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Review

Current Status of Extracorporeal Membrane Oxygenation as a Treatment Strategy for Primary Graft Dysfunction after Lung Transplantation

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Primary graft dysfunction (PGD) is one of the major risk factors affecting patients' short- and long-term survival after lung transplantation. No particular management strategy has been established for PGD; supportive care is the mainstay of PGD treatment. When a supportive strategy fails, the patient may require the introduction of extracorporeal membrane oxygenation (ECMO) as the last-resort measure for severe PGD. A variety of study of ECMO as a PGD treatment was reported and the management of PGD patients developed so far. Early recognition of a patient's need for ECMO and its prompt initiation are critical to improved outcomes. The use of venovenous-ECMO became the preferred procedure for PGD rather than venoarterial-ECMO. However, the current ECMO strategy has limitations, and using ECMO to manage patients with PGD is not sufficiently effective. Further studies are required to develop this promising technology.

Key words: lung transplantation, primary graft dysfunction, extracorporeal membrane oxygenation, *ex vivo* lung perfusion

Primary graft dysfunction (PGD) is one of the major risk factors that affect patients' short- and long-term survival after lung transplantation (LTx). There is currently no consensus regarding the treatment of PGD. However, extracorporeal membrane oxygenation (ECMO), first reported by Glassman in 1995 [1], has been used as one of the several available intervention strategies for severe PGD cases. A variety of ECMO strategies and other perfusion systems have been developed to manage PGD. This review summarizes the current understanding of and evidence regarding PGD and the treatment strategy for PGD, establishing the present status and the potential of ECMO strategies.

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Primary Graft Dysfunction

PGD is a form of acute lung dysfunction that may occur early after LTx. Its clinical features include progressive hypoxemia and pulmonary edema. After the International Society for Heart and Lung Transplantation (ISHLT) consensus definition of PGD was published in 2005, centers around the world began adopting the definition [2]. The reported incidence of grade 3 PGD early after lung transplantation has been ~30% [3-7], and in a more recent multicenter analysis, 25.7% of LTx patients experienced PGD [8] (Table 1).

PGD results from ischemia reperfusion injury. The risk of PGD depends on the severity of ischemic injury, measured as the organ ischemic time [9]. Prolonged

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Table 1 PGD incidence

Authors, year of report	n	Definition	Incidence	Reference
Whitson BA *et al*., 2006	402	grade 3 PGD within 48 h	29.6%	[3]
Kreisel D *et al*., 2011	1,000	PGD of all grade	22.1%	[4]
Diamond JM *et al*., 2013	1,255	grade 3 PGD within 72 h	30.8%	[5]
		grade 3 PGD at 48 or 72 h	16.8%	
Samano MN *et al*., 2014	118	grade 3 PGD at 48 h	19.8%	[6]
		grade 3 PGD at 72 h	15.4%	
Felten ML *et al*., 2012	122	grade 3 PGD at 6 h (patients with cystic fibrosis)	34%	[7]
Cantu E *et al*., 2022	1,528	grade 3 PGD at 48 or 72 h	25.7%	[8]

PGD, primary graft dysfunction.

ischemic times are associated with the post-operative extracorporeal life support (ECLS) for grade 3 PGD [10]. PGD is also driven by both recipient and donor characteristics [9].

PGD is a major cause of early post-transplant morbidity and mortality. In a retrospective report, PGD was associated with lower survival at 1, 5, and 10 years (PGD: 72.8%, 43.9%, and 18.7%; no PGD: 87.1%, 59.8%, and 35.7%, respectively) [4]. PGD accounts for 50% of all-cause mortality in the first 30 days after LTx [11]. In addition, PGD is associated with both early mortality and late complications. Even if patients survive PGD over the short term, they have an increased risk of chronic lung allograft dysfunction (CLAD), decreased quality of life, and a significantly increased risk of death [12]. CLAD is a major determinant of long-term outcomes after LTx. Chronic inflammation and cell death induced by PGD can contribute to the development of CLAD [13]. PGD that develops within the first 72 h post-transplantation is a risk factor for the development of a predominant type of CLAD, *i.e.*, bronchiolitis obliterans syndrome (BOS) and shortened BOS-free survival [14-16].

