respir Crit Care Med* 2015;191:285–291.
12. Sanchez-Salcedo P, Wilson DO, de-Torres JP, Weissfeld JL, Berto J, Campo A, Alcaide AB, Pueyo J, Bastarrika G, Seijo LM, *et al*. Improving selection criteria for lung cancer screening: the potential role of emphysema. *Am J Respir Crit Care Med* 2015;191:924–931.
13. Young RP, Duan F, Chiles C, Hopkins RJ, Gamble GD, Greco EM, Gatsonis C, Aberle D. Airflow limitation and histology shift in the National Lung Screening Trial: the NLST-ACRIN Cohort Substudy. *Am J Respir Crit Care Med* 2015;192:1060–1067.
14. Church TR, Black WC, Aberle DR, Berg CD, Clingan KL, Duan F, Fagerstrom RM, Gareen IF, Gierada DS, Jones GC, *et al*; National Lung Screening Trial Research Team. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med* 2013;368:1980–1991.
15. Tanner NT, Silvestri GA. Screening for lung cancer using low-dose computed tomography: are we headed for DANTE's paradise or inferno? *Am J Respir Crit Care Med* 2015;191:1100–1101.
16. Tammemägi MC, Church TR, Hocking WG, Silvestri GA, Kvale PA, Riley TL, Commins J, Berg CD. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. *PLoS Med* 2014;11:e1001764.

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A Critical Role for Airway Microvessels in Lung Transplantation

Lung transplantation permits a lifesaving treatment for patients with terminal pulmonary vascular and parenchymal diseases. As blood vessels, lymphatics, and nerves are severed and incompletely restored at the time of transplantation, these

anatomic derangements may contribute to early- and late-arising pathologies. Experimental and clinical evidence is mounting that microvessel damage, in particular, is bad for solid organ allografts, such as lung transplants.

In this issue of the *Journal*, Kraft and colleagues (pp. 552–560) build on prior observations that airways in transplanted lungs are hypoxic at baseline because the bronchial artery circulation is not restored at the time of surgery (1). The Duke investigators confirmed findings made in the original Stanford study (2) that donor tissue oxygen saturations are reduced in airways; they significantly extend these findings by showing that hypoxia-inducible genes are up-regulated in donor lungs and are associated with airway necrosis, central airway stenosis, and worse clinical outcomes. The authors also note a relationship between up-regulation of hypoxic genes in transplanted airways with prolonged respiratory failure and prolonged hospitalization; however, these latter results could be dependent on factors more important than airway hypoxia, making these findings harder to attribute to a missing bronchial artery circulation.

Anatomy and Fate of Airway Microvasculature after Lung Transplantation

The bronchial arteries carry highly oxygenated blood to supply the bronchial mucosa as well as the visceral pleura. The bronchial circulation is not routinely reanastomosed at the time of transplantation. As indicated by the Duke and Stanford studies, loss of this native circulation renders airways relatively hypoxic after transplantation and dependent on blood originating from the pulmonary circulation, emerging collateral vessels, and ambient air.

Optimization of surgical techniques has significantly limited central airway complications, such as stenosis and dehiscence, but the current study raises the concern that despite these refinements, transplanted airways are compromised because of an altered microcirculation. Beyond creating a predisposition for large airway complications, as suggested by the current study, the later loss of airway microvasculature resulting from alloimmune rejection may be an important reason for developing the bronchiolitis obliterans syndrome (BOS).

An autopsy study demonstrated a significant dropout of microvasculature in pre-BOS airways contiguous with BOS airways, suggesting that microvascular loss and airway ischemia is a preceding condition to airway fibrosis (3). As noted, the late dropout of microvessels in pre-BOS airways could be a result of immune-mediated injury. On the heels of this discovery, it has been reported that the loss of the airway microcirculation identified those airway grafts that could not be rescued from fibrosis with immunotherapy (4). This preclinical study suggested that steroid resistance in chronic rejection may be attributable, in part, to the destruction of the microvasculature in grafts. In summary, a compromised microcirculation resulting from missing bronchial arterial blood flow at the time of transplantation appears to have clinical importance for central airway health, whereas alloimmune-mediated microvascular attrition may significantly contribute to chronic rejection. The graft microenvironment appears to have a strong effect on the development of chronic allograft dysfunction. Not only does alloimmune inflammation lead to the destruction of microvessels and regions of hypoxic tissue beds, but it is also likely that the resulting tissue ischemia fosters dysregulated angiogenesis and abnormal blood flow (5, 6).

