Défaillance primaire du greffon (DPG)

F Parquin
USIR
Hôpital Foch
Suresnes

DPG

- Principale complication précoce post TP dans les 72 h (saignement exclu)
- Gravité très variable
- Oedème pulmonaire clinique, hypoxémie et opacités pulmonaires alvéolaires diffuses
- En rapport avec Ischémie reperfusion

Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part II: Definition. A Consensus Statement of the International Society for Heart and Lung Transplantation

Table 1 2005 ISHLT primary graft dysfunction taxonomy

Grade at T0, T24, T48, T72	Radiographic infiltrates consistent with diffuse pulmonary edema	PaO_2:FiO_2	Specific exceptions
0	–	Any	
1	+	> 300	On nasal cannula or $FiO_2 < 0.3$
2	+	200–300	
3	+	< 200	Any patients on ECMO or on NO with $FiO_2 > 0.5$ MV

Abbreviations: ECMO, extracorporeal membrane oxygenation support; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; ISHLT, International Society of Heart Lung Transplantation; MV, mechanical ventilator; NO, nitric oxide; PaO_2, partial arterial oxygen tension (mmHg); PEEP, positive end expiratory pressure.
Source: Adapted from reference 1.
T0 is defined as within 6 hours of final lung reperfusion or at the admission to the ICU.
Patients are not considered having primary graft dysfunction without radiographic infiltrates.
PaO_2:FiO_2 should ideally be measured on PEEP of 5 cm H_2O at FiO_2 of 1.0 while patients are on MV.

Exclusion criteria
• Cardiogenic pulmonary edema • Pneumonia and aspiration • Hyperacute rejection • Pulmonary venous anastomotic obstruction
Limitations
• Exclusion pathology can be missed clinically • Exclusion pathology can exist at the same time • Interobserver reliability of CXR reading • Variability in clinical settings and conditions – Single vs bilateral LTXP – Patients intubated vs. extubated – Extubated on oxygen mask vs. on CPAP – Arterial line removed, no P/F ratio available – Mode of ventilation and ventilator settings – Changes in cardiac output – Multiple blood gasses close to the time point[a]

Trali, TACO

Incidence

DPG 3 : 16,8 % H48 ou H72

DPG 3 : 30,8 %H0-H72

(Diamond AJRCCM 2013)

Pathogénie complexe et non encore bien élucidée

Nombreux travaux en cours !

Table 2

Human translational studies exploring the pathogenesis of PGD

Pathway	Human translational studies
Epithelial cell injury	Higher blood and BAL levels of *RAGE* were associated with PGD
	Preexisting or de novo antibodies against type V collagen were associated with lower P/F ratio and PGD
	Elevated levels of CC16 were associated with higher odds of PGD
	Higher donor levels of HMGB1 correlated with lower P/F before and after transplantation.
Endothelial dysfunction	Grade 3 PGD was associated with higher VEGF levels than lower grades of PGD
	Increased pretransplant endothelin-1 levels were associated with PGD
	Angiopoietin-2 levels were elevated in PGD
Chemotaxis and cytokines	Higher plasma levels of MCP-1, IP-10, and IL-2R were associated with PGD
	Elevated serum IL-8 levels were associated with PGD
	Higher blood and BAL levels of IL-6 were associated with grade 3 PGD
Innate immunity	Upregulation in the expression of genes involved in inflammasome and TLR pathways were found in BAL of patients with grade 3 PGD
	TLR4 mutations associated with innate immune hyporesponsiveness were associated with a lower PGD risk
	Higher plasma *PTX3* levels were seen in those with grade 3 PGD
	Single nucleotide polymorphisms associated with higher levels of *PTX3* were associated with grade 3 PGD
	Innate lymphoid cells were isolated from BAL of lung transplant recipients

Diamond AJT 2017 epub
Porteus Curr Opin Organ Transplant 2015

Facteurs de risque

Table 4 Clinical risk factors for PGD

Category	Risk factors for PGD
Donor-inherent variables	Age > 45 y, age < 21 y African American race Female gender **History of smoking** > 20 py, > 10 py, current, **any**
Donor-acquired variables	Prolonged mechanical ventilation Aspiration Head trauma Hemodynamic instability after brain death
Recipient variables	**Obesity body mass index > 25** Female gender **Diagnosis of idiopathic pulmonary hypertension** Diagnosis of secondary pulmonary hypertension Diagnosis of idiopathic pulmonary fibrosis **Diagnosis of sarcoidosis** **Elevated pulmonary arterial pressure at time of surgery**
Operative variables	**Single-lung transplantation** Prolonged ischemic time **Use of cardiopulmonary bypass** **Blood products transfusion > 1 L** **High FiO2 > = 0.4 at reperfusion** Use of intracellular (hyperkalemic) type (Euro-Collins) preservation solution