The Definition and Classification of PGD

The ISHLT defined PGD in 2005, and in 2016 the classification system was updated. The criteria for the definition of PGD are (*i*) pulmonary edema on chest X-ray and (*ii*) a decreased ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (FiO_2) (*i.e.*, the P/F ratio), within the first 72 h post-transplantation [17]. The diagnosis of PGD requires the exclusion of mechanical, immune, and infectious causes of a patient's hypoxemia.

The PGD grading system is also based on chest radiographs and the P/F ratio, which is ideally measured with a positive end-expiratory pressure of 5 cmH_2O at a FiO_2 value of 1.0. All post-transplant patients receive a PGD grade, and the severity of PGD is graded from 0 to 3 (mildest to most severe). Patients with radiographic lung infiltrates and a P/F ratio < 200 are defined as having grade 3 PGD (Table 2). Patients with opacities on chest radiography while on ECLS are automatically classified as having grade 3 PGD [9]. A multicenter study conducted in the United States reported that among patients with grade 3 PGD at 48 or 72 h after LTx, the 90-day and 1-year mortality rates were 23% and 34%, respectively [5].

PGD Treatment Strategies

No particular management strategy has been established for PGD, and supportive care is the mainstay of PGD treatment. PGD has many features in common with those of acute respiratory distress syndrome (ARDS), and the majority of the care strategy for PGD is based on the evidence obtained regarding ARDS. Use of low tidal volume ventilation and a restrictive fluid strategy is adopted as lung-protective strategy. As with ARDS, protecting a PGD patient's allograft from the

Table 2 Classification of PGD (A 2016 ISHLT consensus statement)

PGD grade	Pulmonary edema on chest X-ray	P/F ratio
grade 0	No	Any
grade 1	Yes	> 300
grade 2	Yes	200 to 300
grade 3	Yes	< 200

ISHLT, International Society for Heart and Lung Transplantation; P/F ratio, partial pressure of arterial oxygen to fraction of inspired oxygen ratio; PGD, primary graft dysfunction.

volutrauma and barotrauma that are associated with mechanical ventilation and oxidative stress allows the injured lungs time to rest and recover from the PGD [9, 18].

There is increasing evidence of benefits of low tidal volume ventilation even in patients without ARDS [19]. A fluid-restrictive management strategy may be also useful in limiting pulmonary edema [20] because transplanted lungs have varying degrees of pulmonary edema as a result of increased vascular permeability and reduced lymphatic drainage [21]. The provision of inhaled nitric oxide (iNO) is also used as supportive care. Administering iNO might be useful for reducing pulmonary vasoconstriction and enhancing ventilation-perfusion matching. Early patient mobilization and the treatment of underlying infection are also important [13].

However, when a supportive strategy for a patient with PGD fails, the patient may require the initiation of ECMO to provide cardiopulmonary support. The general indication for ECMO in a patient with PGD is severe hypoxemia (P/F ratio < 100) that is not responsive to pulmonary vasodilation, with or without hypercapnia, acidosis, and right ventricular dysfunction [22]. ECMO can manage a patient's hypoxemia and give an injured graft the chance to rest and recover at the same time.

Most transplant centers tailor their therapies for PGD based on extrapolated treatments of ARDS [5, 11]. Data from the use of ECMO in patients with severe PGD have been reported [23-25]. For example, a 2007 review of studies of ECMO use for PGD after LTx in recipients who were part of the Extracorporeal Life Support Organization revealed that ECMO was discontinued in 93 of 151 patients due to lung recovery; 63 of these patients survived the hospital stay [23]. Recent technological advancements have improved the safety and efficacy of ECMO, further solidifying its role in LTx [26]. Although no PGD-specific therapy exists at this time, supportive care remains paramount, and the initiation of ECMO can improve outcomes in select patients [13] (Table 3).

