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Editorial commentary: What can lung transplantation teach us about the mechanisms of atrial arrhythmias?

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Lung transplantation is an increasingly performed procedure, with 50% survival at 5 years [1] and whose immediate and long-term prognosis may be complicated by atrial arrhythmias. Operatively, the procedure involves transplantation of one or both lungs with their proximal airways, together with anastomosis of the vascular pedicle (pulmonary veins and arteries) to the recipient heart. This results in surgical isolation of the donor pulmonary veins to the recipient left atrium, providing a valuable opportunity to examine incident atrial fibrillation (AF) and its mechanistic relation to the pulmonary veins [2].

Atrial arrhythmias in the early post-operative period are mostly AF, whereas late arrhythmias are mostly atrial tachycardias (AT) [3]. It is unclear if these phenotypes reflect differences in the physiological milieu, e.g., higher autonomic tone or inflammation in the early post-operative period vs. the formation of structural barriers enabling subsequent stable re-entrant or focal atrial tachycardias in the later period. Explaining these arrhythmias may help manage these patients, and the pulmonary vein isolation (PVI) due to surgical anastomoses may shed light into the natural history and progression of AF in other patients.

In this issue of *Trends*, Roukoz et al. [4] comprehensively review the literature on atrial arrhythmias following lung transplantation. Few prior studies have studied potential mechanisms with data particularly limited on the invasive mapping and ablation of these arrhythmias. Roukoz et al. have advanced our understanding of this field by consolidating and synthesizing occasionally conflicting reports.

They [4] find consensus that early post-operative atrial arrhythmias are often AF, whereas later onset arrhythmias are almost exclusively atrial tachycardias. Risk factors for AF are similar to those for AF in the general population, i.e., components of the CHADS2VASc score, which is notable given their extensive surgical procedure. However, the authors report a discrepancy in the literature regarding elevated pulmonary artery (PA) pressures and double (vs. single) lung transplant, being protective factors in occurrence of AF post-operatively. The predilection for early postoperative AF suggests a role for systemic inflammation and post-operative pericarditis [5,6], or operative trauma to the posterior left

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atrium, both of which also occur following MAZE surgery for AF [7,8]. Alternatively, this may reflect autonomic imbalance produced by surgery. These factors may create the substrate to sustain AF via putative multiwavelet reentry or localized drivers [9,10].

Roukoz et al. [4] conclude that surgical PVI explains the low incidence of late AF post-lung transplantation. Nevertheless, it is unclear why lung transplant recipients with surgical PVI do not have a lower incidence of post-operative AF compared to recipients of other cardiothoracic surgical procedures, where the pulmonary veins are not isolated [11]. This may reflect extra-PV mechanisms for post-operative AF, as supported by a recent randomized trial by Skanes et al., which showed no benefit of intraoperative PVI on development of postoperative AF following coronary artery bypass graft surgery [12]. These findings suggest a role for non-PV triggers or atrial 'substrate', i.e., mechanisms that sustain AF after it has been triggered, in post-operative AF, recently shown in the right atrium of patients undergoing elective CABG [13].

Indeed, the low late occurrence of AF following double lung transplantation is remarkable. It is particularly unclear why such patients do not develop AF from non-PV triggers and/or atrial substrates, as would be the expected natural history in patients with similar high CHADS₂VA₂Sc scores. One possibility is demographic and survival bias—patients are relatively young (for transplant eligibility) and have a 5-year survival of only 50%. On the other hand, it is not uncommon to see general patients of this age for AF ablation. Thus, at present, the lack of non-PV related AF in these patients remains unanswered.

It is intriguing to compare these data against heart transplant patients who also have surgical PVI but whose incidence of post-operative AF is lower still. This may reflect cardiac autonomic denervation in donor hearts, although that hypothesis is not supported by AFACT [14] and other trials in which autonomic ablation minimally suppressed arrhythmia recurrence after surgical AF ablation. Another explanation is that recurrent arrhythmias in lung transplant patients are related to (and predicted by) a history of prior arrhythmias and increased left atrial size, both of which are removed with the explanted heart.

Various mechanisms of atrial flutter or tachycardia have been described in lung transplant patients, consistent with established principles for macro-reentry including roof-dependent flutter between the anastomotic PV cuffs, typical flutter (cavotricuspid isthmus dependent) and atypical flutter (e.g., mitral isthmus dependent). An interesting subset of lung transplant patients may have atrial tachycardias using donor-to-recipient conduction across an anastomotic line. This has been supported by 2 case reports [3,15] but disputed by some studies including a series of 25 patients in whom electrophysiological mapping showed that all PV antral arrhythmias arose from recipient not donor myocardium [16].

Finally, Roukoz et al. [4] touch upon stroke prevention and conclude that anticoagulation may not be necessary in double lung recipients after bilateral PV isolation. However, the current recommendation in non-transplant patients who have undergone PVI ablation is to continue anticoagulation regardless of successful PVI or arrhythmia freedom [17]. More data are needed to guide therapy on this issue.

In conclusion, Roukoz et al. [4] provide a timely and important synthesis of the literature on atrial arrhythmias post lung transplant. These data confirm the central role of PV isolation in preventing AF. Further studies and detailed electrophysiological mapping in such patients may continue to illuminate the mechanisms of atrial arrhythmias in the general population.

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