Abbreviations: FiO_2, fraction of inspired oxygen; LTOG, Lung Transplant Outcomes Group; PGD, primary graft dysfunction; py, pack-year; UNOS, United Network of Organ Sharing.
Source: Adapted from references 5,16,29,39–41.
Note: Boldface within table represents independent risk factors for PGD in LTOG multicenter study.[29]

Pronostic

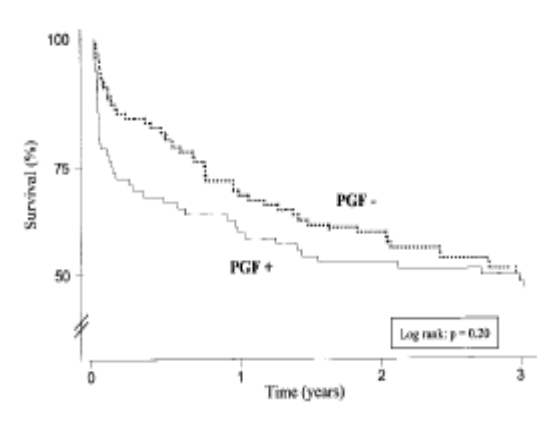


Table 3—*Relationship Between Severity of Hemodynamic Failure and Gas Exchange**

Hemodynamic Failures	Worst PaO_2/FIO_2 Ratio
None (n = 61)	152.5 ± 60.8†‡
Moderate (n = 31)	119.1 ± 63.9§
Severe (n = 39)	74.2 ± 38.8

*Data are provided as mean ± SD. Comparison of the three means by analysis of variance yields p = 0.01.
†p = 0.045, none vs moderate.
‡p < 0.001, none vs severe.
§p < 0.009, moderate vs severe.

Table 4—*Multiple Logistic Regression Model With OR for ICU Mortality**

Variables	OR	95% CI	p Value
Graft ischemic time, by 2-h increase above 2 h	2.6	1.1–6.4	0.03
Age, per 10-yr increase above 20 yr old	2.5	1.2–5.3	0.01
PaO_2/FIO_2 ratio, per 50-point decrease under 250 points	5.3	1.9–14.3	0.001
Severe EHF	6.1	1.2–32.3	0.03

*CI = confidence interval.

(Thabut Chest 2002)