The Efficacy of the Early Initiation of ECMO for PGD Management

An early initiation of ECMO can limit the extent of ventilator-induced allograft injury by reducing the patient's barotrauma and exposure to oxygen free radicals [9]. Early initiation can also help avoid prolonged sedation and the use of a neuromuscular blockade [20], and these merits have the potential to improve the outcomes of PGD patients. The use of ECMO for PGD was first reported in 1995 by Glassman [1], who also stated that an early initiation of ECMO, *i.e.*, within 7 days of transplantation, would improve recipients' outcomes.

Studies published after Glassman's 1995 report also showed that an early initiation of ECMO is associated with better survival for PGD patients. Meyers and colleagues described their experience with ECMO for PGD, and they concluded that an early institution of ECMO increases the likelihood of success; all seven survivors among their study's 12 patients had begun receiving ECMO support by post-transplantation day 1 [27]. Wigfield *et al.* described their investigation of patients with severe PGD, some of whom received ECMO within 24 h after LTx and others whose ECMO treatment was introduced > 24 h after LTx [28]. Those authors observed that the early-ECMO group had improved outcomes (49% 5-year survival; 100% mortality in the late-ECMO group). Harano and colleagues reported that a > 48-h length of time post-transplant before the initiation of ECMO for refractory PGD was independently associated with worse outcomes [29]. They also reported that when patients were placed on ECMO > 48 h after LTx, the patients had a significantly higher in-house mortality rate (hazard ratio [HR] 2.79, $p = 0.016$), a significantly higher 1-year mortality rate (HR 2.72, $p = 0.013$), and a significantly higher 3-year mortality rate (HR 2.30, $p = 0.022$) regardless of the patients' preoperative conditions or complexity of LTx.

In each of the studies mentioned above [27-29], a delayed initiation of ECMO after transplantation was associated with higher mortality rates, which suggests that the early recognition of a patient's need for ECMO is important toward the goal of improved outcomes. The introduction of ECMO should be considered early, *i.e.*, before the volutrauma and barotrauma associated with mechanical ventilation and oxidative stress are observed.

Which ECMO Strategy Is Preferred: Venoarterial or Venovenous ECMO?

As mentioned above, transplanted lungs have varying degrees of pulmonary edema as a result of increased vascular permeability. In this situation, offloading the patient's pulmonary circulation has seemed advanta-

Table 3 Transition of ECMO survival rate

Authors, year of report	Population, n	Article type	Type of ECMO	Outcomes	Reference
Hartwig MG *et al*., 2005	Patients requiring post-LTx ECMO, n=23 (VA-ECMO: 15, VV-ECMO: 8)	Retrospective single institution analysis	VA-ECMO VV-ECMO	30-day graft survival: 0% 30-day graft survival: 88%	[35]
Wigfield CH *et al*., 2007	Patients requiring post-LTx ECMO, n=22	Retrospective single institution analysis	All	30-day survival: 74.6% 1-year survival: 54% 3-year survival: 36%	[28]
Fischer S *et al*., 2007	Patients requiring post-LTx ECMO, n=151	Review of Extracorporeal Life Support Organization (ELSO) registry	All	hospital stay survival: 42%	[23]
Bermudez CA *et al*., 2009	Patients requiring post-LTx ECMO, n=58 (VA-ECMO: 26, VV-ECMO: 32)	Retrospective single institution analysis	All VA-ECMO VV-ECMO	30-day survival: 56% 1-year survival: 40% 5-year survival: 25% 30-day survival: 58% 1-year survival: 42% 5-year survival: 29% 30-day survival: 55% 1-year survival: 39% 5-year survival: 22%	[24]
Hartwig MG *et al*., 2012	Patients requiring post-LTx VV-ECMO, n=28	Retrospective single institution analysis	VV-ECMO	30-day survival: 82% 1-year survival: 64% 5-year survival: 49%	[25]
Mulvihill MS *et al*., 2017	Patients requiring post-LTx ECMO, n=107	Review of United Network for Organ Sharing (UNOS) registry	All	6-month survival: 62.2%.	[10]
Bellier J *et al*., 2019	Patients requiring post-LTx VA-ECMO, n=24	Retrospective single institution analysis	VA-ECMO	3-month survival: 50%	[33]
Harano T *et al*., 2021	Patients requiring post-LTx ECMO, n=52	Retrospective single institution analysis	All	90-day survival: 67.3% 1-year survival: 50.0% 5-year survival: 31.5%	[29]
Takahashi T *et al*., 2023	Patients requiring post-LTx ECMO for grade 3 PGD, n=38 (VA-ECMO: 13, VV-ECMO: 25)	Retrospective single institution analysis	All VA-ECMO VV-ECMO	30-day survival: 84.2% 1-year survival: 73.7% 30-day survival: 61.5% 1-year survival: 53.8% 30-day survival: 96.0% 1-year survival: 84.0%	[36]

