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Protective Mechanical Ventilation in Organ Donors: A Lifesaving Maneuver

Lung transplantation has become an effective lifesaving intervention for patients with end-stage lung disease. However, the number of available organs does not meet the current demand, with only around 15–25% of lungs being procured from potential donors (1), leading to persistently high mortality rates on the waiting list. Thus, strategies to enhance lung procurement have been suggested as means to reduce the mismatch between organ demand and supply (2) and include extended lung-donor selection criteria (1), *ex vivo* lung perfusion (EVLP) (3), and optimization of donor management (4).

Use of extended lung-donor selection criteria may easily increase the availability of organs within the donor pool. Nonetheless, it may increase the risk of post–lung transplantation primary graft dysfunction, which occurs in about 20% of recipients and is associated with increased morbidity and mortality (5). EVLP has shown excellent reliability for donor lung assessment. Organs that would be declined for transplantation according to standard criteria can be maintained viable for up to 6 hours in clinical settings but up to 24 hours in experimental conditions. This allows a rigorous anatomical, mechanical, functional, and biological evaluation of the donor lung properties, which can more accurately inform the risk–benefit profile of transplantation. This approach has resulted in an impressive increase in the number of lung transplantations worldwide with encouraging long-term outcome (6). However, EVLP is a complex strategy and requires specific skills and advanced resources.

Optimizing management of the lung in the donor may be the strategy that can provide the greatest expansion in organs suitable for transplant without significant increase in resource utilization. Potential lung donors are prone to develop acute lung injury from the exposure to a series of potential mechanical and inflammatory insults, including brain death, atelectasis, lung trauma, aspiration pneumonitis, and ventilator-associated pneumonia (7, 8). These conditions make donor lungs particularly vulnerable and susceptible to the so-called ventilator-induced lung injury (VILI) (9). Mechanical ventilation, although necessary in donors to ensure adequate oxygenation to protect organs potentially suitable for transplant, can itself cause lung injury from excessive regional alveolar stress and strain and tidal recruitment, with the consequent exacerbation of pulmonary and systemic inflammation (9). Lung-protective mechanical ventilation strategies aiming to avoid VILI can hence potentially determine a great impact on lung availability for transplantation.

A prior landmark randomized clinical trial (10) implementing low V_T (6–8 ml/kg of predicted body weight [PBW]), higher positive end-expiratory pressure (PEEP; 8–10 cm H_2O), and derecruitment preventive strategies (inline suctioning and continuous positive airway pressure during the apnea test) showed increased rates of organ procurement with similar survival rates. However, the trial was stopped earlier than planned, thereby introducing an important bias in the analysis of its findings.

In this issue of the *Journal*, Mal and colleagues (pp. 250–258) assessed in organ donors the impact of lung-protective ventilation, defined as PEEP $\geq$8 cm H_2O and V_T $\leq$8 ml/kg PBW, on the rate of lung procurement and recipient survival (11). The authors

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carried a nationwide cohort observational study in France, including brain-dead donors with at least one procured organ, mainly focusing on respiratory management. The association between lung procurement and lung-protective ventilation was assessed by multivariate logistic regression analysis stratified by propensity score quintiles, and recipient survival was assessed at 1 year.

The study population included 1,626 potential lung donors, out of which 1,109 (68%) had at least one lung proposed for transplant, and 678 (61%) then proceeded to lung procurement. Interestingly, only 25% of donors were ventilated with a protective ventilation strategy as described. The majority of potential donors (53%) were ventilated with PEEP $<$8 cm H_2O, and around 13% had PEEP $<$8 cm H_2O and V_T $>$8 ml/kg PBW. After adjusting for confounders and propensity score, the chance of lung procurement was significantly higher (odds ratio, 1.43; 95% confidence interval, 1.03–1.98; $P = 0.03$) in the group receiving protective ventilation. Lung transplant recipient survival did not differ according to the use or not of lung-protective ventilation.

These results from a large multicenter cohort of patients are clinically very important because they confirm the findings of the randomized controlled trial conducted by Mascia and colleagues (10). It is therefore now established that avoiding VILI in organ donors with the delivery of lung-protective mechanical ventilation significantly increases the number of lungs suitable for lung transplantation. Considering the low percentage of organ donors receiving lung-protective ventilation in this observational study (about 25%), the delivery of optimal mechanical ventilation settings could potentially result in a remarkable increase of donor lung procurements.

However, the best strategy to avoid VILI in this population needs further investigation.

It is still unclear whether the improvement in organ procurement is associated with the combination of lower V_T and higher PEEP or to the separate effect of each component. In this regard, the study of Mal and colleagues failed to show increased organ procurement rates in the complementary analysis using $V_T \leq 8$ ml/kg PBW alone as definition of protective ventilation. The consequent change in sample size in this complementary analysis may explain the different findings, as mentioned by the authors. Alternatively, these results may indicate that reducing the risk of regional alveolar overdistension by limiting V_T alone may not be sufficient to protect donor lungs from VILI. Instead, avoiding atelectasis with higher PEEP may provide the main benefit. Indeed, several experimental evidences demonstrate that the presence of atelectasis in donor lungs, especially during the time of cold static preservation, results in worst pulmonary function, likely from the deleterious consequences of localized parenchymal hypoxia. In addition, avoiding atelectasis results in a more homogeneous distribution of the mechanical forces during artificial ventilation, thereby reducing the risk of regional overdistension. Even safe levels of alveolar distending pressure can be converted into locally injurious stress by the presence of areas of atelectasis and lung inhomogeneity (12). In this regard, a very effective strategy to improve lung recruitment and reduce alveolar inhomogeneity is prone positioning, a strategy that should be further investigated in multiorgan donors.

