Transplant International

INVITED COMMENTARY

Primary graft dysfunction and beyond after lung transplantation in the current era

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Transplant International 2019; 32: 241–243

Received: 29 November 2018; Accepted: 30 November 2018

When encountering early signs of primary graft dysfunction (PGD) at the end of the procedure following lung transplantation in operating rooms, aside from lung protective ventilation strategies, two key players as currently available therapeutic options include inhaled nitric oxide (iNO) and/or extracorporeal membrane oxygenation (ECMO) [1]. While iNO plays a unique and relevant therapeutic role in the current clinical lung transplantation, its impact on posttransplant outcomes remains unclear mostly because of a large variety of iNO usage in clinical practice intraoperatively, perioperatively, and postoperatively among the institutions [2,3].

In this issue of the *Transplant International*, Fessler *et al.* [4] from Hospital Foch in France, presented their study to aim to characterize the patients who required prolonged support of iNO following lung transplantation and evaluate the impact of such iNO dependency on posttransplant outcomes in particular with the incidences of severe PGD. Fessler and colleagues nicely demonstrate the strong correlation between iNO dependency and suboptimal short- and long-term outcomes following lung transplantation, which will lead to early identification of those high-risk patients and moving forward the potential additional treatments in order to improve their subsequent outcomes.

Prior to looking into their interesting findings, we need to understand their institutional unique protocol using ECMO as cardiopulmonary mechanical support during and following lung transplantation:

1. Peripheral veno-arterial (V-A) ECMO is their preference during lung transplantation; those cases that required full cardiopulmonary bypass intraoperatively were excluded from the study.
2. At the end of the procedure, if the patients could not wean from V-A ECMO, they stayed on V-A instead of attempting to switch to veno-venous (V-V) ECMO; these patients who failed to wean from ECMO in operating rooms were also excluded from the study (however, their data are provided as 'prolonged ECMO group' in the supplement file).

doi:10.1111/tri.13385

Keeping the above conditions borne in mind, the additional findings from the study that I find particularly intriguing are as follows:

With their current protocol, the incidence of PGD 3 in the prolonged iNO group was 35% (6/17) while secondary ECMO was required for half of them (17%). If those who failed to wean and stayed on ECMO after the procedure (prolonged ECMO group, $n = 40$) are added to PGD 3, then their total incidence of PGD 3 was 19.4% (6 + 40/237), which appears to be close to the currently reported results with severe PGD from other major lung transplant centers [5]; however, it may be higher given that the complicated cases such as those requiring full cardiopulmonary bypass during the procedure and with ECMO bridged to transplantation were excluded from the study. In spite of such a relatively large number of patients who experienced severe PGD after transplantation; however, their long-term survival at 3 year in prolonged ECMO and prolonged iNO groups was 67% and 71%, respectively, which appears to be equivalent or even better as compared to the one from the registry reported by international society of heart and lung transplantation (ISHLT) [6]. Interestingly, the recent report from Barnes Jewish Hospital and Washington University School of Medicine in St. Louis, Missouri, a high-volume center as well as one of the most historic transplant institutions in United States, which details their single-institution experience with lung transplantation in 1500 patients over a 30-year period and compares patient characteristics and outcomes before and after the introduction of the lung allocation score (LAS) in 2005 [7], yields similar trends in their outcomes. In the report, they demonstrate improved long-term survival outcomes despite transplanting high-acuity patients more frequently in the post-LAS era where the patients in the post-LAS era had a higher incidence of severe PGD as compared with those in the pre-LAS era (Grade 3 PGD, 31% vs. 22%), but still had improved long-term survival and freedom from bronchiolitis obliterans syndrome (BOS).

Whereas many series of clinical studies have shown that the PGD incidences at all time points and all PGD grade have positive correlation with BOS development [8], given these recent studies demonstrating that such correlation is not always the case in the current era, the drivers of both short- and long-term survival may remain to be fully understood [9]. While we should continue to prioritize research to understand the drivers underlying PGD and new therapeutic strategies to minimize its occurrence, it also should be reminded that improvements to the surgical techniques used for lung transplant including lung preservation/protection as well as utilization of cardiopulmonary support during the procedure may reduce PGD and/or BOS; however, the standard surgical techniques for lung transplant have basically remained unchanged for the last two decades, and only a few modifications to these techniques have improved long-term outcomes [10,11]. As the only solid organ transplant procedure without surgical connection of all major viable arteries to the allograft, the conducting airways, from the main bronchus to the terminal respiratory bronchioles, in transplanted lung grafts are at risk for complications. Damaged microvasculature and poor perfusion are major determinants of the development of organ graft failure not only in lungs but also in all solid transplanted organs, which all transplant physicians must bear in mind [12].

In this study, the authors eventually conclude that iNO dependency was associated with higher incidences of severe PGD and higher mortality and advocate that iNO dependency is an early sign of PGD suggesting subsequent inferior transplant outcomes. Their ideas of applying iNO for both therapeutic and diagnostic purposes are unique and scientifically rationale; however, one of potential downsides of their idea is that by relying too much on such 'dual' roles of iNO in their protocol, they might miss another effective therapeutic alternatives for severe PGD. One of the complexities in the pathophysiology of PGD is its heterogeneity of the severity and duration inherent within the current graded PGD criteria. Indeed some experts advocate the distinct phenotypes within grade 3 PGD based on the timing of onset and resolution of PGD [13], which may suggest the differences/discrepancies in their response to the treatments including iNO for PGD. Given all together, multiple therapeutic options should lead to optimizing the outcomes while one of such options is V-V ECMO. In their protocol of this study, the option to switch from V-A ECMO to V-V ECMO at the end of the procedure when the patients could not wean from V-A ECMO was not considered. However, while both V-A and V-V ECMO are utilized to allow for recovery of the lung allografts with severe PGD, based on the current literatures, V-V ECMO appears to be more evidence-based first-line treatment for improved survival likely because of the lower frequencies of major neurological complications and sepsis with this strategy [14]. Aside from the ultimate correlation between PGD and BOS, because some severe PGD cases do not necessarily lead to BOS in particular when they have early resolution from PGD, strenuous efforts should be made to change the fate of early detected PGD and improve

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the outcomes by making the best of the most proactive and optimal options.

In conclusion, Fessler *et al.* [4] provide an excellent and useful institutional experience and highlight the challenges encountered in the field. Further studies and research should be encouraged to overcoming the current major limitations in clinical lung transplantation.

Funding

The author has declared no funding.

Conflict of Interest

The author has declared no conflict of interest.

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