Editorial

Primary graft dysfunction in lung transplantation: still a thorn in the side of lung transplant

Kwun Hung Max Wong[1], Kuan Yew Michael Hsin[2]^

[1]Department of Cardiothoracic Surgery, Queen Mary Hospital, Hong Kong, China; [2]Department of Surgery, University of Hong Kong, Hong Kong, China

Correspondence to: Kuan Yew Michael Hsin, MB BChir (Cantab), MD (Cantab), FRCSEd, FRCS (Eng), FCSHK, FHKAM (Surgery). Department of Surgery, University of Hong Kong, 2/F Professorial Block, Queen Mary Hospital, 102 Pok Fu Lam Road, Hong Kong, China.
Email: mkhsin@hotmail.com.

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Lung transplant is the ultimate option for patients with end-stage lung failure who are refractory to medical therapy. The International Society of Heart and Lung Transplantation (ISHLT) reported that in the year 2019, almost 5,000 cases of lung transplants were performed (1). Primary graft dysfunction (PGD) is a clinical syndrome that develops within the first 72 hours after lung transplant that resembles adult respiratory distress syndrome (ARDS). Prior to 2005, PGD was also referred to as ischemia-reperfusion injury, noncardiogenic pulmonary edema, early graft failure, primary nonfunction of the lung, reimplantation oedema, acute lung injury and post-transplant ARDS (2).

PGD is a major cause of early mortality and morbidity and decreased long-term survival following lung transplantation (3,4) with a reported incidence ranging from 10–25% (5,6). Multiple risk factors are known to increase the risk of PGD, such as donor smoking history, donor age, recipient pulmonary arterial hypertension, obesity, use of cardiopulmonary bypass, single lung transplant, higher fraction of inspired oxygen (FiO_2) during reperfusion and prolonged ischemic time (5,7-9).

In 2005, the ISHLT Working Group proposed a standardized grading system for PGD (10). This was based on the evaluation of the partial pressure of arterial oxygen (PaO_2)/FiO_2 (P/F) ratio O_2 and whether there are bilateral infiltrates on chest X-ray. These assessments are carried out at the time-points 6, 24, 48, and 72 hours after the operation. This was subsequently updated in 2016 to address limitations of the original 2005 consensus, and incorporated new parameters, specifically regarding the roles of extracorporeal membrane oxygenation (ECMO), high flow oxygen and pulmonary vasodilators. The absence of pulmonary edema on chest radiograph is classified as PGD 0, regardless of the P/F ratio (11).

The various events involved in lung transplantation from preoperative donor management and procurement, to reperfusion can lead to the development of PGD. These include various insults to the donor lung such as ischemia, microtrauma from handling of the lung during organ explant, method of donor organ preservation, the surgical strategy of organ implantation such as single versus double lung transplant, the use and type of intraoperative circulatory support, and reperfusion. The key pathological hallmarks of PGD are ischemic injury of the pulmonary vasculature, altered permeability of the pulmonary vessels, and diffuse alveolar injury.

^ ORCID: 0000-0001-7006-4382.

The exact pathogenesis of PGD is not fully known, however ischemia reperfusion injury is thought to play a major role. The development of PGD represents an interplay between baseline donor and recipient factors, and a proinflammatory cascade that begins at the time of reperfusion. PGD occurs in two phases: an early phase where donor lung macrophages and lymphocytes play important roles, and a later phase which is regulated by recipient neutrophils and lymphocytes. Proinflammatory factors, including free radicals, reactive oxygen species (ROS), cytokines and neutrophilic inflammation are critical to the development of PGD. The recipient inflammatory environment also plays a crucial role in the development of PGD post-transplant (12).

The development of PGD is associated with poor outcomes. These include prolonged intensive care unit (ICU) stay and mechanical ventilation, and increased use of ECMO. Post lung transplant mortality at 90 day is up to 37%, and at 1 year, is up to 34%. The long-term outcome following lung transplant is also negatively affected by PGD. The reported survival rates are 72.8%, 43.9% and 18.7% at 1, 5 and 10 years postoperatively for patients with PGD. PGD is also linked to chronic lung allograft dysfunction (CLAD), a form of chronic lung rejection. The severity of PGD is directly correlated to an increase in the relative risk of bronchiolitis obliterans syndrome, one of the forms of CLAD (12-14).

In this issue of the journal, Toyoda *et al.* looked at risk factors (donor, recipient or intraoperative) that show an association with mild/moderate or severe PGD (15). Retrospective patient data from a single centre at the Northwestern University Medical Centre of Chicago, Illinois, were collected. Outcomes of 151 consecutive patients undergoing single or bilateral lung transplantation from brain death donors were analysed. They did not include lungs that were assessed by ex vivo lung perfusion (EVLP). Clinical characteristics that were more common in patients who developed PGD grade 3 than those with PGD grade 1 or 2 included younger age, use of preoperative venovenous (V-V) ECMO, aetiology of coronavirus disease 2019 (COVID-19), lower haemoglobin, and higher total bilirubin count.

Compared to patients with PGD grade 0, those with PGD grade 1 to 3 had longer operative times, longer ischemic times and higher intraoperative blood transfusion volumes of packed cells, fresh frozen plasma, and platelets. Patients with PGD grade 1 to 3 were more likely to need venoarterial (VA) ECMO; however, the duration of VA ECMO support did not influence the development of PGD of any grade. Multivariate logistic regression analysis did not find any independent risk factors of PGD grade 3 compared to intraoperative use of VA ECMO as a predictive factor for grade 1 or 2. Comparing PGD grade 0 with PGD grades 1–3, operative time was an independent predictor of the development of PGD, according to univariate and multivariate analysis. Receiver operating characteristic (ROC) curve analysis showed that an operative time of 8.18 hours provided the cut-off value for the development of PGD grade 3, as well as high risk of acute kidney failure, dialysis use, and digital ischemia.

