Primary Graft Dysfunction is associated with Increased Radiographic Atelectasis at 3 months Post-Lung Transplant

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Introduction

Primary graft dysfunction (PGD) after lung transplantation is a form of acute lung injury similar to acute respiratory distress syndrome (ARDS) occurring immediately post-operatively, and has also been associated with long term sequalae including lower lung function and overall survival (1). Little is known about the mechanisms by which PGD affects long term lung function.

We assessed radiographic changes on computed tomography lung scans at 3 months post-transplant and their association with future risk of chronic lung allograft dysfunction (CLAD) (2) and baseline lung allograft dysfunction (BLAD) (3) . We hypothesized that radiographic abnormalities would be more frequent in PGD survivors and be associated with increased risk of BLAD and CLAD.

Methods

We conducted a retrospective cohort study of adult double lung transplant recipients at the University of Alberta Hospital transplanted between 2010 and 2016 for whom 3 month CT scans were available. Grade 3 PGD was defined as the presence of pulmonary edema on post-operative CXR and PaO2/FiO2 < 200 mmHg at 48 or 72 hours post-transplant (4).

The primary outcome was the presence of abnormalities on 3 month CT chest: pleural effusion, ground glass opacification, centrilobular opacification, interlobular septal thickening, atelectasis, consolidation, fibrosis, and air trapping. We classified radiographic abnormalities as ranked ordinal variables based on number of involved lobes and used trend testing to assess the relationship between PGD and radiographic change. We accounted for microbiologic changes by culture positive bronchoscopic specimens at 3 month. We tested relationships between associated CT features and future risk of CLAD (ISHLT 2019 definitions) and BLAD (failure to reach both FEV1 and FVC>80%) using Cox and logistic models respectively.

Results

237 patients met inclusion criteria, 50 (21%) of whom developed grade 3 PGD at 48 or 72 hours. Amongst all CT abnormalities, grade 3 PGD was associated with more frequent and/or widely distributed interlobular septal thickening (p = 0.0389) and atelectasis (p < 0.0001) at 3 months. After Bonferroni correction for multiple testing (significance level p<0.00625 [0.05/8 primary outcomes]), only atelectasis remained significantly associated. There was no relationship between clinically relevant bacteria or fungi on 3 month bronchoscopy and any radiographic abnormality.

Atelectasis at 3 months increased the risk of BLAD both unadjusted (OR 3.83 [1.90-8.03], p=0.0002) and adjusted for PGD3 status (OR 3.44 [1.68-7.28], p=0.0007). Neither the unadjusted nor adjusted risk of CLAD was affected by atelectasis.

Table 1. *Patient characteristics*

Characteristic	Overall (n=237)	Grade 3 PGD (n=50)	No grade 3 PGD (n=187)	p-value
Recipient				
Age in years, mean (SD)	54 (12)	55 (9)	54 (13)	0.639
Female sex, n (%)	87 (37)	21 (42)	66 (35)	0.411
BMI, mean (SD)	25 (5)	27 (4)	25 (5)	**0.015***
Diagnosis, n (%)				
Obstructive lung disease	93 (39)	15 (30)	78 (42)	0.093
Interstitial lung disease	101 (43)	25 (50)	76 (40)	
Bronchiectasis	25 (11)	4 (8)	21 (11)	
Pulmonary vascular disease	10 (4)	5 (10)	5 (3)	
Other	58(3)	1 (2)	7 (4)	
Donor				
Age in years, mean (SD)	41 (17)	45 (18)	40 (17)	0.055
Female sex, n (%)	109 (46)	26 (52)	83 (44)	0.344
Smoking > 20 pack years, n (%)	30 (14) (n=218)	8 (18) (n=30)	22 (13) (n=174)	0.335
Total ischemic time in minutes, mean (SD)	345 (124)	357 (155)	342 (114)	0.123
3-Month post transplant microbiology				
Clinically relevant bacterial infection, n (%)	55 (23)	16 (32)	39 (21)	0.130
Clinically relevant fungal infection, n (%)	25 (11)	5 (10)	20 (11)	1.000
Clinically relevant bacterial or fungal infection, n (%)	74 (31)	19 (38)	55 (29)	0.303
Recipient post-operative course				
Intubation time in hours, median (IQR)	70 (29-188)	237 (136-564)	48 (24-112)	**<0.001***
ICU stay in days, median (IQR)	7 (5-14)	19 (12-27)	6 (4-9)	**<0.001***
Length of hospital stay in days, median (IQR)	25 (18-40)	41 (27-71)	22 (17-33)	**<0.001***
1-Year FEV1 % predicted, mean (SD)	83 (22)	76 (23)	85 (22)	**0.029***
CLAD, n (%)	46 (20) (n=233)	11 (23) (n=48)	35 (19) (n=185)	0.545
Time to CLAD in days, mean (SD)	1142 (n=46)	1282 (n=11)	1098 (n=35)	0.469
BLAD, n (%)	89 (38) (n=233)	26 (54) (n=48)	63 (34) (n=185)	**0.013***