In a large body of clinical and experimental evidences, prone positioning has been demonstrated to be beneficial during mechanical ventilation for patients with acute respiratory distress syndrome in improving oxygenation, in reducing VILI, and improving survival (13). In a recent preclinical study, we demonstrated in a pig model of lung donation after cardiac death that prone positioning during warm ischemic time prevented lung atelectasis, inflammation, and cell death, leading to significantly improved lung function during EVLP (14).

Mal and colleagues should be congratulated for confirming in a large cohort study the evidence of VILI in potential organ donors. Future research needs to focus on rapidly identifying the best strategy to avoid VILI in this population to ultimately improve outcomes of patients with end-stage lung diseases. ■

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A Role for the Rho-GTPase Pathway in Pediatric Obese Asthma

Asthma and obesity are two of the most common chronic disorders in the pediatric population. Asthma is a heterogeneous disease characterized by chronic airway inflammation affecting approximately 5.5 million children in the United States (1). Childhood obesity, a growing public health problem, has been shown to disproportionately impact minority populations including African American and Hispanic children (2). Obesity is both a risk factor and an important disease modifier of childhood asthma (3–5). Subjects with obesity and early-onset asthma include a large proportion of African American individuals and those with increased airflow obstruction (6). In addition, subjects with obesity and asthma have increased respiratory symptoms and disease exacerbations (6). Pediatric obese asthma is associated with increased T-helper cell type 1 (Th1) cell polarization (7), which has been postulated as a mechanism underlying the association of this subgroup of patients with decreased responsiveness to inhaled corticosteroids (8). These observations highlight the need to better elucidate the biologic mechanisms that result in the pediatric obese asthma endotype.

Asthma and obesity are complex disorders that are influenced by both genetic and environmental factors. The parallel rise in the prevalence of both disorders worldwide suggests that they may be linked (9). Previous studies have established the importance of numerous environmental exposures, including dietary and nutritional risk factors, on the subsequent development of childhood asthma and obesity (10, 11). But studies investigating shared genetic determinants have been inconsistent with some studies suggesting shared genetics (12, 13) and others failing to demonstrate convincing evidence for shared genetic determinants of obesity and childhood asthma (14, 15). Therefore, epigenetic studies, including DNA methylation changes that result from environmental exposures, may help to elucidate additional relevant biological pathways that influence the susceptibility to pediatric obese asthma. Furthermore, integrative genomics approaches may illuminate novel biologic pathways involved in pediatric obese asthma and may help to identify novel therapeutic targets for this population (8).

In this issue of the *Journal*, Rastogi and colleagues (pp. 259–274) report the results of their genomics and epigenomic analyses of the pediatric obese asthma phenotype in minority populations (16). Using a multiomics approach including differential gene expression from $CD4^+$ Th cells, expression quantitative trait loci (eQTL) mapping, differential methylation, and methylation quantitative trait loci, the authors demonstrate enrichment of genes in the Rho-GTPase pathway in the obese asthma phenotype in African American and Hispanic children. Using deconvolution methods to address differences in Th cell subpopulations that exist between subjects with asthma with and without obesity, the authors also demonstrate that both Rho-GTPase gene expression and methylation changes are robust to differences in Th cell subtype proportion. Although the authors did not identify an enrichment of Rho-GTPase genes in the eQTL analysis, they did demonstrate that genes proximal to the cytosine targets for the methylation quantitative trait loci were enriched with genes in this pathway. The authors also demonstrate the clinical impact of Rho-GTPase genes by demonstrating an association with increased airflow obstruction (reduced FEV_1/FVC) and obesity-related deficits in lung function (reduced expiratory reserve volume). Moreover, the authors demonstrate the functional relevance of Rho-GTPase pathways in Th1 polarization, by transfecting primary human Th cells with siRNA to silence the *CDC42* gene, one of the Rho-GTPase genes identified in their analyses. Silencing *CDC42* resulted in decreased gene expression of IFN-γ, but no change in IL-4 expression, confirming a role for the Rho-GTPase pathway in Th1 polarization.

Although the focus of their integrative genomics analysis was on the Rho-GTPase pathway, the authors also identified a role for the *RPS27L* (ribosomal protein s27-like) gene in pediatric obese asthma. The authors demonstrate that *RPS27L* was downregulated in subjects with obesity. This gene also includes an eQTL that is found with increased frequency in Latino and Afro-Caribbean populations, is associated with lower expression of *RPS27L*, and is associated with obese asthma. These results highlight the impact of the use of integrative genomic approaches on identifying novel biology in populations not often represented in genomic studies.

Previous studies have demonstrated genetic associations with Rho-GTPase polymorphisms with obesity-related metabolic traits (17), and genes in this pathway have been shown to impact adipocyte lipolysis in obesity (18). Although genetic

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