TABLE 3. UNADJUSTED ASSOCIATION OF GRADE 3 PGD AT 48 OR 72 HOURS WITH 90-DAY AND 1-YEAR MORTALITY

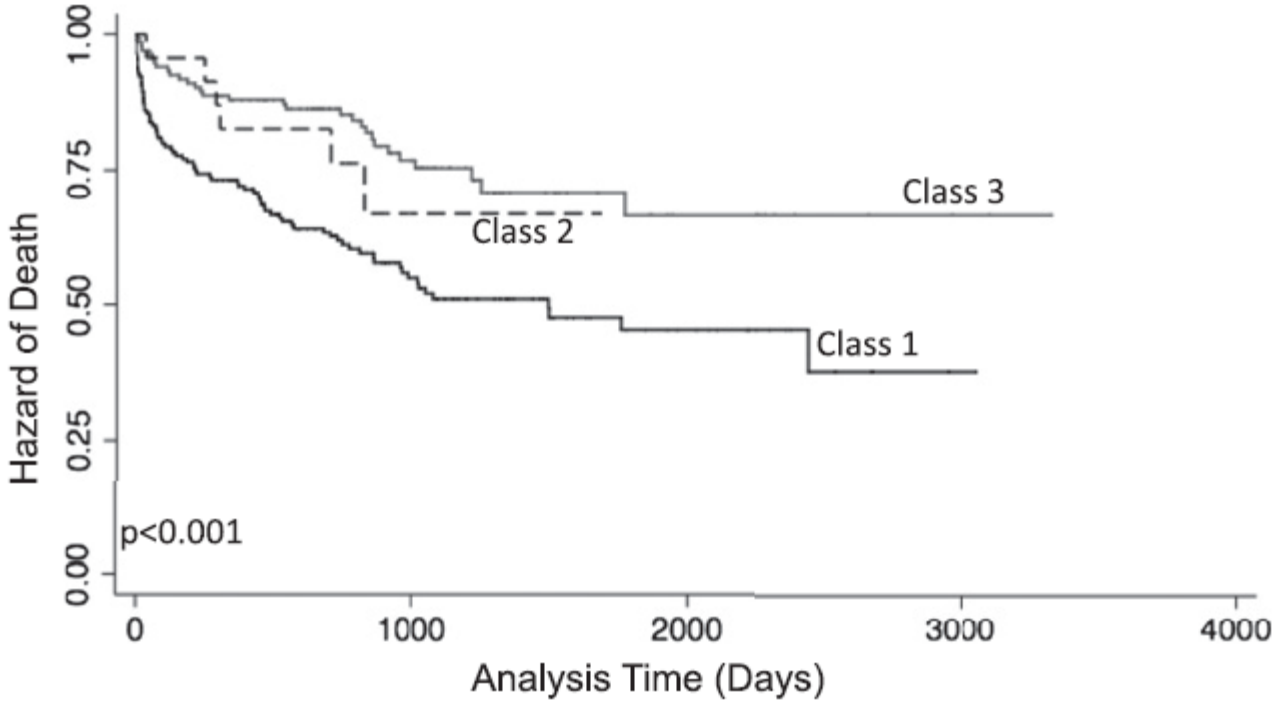
Outcome	Risk in Those with PGD	Risk in Those without PGD	Risk Ratio (95% CI)	Risk Difference (95% CI)	*P* Value
90-d mortality	23%	5%	4.8 (3.3–7.0)	18% (12–24)	<0.001
1-yr mortality	34%	11%	3.0 (2.3–3.9)	22% (15–30)	<0.001

Definition of abbreviations: CI = confidence interval; PGD = primary graft dysfunction.

Diamond AJRCCM 2013

Différents profils associés à des pronostics différents

(Shah Chest 2013)



1 défaillance sévère persistante
2 résolution complète en 72 h
3 amélioration partielle à 72 h

A court terme

- Augmentation durée de ventilation
  - PAVM : faire des prélèvements à visée bactério réguliers
  - Evolution lente discuter corticoides type Meduri (SDRA) en l'absence d'infection er de rejet
- Augmentation durée de séjour en réanimation
- Augmentation durée de séjour hospitalier

Traitement

- Symptomatique
  - Oxygénothérapie haut débit, VNI
  - Ventilation mécanique protectrice
  - NO si HTAP
  - « Versant sec » dés que possible
- Propositions nombreuses
  - NO inhalé
  - Nac
  - C1Inh
  - Surfactant….
- Prévention
  - Statines ….

Late Primary Graft Dysfunction After Lung Transplantation and Bronchiolitis Obliterans Syndrome

American Journal of Transplantation 2008; 8: 2454–2462

Table 4: Multivariable Cox proportional hazards models of risk factors for BOS stage including PGD graded at 72 h

	BOS stage 1		BOS stage 2		BOS stage 3	
Variable	RR (95% CI)	p-Value	RR (95% CI)	p-Value	RR (95% CI)	p-Value
Acute rejection grade ≥ A2	1.50 (1.07–2.09)	0.018	1.50 (1.01–2.26)	0.045	1.55 (1.01–2.15)	0.048
Lymphocytic bronchitis ≥ B2	1.58 (1.11–2.24)	0.01	1.48 (0.98–2.26)	0.06	1.54 (0.94–2.51)	0.078
CARV infection[1]	1.64 (0.98–2.74)	0.06	2.06 (1.16–3.65)	0.013	1.93 (1.01–3.71)	0.047
PGD at T72		<0.0005		<0.0005		0.001
PGD 0 (reference)	1.00		1.00		1.00	
PGD 1	2.07 (1.28–3.34)	0.003	2.40 (1.27–4.53)	0.007	3.02 (1.29–7.03)	0.01
PGD 2	2.81 (1.42–5.59)	0.003	3.68 (1.55–8.71)	0.003	4.72 (1.58–14.1)	0.006
PGD 3	4.25 (2.15–8.41)	<0.0005	7.24 (3.19–16.4)	<0.0005	7.99 (2.86–22.3)	0.0005

[1]Time-dependent variable.
BOS stage 1 model chi-square = 43.73, $p < 0.0005$.