Results

Table 2. *Radiographic abnormalities in lung transplant recipients stratified by grade 3 PGD status.*

CT finding	Overall (n = 237)	PGD3 (n = 50)	No PGD3 (n = 187)	p-value
Pleural effusion				0.080
None	127 (54)	21 (42)	106 (57)	
Trace unilateral	5 (2)	1 (2)	4 (2)	
Trace bilateral	6 (3)	2 (4)	4 (2)	
Small unilateral	28 (12)	8 (16)	20 (11)	
Small bilateral	38 (16)	8 (16)	30 (16)	
Medium unilateral	15 (6)	4 (8)	11 (6)	
Medium bilateral	14 (6)	5 (10)	9 (5)	
Large unilateral	1 (0)	1 (2)	0 (0)	
Large bilateral	3 (1)	0 (0)	3 (2)	
Consolidation (lobes)				0.510
0	221 (93)	45 (90)	176 (94)	
1	7 (3)	2 (4)	5 (3)	
2	8 (3)	3 (6)	5 (3)	
3	0 (0)	0 (0)	0 (0)	
4	0 (0)	0 (0)	0 (0)	
5	1 (0)	0 (0)	1 (0)	
Atelectasis (lobes)				**<0.001***
0	112 (47)	15 (30)	97 (52)	
1	37 (16)	5 (10)	32 (17)	
2	48 (20)	15 (30)	33 (18)	
3	20 (8)	5 (10)	15 (8)	
4	1 (0)	0 (0)	1 (1)	
5	19 (8)	10 (20)	9 (5)	
Centrilobular nodules (lobes)				0.051
0	215 (91)	42 (84)	173 (93)	
1	9 (4)	3 (6)	6 (3)	
2	4 (2)	1 (2)	3 (2)	
3	5 (2)	2 (4)	3 (2)	
4	0 (0)	0 (0)	0 (0)	
5	4 (2)	2 (4)	2 (1)	
Ground glass opacification (lobes)				0.128
0	181 (76)	35 (70)	146 (78)	
1	29 (12)	6 (12)	23 (12)	
2	15 (6)	6 (12)	9 (5)	
3	5 (2)	0 (0)	5 (3)	
4	0 (0)	0 (0)	0 (0)	
5	7 (3)	3 (6)	4 (2)	
Interlobular septal thickening (lobes)				**0.039***
0	176 (74)	34 (68)	142 (76)	
1	14 (6)	2 (4)	12 (6)	
2	22 (9)	5 (10)	17 (9)	
3	8 (3)	2 (4)	6 (3)	
4	2 (1)	0 (0)	2 (1)	
5	15 (6)	7 (14)	8 (4)	
Air trapping				0.306
Present	44 (19)	12 (24)	32 (17)	
Absent	193 (81)	38 (76)	155 (83)	
Fibrosis				0.044
Present	2 (1)	2 (4)	0 (0)	
Absent	235 (99)	48 (96)	187 (100)	

Conclusions

1. **Grade 3 PGD is associated with increased radiographic atelectasis** at 3 months post-transplant
2. **Atelectasis appears to mediate increased the post-PGD risk of BLAD but not CLAD**. This may suggest a role for persistent surfactant abnormalities and/or type II pneumocyte dysfunction in post-PGD lungs.

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