ECMO, extracorporeal membrane oxygenation; VA-ECMO, venoarterial-extracorporeal membrane oxygenation; VV-ECMO, venovenous-extracorporeal membrane oxygenation.

geous in the management of PGD, and venoarterial (VA)-ECMO might thus be preferred. Although VA-ECMO may be required in cases of severe hemodynamic instability, some transplantation centers favor its use even in patients without hemodynamic compromise [30]. However, the question of whether VA-ECMO can protect injured lungs better than venovenous (VV)-ECMO is a topic of continued controversy.

VV-ECMO is commonly employed for patients with hypercapnic or hypoxic respiratory failure. In the absence of hemodynamic instability, VV-ECMO is considered a bridge to recovery from PGD [9]. VA-ECMO, on the other hand, is extended to the post-operative setting to support graft recovery, hemodynamics, and RV unloading in patients with hemodynamic instability and/or right ventricular (RV) dysfunction [9]. Unlike VA-ECMO, under VV-ECMO the lungs receive full cardiac output. In a 2017 registry study, Mulvihill and colleagues reported the outcomes of patients who required post-LTx ECMO, but they did not describe the VA-ECMO and VV-ECMO cases separately [10].

In their investigation of VA-ECMO, Tudorache *et al*. considered the post-transplant prophylactic extension of VA-ECMO for pulmonary arterial hypertension (PAH) [31]. They noted that all of the following parameters were significantly shorter in the group of patients who had VA-ECMO extended post-operatively: the duration of mechanical ventilation ($p<0.0001$), the length of stay in the intensive care unit (ICU) ($p=0.0005$), and the total length of stay post-transplantation ($p=0.0023$). The Vienna Lung Transplant Group also uses extended VA-ECMO in the post-operative setting for a period of hours to days in order to facilitate a prolonged and controlled reperfusion of the allograft, following the criteria of ECMO prolongation [32]. Bellier and colleagues compared the cases of patients with grade 3 PGD who did not receive ECMO support (conventional treatment) and those who required VA-ECMO support [33]. Although the 3-month mor-

tality of the VA-ECMO group was increased, their long-term survival was similar to that of the conventional treatment group, and the use of VA-ECMO was not associated with the occurrence of CLAD in their series. They concluded that VA-ECMO appears to be suitable for the management of PGD after LTx.

VV-ECMO is generally the preferred strategy for PGD patients without hemodynamic dysfunction. There are several advantages to using VV-ECMO; the cannulation is less prone to local vascular complications, anticoagulation can be tempered with less concern for hemorrhagic or neurologic complications, and the lungs themselves continue to receive oxygenated blood, a factor that may be particularly important to the fresh bronchial anastomoses [30]. VV-ECMO can maintain the physiologic direction of a well-oxygenated, pulsatile blood flow through the pulmonary vascular bed, allowing the lung parenchyma time to recover from hypoxic and ischemic insults [34]. In addition, the correction of hypoxemia and acidosis with VV-ECMO and pulmonary vasodilation due to oxygenated blood perfusing the lungs often leads to rapid hemodynamic improvement, which nullifies the need for VA-ECMO [22].