Formes graves : ECMO

Early Institution of Extracorporeal Membrane Oxygenation for Primary Graft Dysfunction After Lung Transplantation Improves Outcome

Christopher H. Wigfield, MD, FRCS,[a] Joshua D. Lindsey, MBS,[a] Thomas G. Steffens, CCP,[a]

[redacted] Thirty-day, 1-year and 3-year survival of LTx recipients with ECMO support post-operatively were 74.6%, 54% and 36%, respectively. MOF was the predominant cause of death (58.3%) in patients on ECMO support for PGD.

Institutional experience with extracorporeal membrane oxygenation in lung transplantation☆

European Journal of Cardio-thoracic Surgery 31 (2007) 468–474

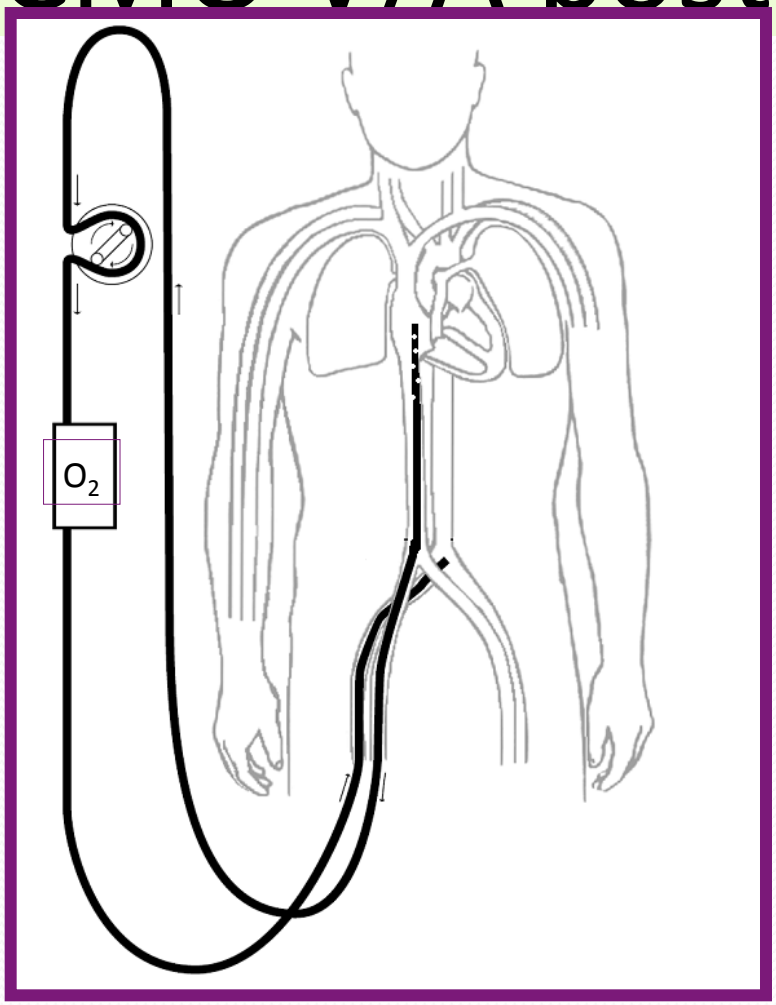
Extracorporeal membrane oxygenation post lung transplantation

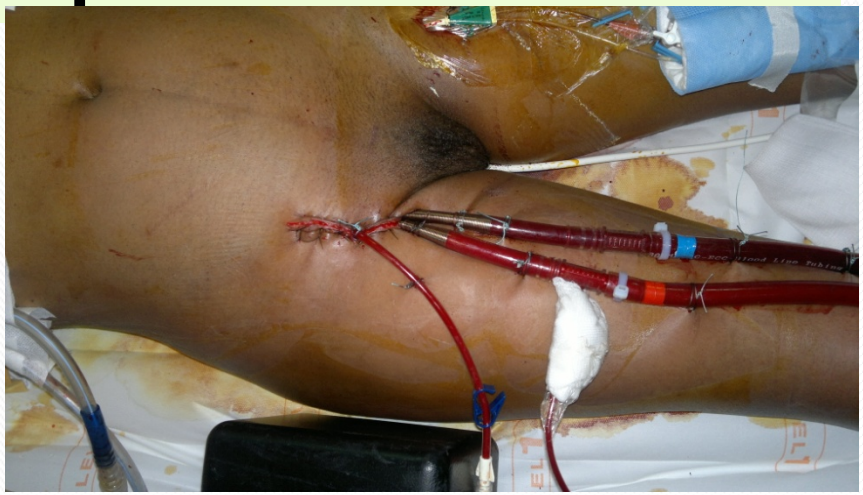
Curr Opin Organ Transplant 2013, 18:524–530

