Primary Graft Dysfunction increases Risk of Baseline Lung Allograft Dysfunction but not Chronic Lung Allograft Dysfunction after Lung Transplantation

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Introduction

Primary graft dysfunction (PGD) is a life-threatening complication resulting in reperfusion lung injury and inflammation that occurs in the first 72 hours after lung transplantation (1).

In addition to being the most important contributor to early mortality in lung transplant recipients (1), previous work suggests that PGD also increases the risk of developing chronic lung allograft dysfunction (CLAD) (2), a progressive decline in graft function. However, the relationship between PGD and baseline lung allograft dysfunction (BLAD), or failure to normalize graft function, is not known.

Our objective was to assess the association between severe PGD and BLAD as well as CLAD in a single cohort. We hypothesized that PGD survivors would be at greater risk for *both* BLAD and CLAD.

Methods

We reviewed all double lung transplant recipients transplanted at the University of Alberta Hospital between 2004 and 2016. The outcome was grade 3 PGD (PGD3) defined as lung edema on chest x-ray as interpreted by the radiologist and PaO2/FiO2 ratio < 200 mmHg at 48 or 72 hours post-transplant. This is the timing and severity of PGD most associated with mortality (3)

We assigned CLAD status and grade according to the 2019 ISHLT consensus criteria (4) and BLAD according to our published definition (5) (failure to achieve both FEV1 and FVC > 80% predicted on 2 consecutive tests > 3 weeks apart).

We used chi-square and Cochran Armitage trend tests and logistic regression modelling (adjusted for age, gender, indication for transplant, donor smoking status and donor age) to evaluate the association between PGD and BLAD status and grade.

We used proportional hazards modelling to test the association between PGD and CLAD, adjusted for the above listed variables as well as for these variables plus BLAD status.

Table 1. *ISHLT grading for CLAD*

Grade	Current FEV1 on Spirometry
CLAD 0	> 80% FEV1 baseline
CLAD 1	>65-80% FEV1 baseline
CLAD 2	>50-65% FEV1 baseline
CLAD 3	>35-50% FEV1 baseline
CLAD 4	≤35% FEV1 baseline

Table 2. *Grading system for BLAD*

Grade	Baseline FEV1% Predicted
BLAD 0	Normal baseline
BLAD 1	≥ 65%
BLAD 2	>50-65%
BLAD 3	≤50%

Results

446 patients met inclusion criteria, 76 (17%) of whom developed PGD3 at 48- or 72-hours post-transplant. Patients who developed PGD3 were more likely to have interstitial lung disease or pulmonary vascular disease, a higher BMI and received lungs from older donors.

Patients with PGD3 more frequently developed BLAD (58% vs. 36%; p=0.0008) and more severe BLAD (p<0.0001). PGD3 increased the odds of BLAD in our fully adjusted model (OR 2.09 [95% CI 1.19-3.70]; p = 0.0105).

In contrast, we found no association between PGD3 status and cumulative incidence of CLAD onset (26% vs. 29%; p=0.6773) or severity (p=0.6857). PGD3 was not associated with time to CLAD onset in a fully adjusted Cox model (HR 1.16 (95%CI 0.68-1.87), p = 0.5701) , even when BLAD status was added to the model (HR 1.08 [95%CI 0.65-1.73], p = 0.7483).

Results

Table 3. *Patient characteristics*

Characteristic	Overall (n=446)	Grade 3 PGD (n=76)	No Grade 3 PGD (n=370)	p-value
Donor				
Age in years, mean (SD)	39 (17)	44 (17)	38 (17)	**0.002**
Female sex, n (%)	206 (46)	39 (51)	167 (45)	0.377
BMI, mean (SD)	25.4 (5.4)	25.6 (5.4)	25.4 (5.4)	0.780
Smoking >20 pack years, n (%)	59 (14) (n=410)	16 (23) (n=70)	43 (13) (n=340)	**0.038**
Ischemic time in minutes, mean (SD)	351 (119)	373 (130)	347 (116)	0.083
Recipient				
Age in years, mean (SD)	52 (14)	54 (11)	51 (14)	0.188
Female sex, n (%)	154 (35)	28 (37)	126 (34)	0.692
BMI, mean (SD)	24.7 (5.0)	26.7 (5.0)	24.2 (4.9)	**<0.001**
Max FEV1 % predicted, mean (SD)	92 (21)	81 (23)	94 (20)	**<0.001**
Diagnosis, n (%)				
Bronchiectasis	70 (16)	6 (8)	64 (17)	**<0.001**
Interstitial lung disease	167 (37)	37 (49)	130 (35)	
Obstructive lung disease	183 (41)	22 (29)	161 (44)	
Pulmonary vascular disease	17 (4)	9 (12)	8 (2)	
Other	9 (2)	2 (3)	7 (2)	
Recipient post-operative course				
Intubation time in hours, median (IQR)	63 (33-171)	54 (29-150)	96 (48-245)	**<0.001**
ICU LOS in days, median (IQR)	7 (4-13)	19 (11-28)	6 (4-9)	**<0.001**
Hospital LOS in days, median (IQR)	23 (18-38)	23 (18-36)	29 (19-44)	**0.016**
BLAD, n (%)				**<0.001**
Grade 1 BLAD, n (%)	134 (30)	22 (29)	112 (30)	
Grade 2 BLAD, n (%)	39 (9)	18 (24)	21 (6)	
Grade 3 BLAD, n (%)	6 (1)	4 (5)	2 (1)	
CLAD, n (%)				0.6857
Grade 1 CLAD, n (%)	55 (12)	8 (11)	47 (13)	
Grade 2 CLAD, n (%)	27 (6)	5 (7)	22 (6)	
Grade 3 CLAD, n (%)	22 (5)	3 (4)	19 (5)	
Grade 4 CLAD, n (%)	25 (6)	4 (5)	21 (6)	

Table 4. *Univariable and multivariable models for the association between grade 3 PGD on BLAD and CLAD development*

Characteristic	Odds Ratio / Hazard Ratio	95% CI	p-value
PGD3 effect on BLAD			
Adjusted*	**2.09** (OR)	1.19-3.70	**0.0105**
PGD3 effect on CLAD			
Adjusted*	1.16 (HR)	0.68 – 1.87	0.5701
Adjusted* + BLAD status	1.08 (HR)	0.65 – 1.73	0.7483

**Adjusted indicated multivariable models adjusted for recipient age, recipient gender, pulmonary diagnosism heavy donor smoking history and donor age*

Conclusions

1. **Severe PGD was associated with increased risk and severity of BLAD but not CLAD in this cohort**
2. Our findings emphasize the need to distinguish baseline dysfunction from CLAD as a distinct state of respiratory risk
3. The mechanisms by which PGD mediates poor baseline function require further investigation

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