It has been reported that VV-ECMO decreased patients' pulmonary artery pressure (PAP) values, with an average PAP decrease of 20 mmHg after the initiation of VV-ECMO [22]. In fact, the Duke Group recommends the use of VV-ECMO even when early right-heart dysfunction or a PAP elevation is observed, because improving the gas exchange will resolve pulmonary vasoconstriction [25]. One exception is in patients with primary PAH; for them, VA or veno-venoarterial (V-VA) hybrid ECMO is often extended to the post-transplant period in order to protect the left ventricle from overflow and the subsequent cardiogenic pulmonary edema [22].

No randomized controlled trials of VA- vs. VV-ECMO strategies for PGD have been performed. However, in this era, the majority of the applications of post-transplant ECMO support is VV-ECMO rather than VA-ECMO, which was preferably used before the early 2000s [29]. After Hartwig *et al.*'s retrospective study demonstrated that VV-ECMO provides better outcomes with fewer complications than VA-ECMO [35], VV-ECMO became the preferred procedure for treating PGD. Hartwig *et al.* later reported that successful weaning of VV-ECMO occurred in 96% of their patients (survival rates: 30 days, 82%; 1 year, 64%; and 5 years, 49%). They concluded that advances in ECMO technology, particularly those concerning VV-ECMO, have greatly improved the ability to support patients with severe PGD [25].

In a more recent report, Takahashi and colleagues assessed the outcomes of PGD patients, and they observed that the patients who required VA-ECMO support for grade 3 PGD had significantly worse survival compared to both those who required VV-ECMO support and those who did not require ECMO [36]. The 30-day survival for the patients with ECMO support was 84.2% (VA-ECMO group, 61.5%; VV-ECMO group, 96.0%) compared to 99.4% for the patients who did not require ECMO, and their 1-year survival rate was 73.7% (VA-ECMO group, 53.8%; VV-ECMO group, 84.0%) compared to 93.9% for the patients who did not require ECMO. It should be noted that although patients treated with VA-ECMO might be more compromised by underlying conditions than patients treated with VV-ECMO and the existence of this selection bias must be recognized, the above-cited reports suggest that VA-ECMO treatment for PGD can be used as a risk factor for predicting mortality.

The risks and benefits of VA-ECMO and VV-ECMO must therefore be balanced [22]. Bermudez *et al.* reported that the 30-day survival rate of their patients treated with ECMO was 56% (VA-ECMO, 58%; VV-ECMO, 55%), the 1-year survival was 40% (VA-ECMO, 42%; VV-ECMO, 39%), and the 5-year survival was 25% (VA-ECMO, 29%; VV-ECMO, 22%) [24]. The 30-day graft survival rate was 88% in the VV-ECMO group in a study by Hartwig *et al.*, whereas there was no 30-day graft survival in the study's VA-ECMO group [35]. The differences in these studies' results are likely to be related to (*i*) the improved experience in the management of critically ill patients requiring ECMO support over time, (*ii*) the more recent era of transplantation, and/or (*iii*) recent advances in ECMO support, such as the development of the polymethyl pentene oxygenator, the use of heparin-coated circuits, and the use of centrifugal pumps [36]. In addition, VA-ECMO has the following disadvantages. The reduction of pulmonary perfusion that can occur with VA-ECMO may increase bronchial complications, as bronchial vascularization is dependent on the pulmonary flow in the early post-transplant period. VA-ECMO is also associated with increased vascular

complications from the arterial puncture site, increased neurologic complications, and the need for anti-coagulation [22].

In the present era, VV-ECMO is thus the preferred strategy of choice for patients with severe PGD requiring extracorporeal life support, and its use is increasing.

The Extension of ECMO Use, ECMO Limitations, and Another New Strategy for PGD

The use of ECMO in the LTx field has expanded in parallel with the recent improvements in ECMO technology. Several research groups have recently delved into the potential advantages of intra-operative ECMO. ECMO was examined in conjunction with cardiopulmonary bypass (CPB), revealing fewer complications in the patients who received ECMO [37]. Machuca and colleagues reported that the mechanical ventilation requirement, the length of ICU stay, and the length of hospital stay were all significantly better in their patients treated with ECMO ($p=0.005$, $p=0.026$, $p=0.029$, respectively), and the 90-day mortality for the ECMO group was 6% vs. 15% for CPB [38].