Nonvascular Consequences of Surgical Lung Implantation

Beyond loss of the bronchial artery circulation, the transplanted lung must also endure a disruption of its native lymphatics and neural supply; the implications of these deficits remain poorly understood. A new study by Cui and colleagues addresses how the complete interruption of lymphatic flow may worsen lung transplant outcomes (7). Studies on the disrupted neural supply in lung transplantation, chiefly of the branches afferent to the vagus nerve from the lung, are few and not updated. These branches wire impulses from the lung to the brain, mostly from the neuroepithelial bodies that analyze the hypoxic environment or the inflation status of the lung parenchyma with the smooth muscle-associated airway receptors (8). The inflation inhibitory reflex is greatly reduced in lung transplant patients, and vagal denervation increases breathing pattern variability (9). Lymphatic and neural interruption appear to be an important area of future transplant research.

Strategies to Improve Lung Allograft Function

Bronchial Artery Revascularization

Several studies by Gösta Pettersson's group have demonstrated that this operation can be feasible and beneficial. A single-center experience of en bloc double-lung transplants with bronchial artery revascularization (BAR) performed by Pettersson's Copenhagen group in the 1990s showed excellent success and long-term survival relative to a more recent series of sequential bilateral non-BAR lung transplants from the same institution (10, 11). As might have been predicted by the current article by Kraft and colleagues, a follow-up study at the Cleveland Clinic demonstrated that BAR limited central airway ischemia and anastomotic complications (12). A Norwegian study showed by endoscopic laser Doppler flowmetry that BAR improved airway perfusion (13). However, any putative benefits gained by BAR may be offset by unacceptable risks. Most BAR operations are performed with both lungs explanted as a single unit (i.e., en bloc) in a process described as cumbersome and that adds to an already lengthy operation (14). Refined surgical techniques have significantly diminished the incidence of anastomotic complications and, in so doing, remove one of the major reasons for performing the revascularization procedure (15). Nevertheless, the issue of vascular compromise remains an open one, and the Duke study in this issue of the *Journal* raises again the question of what can be safely done to optimize transplant health.

Ex Vivo Lung Perfusion Reconditioning

The donor lung management using *ex vivo* lung perfusion systems could potentially prevent collapse of microvasculature during preservation and decrease cold ischemia-related damage (16). In addition, dual *ex vivo* lung perfusion using both pulmonary and bronchial artery perfusion has been shown to increase microvasculature and perfusion compared with organs maintained on standard *ex vivo* lung perfusion. This resulted in better posttransplant outcomes in an experimental model (17).

Other Medical Therapies

As suggested by the authors, application of intermittent hyperbaric oxygen therapy in a posttransplant period may improve airway healing and reduce anastomotic complications (18, 19). The promotion of therapeutic lymphangiogenesis and airway microvascular regeneration are other promising strategies that might improve post-lung transplant outcomes (6, 7, 20).

Summary and Future Directions

Since its inception, the field of solid organ transplantation has focused, with good reason, on limiting destructive alloimmune responses. However, not withstanding immunity issues, increasing attention is now being given to how the actual anatomy of the intra-graft microenvironment influences short- and long-term airway health.

Although there is ongoing disagreement about the merits of performing BAR, several things are clear: even if BAR were routinely performed, the airway microcirculation would remain vulnerable to alloimmune injury and the lymphatic circulation and airway neural system would still remain disrupted. Medical strategies that can promote vascular, lymphatic, and neural regrowth is a promising approach that can be undertaken as the BAR question is resolved by the transplant community (6, 7, 20). The Kraft study (1) is an important step forward in advancing the argument that additional steps can and should be taken at the time of lung transplantation to restore transplant anatomy and physiology. ■