The authors hypothesized that the absence of identifiable independent risk factors for PGD grade 3 can be explained by the low patient numbers compared to number of variables in the cohort. The authors concluded that the risks factors for PGD grade 1 or 2 were similar to PGD grade 3, suggesting that PGD is a constant disease group with common risk factors. The limitations of study include the study design of a single centre retrospective review, with a small cohort and therefore a small event number, thus preventing examination of PGD grades 1 and 2 separately. Long-term postoperative results were not able to be analysed because of the short follow up periods. Because the all-cause mortality was only 25.2%, the authors were unable to examine disease specific mortality.

Some other inherent issues of the current PGD classification, not touched on by Toyoda and colleagues, warrant further elaboration. The Toyoda study looked at the subgroups of PGD 1, 2 and 3. One concern is the potential confounder of radiographic discordance in the assessment of chest radiograph. The grading system of PGD ranges from 0 to 3, based on the presence or absence of infiltrates on chest X-ray and the P/F ratio. According to the 2017 updated ISHLT criteria, in the absence of radiographic infiltrates on chest radiograph, the patient is graded as PGD 0, regardless of the P/F ratio. Theoretically, a patient with a PF ratio of <200 may be classified as either PGD 3, or PGD 0, based on presence or absence of infiltrates of the chest X-ray. However, chest X-ray assessment may be difficult in the early period after lung transplant.

A retrospective study by Schwarz from the Vienna group addressed this issue. They studied whether there was interobserver variability among radiologists on the assessment of chest X-rays after lung transplant, and if variability is present, how this might affect the grading of PGD. Out of 1,988 chest radiographs taken in the early post lung transplant period, full agreement of all the five

participating radiologists was achieved in only 43% of the entire cohort. As a result of the variation in chest X-ray assessment, the rate of PGD grade 3 would vary from 28.4% to 8.4% on arrival in ICU, 4.8% to 1.8% at 24 hours after transplant, 5.3 % to 2% at 48 hours after transplant, and 3.1% to 0.2% at 72 hours after transplant. Increased interobserver variability was associated with recipients with higher body mass index (BMI), and cases of significant donor/recipient size mismatch where lung volume reduction had to be performed on the graft.

In recipients with an increased BMI, the development of atelectasis would be more likely during the weaning of ventilatory support, and the chest radiographic changes might be misinterpreted as lung infiltrates in PGD. Where lung volume reduction was performed in the graft for size mismatch, these are commonly done in the right middle lobe and/or lingula, resulting in lung opacities which may be misinterpreted as lung infiltrates of PGD. The Schwarz study demonstrated significant interobserver variability in chest X-ray interpretation after lung transplant, leading to high variation of PGD grades in the present system of grading.

In theory this could be improved by strict chest X-ray interpretation by experienced clinicians, however this may not be easily put into practice in the real world (16,17).

Another issue worth considering is the construct validity of the current PGD classification in the grading of PGD. The Lung Transplant Outcomes Group (LTOG) investigated whether higher-severity grades of PGD was worthwhile. The authors interrogated the dataset of the LTOG, which is a large, prospectively collected dataset on PGD. They defined an additional 'very severe' PGD with P/F ratio <100, and demonstrated that having this extra subgroup of very severe PGD did not influence the risk of long-term mortality; however, the presence of this extra category might alert clinicians of patients at high risk of early death, and therefore might lead to more aggressive early intervention (18,19).

In recent years, there has been ongoing change in the donor profile. These include increasing donor age, increased utilization of donors with extended donor criteria, the wider adoption of donors after cardiac death. The introduction of normothermic EVLP into clinical practice has substantially increased the donor lung utilization in some experienced centers, by allowing objective evaluation of marginal donor lungs that would have been declined by conventional selection criteria. The Toronto group showed that the use of EVLP has increased the lung transplant volume by 20%. The same group also reported that there was no difference in PGD 3 at 72 hours post-transplant, 30-day mortality and 1-year survival between recipients of the marginal lungs used for transplant after EVLP evaluation and control lungs (20,21). Another EVLP study using a different EVLP platform, the INSPIRE trial, reported that PGD 3 was significantly lower in the EVLP group compared to the cold storage group (17.7% *vs.* 29.7%). Whether the reduced incidence of PGD 3 might lead to earlier recovery and better post-transplant long-term outcomes requires further research (22). The potential of EVLP to recondition donor lungs may be extended to EVLP as platform of therapy, and some preclinical studies have shown promise. Infection of the donor lung is thought to contribute towards PGD (11). Antimicrobial treatment *in vivo* may be limited by the toxicity towards other donor or recipient organs such as the kidney or liver. However, when the donor lung is perfused in isolation during EVLP, supra-therapeutic doses of drug could be administered without any concern regarding injury to other organs (23,24).

One exciting new direction of preclinical lung transplant/EVLP research is the use of cross-circulation to maintain injured donor lungs. Hozain *et al.* from Columbia studied human lungs rejected for clinical lung transplantation, and used EVLP to maintain the lungs while connecting the circuit by cross circulation to anesthetized xenogenic pigs with immunosuppression. They showed that the xenogenic cross circulation platform provided explanted lung grafts a physiologically supportive environment. The authors reported marked improvement in physiological parameters and in the observed areas of damage of the donor lungs after perfusing the grafts for 24 hours. Importantly, they also showed significant improvement of the vascular endothelium, airway and alveolar epithelium, suggesting the presence of repair process. At the same time, the levels of important markers of acute inflammation were attenuated (25). These new areas of research provide a glimpse into possible advanced treatment of donor lungs, which may have important impact on the amelioration of PDG in clinical lung transplantation.

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