The ECMO group in a study reported by Biscotti *et al.* required fewer transfusions and had less bleeding, fewer reoperations, and less severe PGD than the CPB group [39]. The CPB group had significantly higher rates of PGD at 24 and 72 h (74.5% vs. 48.9%, $p=0.008$; 76.4% vs. 56.5%, $p=0.034$, respectively). A comparison of off-pump, ECMO, and CPB LTx cases by Loor *et al.* revealed that the rates of grade 3 PGD rates during the 48- to 72-h post-transplant period were 12.1% for off-pump, 28.9% for ECMO, and 42.7% for CPB [40], and thus ECMO was associated with a greater risk of grade 3 PGD compared to off-pump transplantation but a lower risk compared to CPB.

For these reasons, ECMO has replaced CPB in most centers as the intraoperative support strategy of choice during LTx surgery. VA-ECMO in particular is increasingly used at high-volume centers to support complex transplant recipients [40]. A routine use of intra-operative ECMO in LTx cases allows controlled reperfusion and protective ventilation of the graft while reducing the risk of ischemia-reperfusion injury and improving post-operative PGD rates [37]. However, the benefits of CPB have been highlighted in reports emphasizing its superior cardiac drainage, which provides a better surgical field, and its maximization of patient outcomes through more precise controlled reperfusion, ultimately leading to favorable post-lung transplant results [41]. There are no randomized studies comparing ECMO and CPB for intraoperative circulatory support, and the choice between these procedures is currently based on institutional preferences and the surgeon's discretion in each case.

As noted above, as an extension use of ECMO, some centers have advanced the concept further to leave patients on ECMO for a period of recovery. Li *et al.* compared groups of patients who underwent immediate VV-ECMO weaning and patients who underwent delayed VV-ECMO weaning, and the comparison demonstrated that delayed weaning was associated with a significantly shorter hospital stay ($p<0.05$), a significantly lower incidence of PGD (6.4% vs. 29.3%, $p<0.05$), and a significantly lower rate of respiratory failure ($p<0.05$) [42]. Multivariable logistic regressions in that study revealed that VV-ECMO weaning after LTx was independently and significantly correlated with an increased risk of developing PGD (odds ratio [OR] 5.97, $p=0.033$) compared to delayed VV-ECMO weaning. The study's authors concluded that delayed VV-ECMO after LTx can facilitate the patients' rehabilitation.

However, the uses of ECMO strategies to manage PGD have some limitations to consider. An evaluation of the use of ECMO after LTx in the patient cases enrolled in the United Network for Organ Sharing registry conducted by the Duke Group revealed a 6-month survival rate at 62% [12]. A recent single-institution analysis of patients requiring ECMO after their lung transplantation obtained the following survival rates: 90-days, 67.3%; 1-year, 50%; and 5-years, 31.5% [13]. In another investigation, the post-transplant maximum forced expiratory volume in one second (FEV_1) was significantly worse in the patients who required ECMO compared to those who did not (peak FEV_1: 58% in ECMO vs. 83% in non-ECMO, $p=0.001$) [25]. Takahashi and colleagues reported that their patients who required ECMO for grade 3 PGD after LTx were significantly more likely to have perioperative complications compared to their grade 3 PGD patients who did not require ECMO support, and the patients who required ECMO support had worse survival compared to those who did not [36]. It thus appears that PGD patients requiring ECMO still have worse outcomes than patients without the need for ECMO.

A very important intervention is the prevention of PGD. *Ex vivo* lung perfusion (EVLP) is one of the new

modalities designed to prevent PGD. Initial success with EVLP platforms has been observed with respect to decreasing the PGD risk and increasing the lung transplant volume; however, the precise impact of EVLP on patients' survival is not yet known [13]. EVLP is a promising technology that may address many shortcomings of traditional lung donation, including the low overall utilization rates of available donor lungs [43]. The data regarding PGD are less clear: in the largest cohort study conducted to date, there was no significant difference in the incidence of severe PGD at 72 h between EVLP-treated and control lungs [44]. However, more recent studies showed decreased PGD rates by EVLP use compared to traditional cold storage (17.7% vs. 29.7%) [45]. The use of EVLP prior to transplantation was also associated with a significantly decreased likelihood of the development of grade 3 PGD (OR 0.70, $p < 0.001$) [46]. Although the available data suggest that EVLP might decrease the PGD rate, it has been observed that the short- and long-term survival and functional outcomes of cases in which EVLP was administered are similar to those provided by traditional transplantation [13]. Long-term follow ups are necessary to clarify the effectiveness of EVLP in patients with PGD.