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References

- Kraft BD, Suliman HB, Colman EC, Mahmood K, Hartwig MG, Piantadosi CA, Shofer SL. Hypoxic gene expression of donor bronchi linked to airway complications after lung transplantation. *Am J Respir Crit Care Med* 2016;193:552–560.
- Dhillon GS, Zamora MR, Roos JE, Sheahan D, Sista RR, Van der Starre P, Weill D, Nicolls MR. Lung transplant airway hypoxia: a diathesis to fibrosis? *Am J Respir Crit Care Med* 2010;182:230–236.
- Luckraz H, Goddard M, McNeil K, Atkinson C, Sharples LD, Wallwork J. Is obliterative bronchiolitis in lung transplantation associated with microvascular damage to small airways? *Ann Thorac Surg* 2006;82:1212–1218.
- Babu AN, Murakawa T, Thurman JM, Miller EJ, Henson PM, Zamora MR, Voelkel NF, Nicolls MR. Microvascular destruction identifies murine allografts that cannot be rescued from airway fibrosis. *J Clin Invest* 2007;117:3774–3785.
- Bruneau S, Woda CB, Daly KP, Boneschansker L, Jain NG, Kochupurakkal N, Contreras AG, Seto T, Briscoe DM. Key features of the intra-graft microenvironment that determine long-term survival following transplantation. *Front Immunol* 2012;3:54.
- Jiang X, Khan MA, Tian W, Beilke J, Natarajan R, Kosek J, Yoder MC, Semenza GL, Nicolls MR. Adenovirus-mediated HIF-1 α gene transfer promotes repair of mouse airway allograft microvasculature and attenuates chronic rejection. *J Clin Invest* 2011;121:2336–2349.
- Cui Y, Liu K, Monzon-Medina ME, Padera RF, Wang H, George G, Toprak D, Abdelnour E, D'Agostino E, Goldberg HJ, et al. Therapeutic lymphangiogenesis ameliorates established acute lung allograft rejection. *J Clin Invest* 2015;125:4255–4268.
- Adriaensen D, Brouns I, Timmermans JP. Sensory input to the central nervous system from the lungs and airways: A prominent role for purinergic signalling via P2X2/3 receptors. *Auton Neurosci* 2015;191:39–47.
- Iber C, Simon P, Skatrud JB, Mahowald MW, Dempsey JA. The Breuer-Hering reflex in humans: effects of pulmonary denervation and hypocapnia. *Am J Respir Crit Care Med* 1995;152:217–224.
- Pettersson G, Nørgaard MA, Arendrup H, Brandenhof P, Helvind M, Joyce F, Stentoft P, Olesen PS, Thijs JJ, Efsen F, et al. Direct bronchial artery revascularization and en bloc double lung transplantation: surgical techniques and early outcome. *J Heart Lung Transplant* 1997;16:320–333.
- Burton CM, Milman N, Carlsen J, Arendrup H, Eliassen K, Andersen CB, Iversen M; Copenhagen National Lung Transplant Group. The Copenhagen National Lung Transplant Group: survival after single lung, double lung, and heart-lung transplantation. *J Heart Lung Transplant* 2005;24:1834–1843.
- Pettersson GB, Karam K, Thuita L, Johnston DR, McCurry KR, Kapadia SR, Budev MM, Avery RK, Mason DP, Murthy SC, et al. Comparative study of bronchial artery revascularization in lung transplantation. *J Thorac Cardiovasc Surg* 2013;146:894–900.
- Sundset A, Tadjikarimi S, Khaghani A, Kvernebo K, Yacoub MH. Human en bloc double-lung transplantation: bronchial artery revascularization improves airway perfusion. *Ann Thorac Surg* 1997;63:790–795.
- Huddleston CB. Airway complications in children following lung transplantation. In: Cooper DK, Miller LW, Patterson GA, editors. The transplantation and replacement of thoracic organs: the present status of biological and mechanical replacement of the heart and lungs, 2nd ed. Lancaster, UK: Kluwer Academic Publishers; 1996.
- Patterson GA. Airway revascularization: is it necessary? *Ann Thorac Surg* 1993;56:807–808.
- Cypel M, Keshavjee S. Extending the donor pool: rehabilitation of poor organs. *Thorac Surg Clin* 2015;25:27–33.
- Tanaka Y, Noda K, Isse K, Tobita K, Maniwa Y, Bhama JK, D'Cunha J, Bermudez CA, Luketich JD, Shigemura N. A novel dual ex vivo lung perfusion technique improves immediate outcomes in an experimental model of lung transplantation. *Am J Transplant* 2015;15:1219–1230.
- Dickhoff C, Daniels JM, van den Brink A, Paul MA, Verhagen AF. Does hyperbaric oxygen therapy prevent airway anastomosis from breakdown? *Ann Thorac Surg* 2015;99:682–685.
- Stock C, Gukasyan N, Muniappan A, Wright C, Mathisen D. Hyperbaric oxygen therapy for the treatment of anastomotic complications after tracheal resection and reconstruction. *J Thorac Cardiovasc Surg* 2014;147:1030–1035.
- Jiang X, Malkovskiy AV, Tian W, Sung YK, Sun W, Hsu JL, Manickam S, Wagh D, Joubert LM, Semenza GL, et al. Promotion of airway anastomotic microvascular regeneration and alleviation of airway ischemia by deferoxamine nanoparticles. *Biomaterials* 2014;35:803–813.

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