Décision en fin d'intervention

- $PaO_2/FiO_2 > 300$: extubation
- $100 < PaO_2/FiO_2 < 300$: maintien de la ventilation contrôlée
- **$PaO_2/FiO_2 < 100$ malgré optimisation de la ventilation : ECMO pour défaillance primaire du greffon grade 3**

ECMO V/A post-opératoire





- Héparine 50 Ui/Kg + 1000UI dans la pompe
- Reperfusion de membre systématique

ECMO post opératoire

- ECMO veino artérielle
  - DPG grade 3 souvent associée à une part de défaillance cardiaque
  - Diminution du flux sanguin pulmonaire
- Ventilation pulmonaire protectrice ++++
- Assistance cardiaque partielle : éviter l'ischémie chaude du greffon +++
  - Monitorer PAP ou etCO2
- Durée : 5 à 8 j
- Conversion possible en V-V

ECMO

- Complications
  - Hémorragiques
  - Ischémie membre inférieur
  - Infectieuses
- Nécessité d'une équipe médicale et paramédicale formée et entrainée
- Techniciens pompistes

Sevrage ECMO en post-greffe

- Aspect de la radio de thorax
- Réponse à la Diminution de Fio2
  - Oxygénation
- Réponse à la diminution de Débit
  - Hémodynamique et évaluation de la fonction cardiaque
- Déplétion débutée

Test de sevrage :
-FiO2 30%
-Débit 1500ml

GDS
ETT
Hémodynamique

Le recours à l'ECMO doit être discuté très précocément dès le BO ou dans les premières heures +++

L'utilisation large de l'ECMO en péri-opératoire a permis d'améliorer le pronostic des DPG sévères.

2 Situations particulières

Ex vivo

Donneurs cœur arrêté Maastricht 3

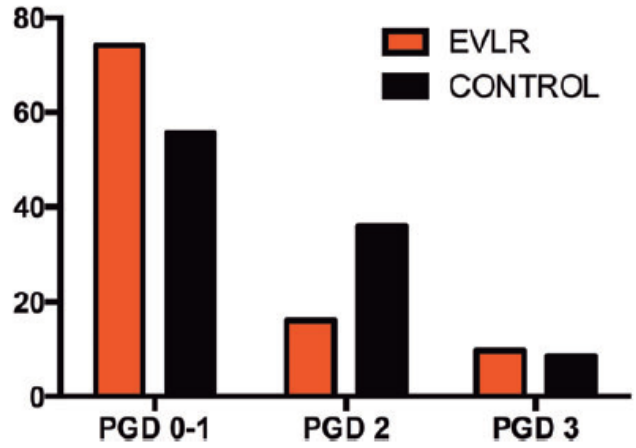


Figure 3: Primary graft dysfunction (PGD) at 72 h.

Sage ECJTS 2014

Normothermic *Ex Vivo* Perfusion Prevents Lung Injury Compared to Extended Cold Preservation for Transplantation

American Journal of Transplantation 2009; 9: 2262–2269

Table 2 - Short-term outcome after DCD and DBD lung transplantation

	DCD	**DBD**	**p-value**
Mechanical ventilation, days	9.9 (±2.3)	6.9 (±0.6)	0.59
ICU stay, days	16.3 (±2.7)	14.4 (±0.9)	0.74
Hospital stay, days	41.1 (±4.0)	38.1 (±1.3)	0.99
Highest PGD < 72 hrs, PGD = 3: n (%)	26 (44.1)	158 (47.7)	0.67

Short- and Long-Term Outcome After Lung Transplantation From Circulatory-Dead Donors: A Single-Center Experience

Transplantation Publish Ahead of Print

Conclusion

- DPG complication précoce post TP
- DPG 3 mauvais pronostic à court et lg terme
- Facteurs de risque liés au donneur au receveur à la phase opératoire
- Pas de traitement spécifique
- ECMO dans les formes graves