Other strategies to treat PGD were recently proposed. In 2023, Lindstedt *et al.* investigated the possibility of cytokine filtration [47]. Cytokines play a critical role in initiating, amplifying, and maintaining the inflammation that leads to PGD. In a preclinical porcine model of LTx, cytokine filtration was observed to have the ability to improve oxygenation and decrease the likelihood of the development of PGD [48]. And they are now conducting clinical trial comparing cytokine filtration after LTx with a standard treatment with no cytokine filtration to evaluate the efficacy of cytokine filtration for improving LTx outcomes, including the incidence and severity of PGD [47].

As the Okayama Group, we have also suggested a new strategy for PGD based on our 2024 pre-clinical study [49]: *in vivo* lung perfusion (IVLP). The role of EVLP is currently limited to pre-transplant settings, and we established an isolated circuit for injured grafts after implantation, as a technique in which an EVLP rig is applied *in vivo*. We explored the effectiveness of treatment with IVLP by using an experimental swine LTx PGD model, and we observed that the use of IVLP resulted in marked improvement in transplanted lung functions, *i.e.*, oxygenation, airway compliance, and pathological status. Each of the above-described strategies may be effective methods for the management PGD. Further studies are required prior to the new strategies' applications in clinical settings, however (Table 4).

Table 4 Comparative summary of PGD management strategy

Intervention	Strategy	Advantage	Points of attention
ECMO	Postoperative treatment of PGD	Managing hypoxemia providing cardiopulomonary support	PGD patients requiring ECMO still have worse outcome than patients without the need for ECMO.
VV-ECMO		Less local vascular complications Less hemorrhagic or neurologic complications Pulmonary cicuration with oxygenated blood (that may be important to the fresh bronchial anastomoses, and often leads to rapid hemodynamic improvement)	Lungs receiving full cardiac output Difficult to use for patients with primary PAH
VA-ECMO		Offloading the pulmonary circulation Possible to use for patients with primary PAH to protect the left ventricle from over flow	Bronchial complications Vascular complications from the arterial puncture site Neurologic complications Need for anti-coagulation
New PGD management strategies			
EVLP	Preoperative prevention of PGD	Decreasing PGD risk Decreasing likelihood of PGD grade 3 development Increasing lung transplant volume	Limited to pre-transplant situation Similar of survival and functional outcomes to traditional transplantation in short- and long-term
IVLP	Postoperative treatment of PGD	Enable to apply EVLP rig to in vivo even after grafts implanted Recovering lung function	Still pre-clinical [49]
Cytokine filtration	Postoperative treatment to decrease PGD	Reducing inflammation Improving lung function Reducing the incidence of PGD	Now conducting clinical trial [47]

ECMO, extracorporeal membrane oxygenation; EVLP, *ex vivo* lung perfusion; IVLP, *in vivo* lung perfusion; PAH, pulmonary arterial hypertension; PGD, primary graft dysfunction; -VA-ECMO, venoarterial-extracorporeal membrane oxygenation; VV-ECMO, venovenous-extracorporeal membrane oxygenation.

Conclusion

ECMO (extracorporeal membrane oxygenation) is accepted as a major tool for treating severe PGD (primary graft dysfunction). An early recognition of PGD and early initiation of ECMO are likely to be beneficial. The use of venovenous (VV)-ECMO has become the preferred procedure for PGD rather than venoarterial (VA)-ECMO, but the currently available ECMO strategies are not sufficiently effective for the treatment of PGD, and further studies are required to develop this promising technology or new alternative strategies.

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