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# Pretransplant dyslipidaemia influences primary graft dysfunction after lung transplantation

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## Abstract

**OBJECTIVES**: Primary graft dysfunction (PGD) is a major cause of mortality within the first year following lung transplantation. Pulmonary hypertension, elevated body mass index (BMI), prolonged ischaemic time of the graft, intraoperative blood transfusions >1000 ml and the use of cardiopulmonary bypass or extracorporeal membrane oxygenation increase the risk for PGD. We aimed to evaluate whether dyslipidaemia is an additional risk factor for the development of PGD.

**METHODS**: We retrospectively analysed demographic and clinical data of 264 patients who received their first bilateral lung transplantation between March 2000 and October 2013 at our institution. The endpoint was PGD grade 3 at any time, defined according to the International Society for Heart and Lung Transplantation (ISHLT) criteria. Fasting lipid profiles at listing time or just before transplantation (baseline) were documented and dyslipidaemia was defined as any of the parameters being out of range. Comparisons of continuous variables between patients with PGD grade 3 and patients without were performed with the Mann–Whitney *U*-test, whereas proportions were compared with the $\chi^2$ test. Continuous variables were presented as arithmetic means with standard deviation for ease of comparison, but levels of statistical significance were computed using the appropriate non-parametric statistical test. To identify PGD risk factors, a forward stepwise logistic regression model was used.

**RESULTS**: PGD occurred in 63 recipients (24%). Pretransplant dyslipidaemia was documented in 153 recipients (58%) and was significantly more prevalent among recipients developing PGD (45 vs 108, $P < 0.013$). Despite various underlying pulmonary pathologies, higher triglyceride (TG) levels (1.41 ± 0.78 vs 1.16 ± 0.78, $P < 0.012$), lower high-density lipoprotein-cholesterol (HDL-C) concentrations (1.24 ± 0.55 vs 1.57 ± 0.71, $P < 0.0005$) and higher cholesterol/HDL-C values (3.80 ± 2.02 vs 3.00 ± 0.92, $P < 0.0005$) were associated with a lower incidence of PGD. Patients with PGD had significantly longer ischaemic time (350 ± 89 vs 322 ± 91, $P = 0.017$) and higher BMI (23 ± 5 vs 21 ± 4.4, $P < 0.007$).

**CONCLUSIONS**: Dyslipidaemia seems to be an independent risk factor for PGD after lung transplantation: low circulating levels of HDL-C and hypertriglyceridaemia increase the incidence of PGD. Even if HDL-C levels are difficult to alter today, triglyceride and cholesterol levels can be addressed therapeutically and may have a positive influence on the development of PGD.

**Keywords:** Lung transplantation • Primary graft dysfunction • Inflammation • Dyslipidaemia

## INTRODUCTION

Primary graft dysfunction (PGD) is a major cause of mortality within the first year after lung transplantation [1]. It clinically manifests with progressive, severe hypoxaemia and pulmonary infiltrates on chest X-ray (CXR) without other identifiable causative lung pathology within the first 72 h after transplantation. It encompasses a spectrum of acute lung injury ranging from milder allograft dysfunction to more severe acute respiratory distress syndrome (ARDS). In 2005, a 'PGD Working Group' was summoned by the International Society for Heart and Lung Transplantation (ISHLT) that proposed a classification to standardize the definition of the PGD. PGD grade 3 means $Pa_{O_2}/FI_{O_2}$ in mmHg (P/F ratio) <200 and diffuse allograft infiltrates on CXR within 72 h after lung transplantation [2]. The incidence of PGD has been reported to be at 10–30% [3]. PGD causes prolonged mechanical ventilation and increased length of stay in the intensive care unit. PGD causes worse functional outcome with an increased risk for the

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development of chronic lung allograft dysfunction, particularly bronchiolitis obliterans syndrome. Investigations that specifically evaluate risk factors for PGD may influence the outcome in recipients undergoing lung transplantation [4].

The pathogenesis of PGD is complex and consequent to ischaemia–reperfusion injury resulting from direct damage of ischaemia and preservation, generation of reactive oxygen species at reperfusion and activation of a damage-amplifying pro-inflammatory cascade. Experimental and clinical evidence suggest that PGD develops in a biphasic pattern with the early phase of PGD depending primarily on cells presenting in the donor lung and the later phase of PGD resulting from an influx of recipient cells [5].

The role of dys- and hyperlipidaemia as promoters of inflammation is well known, i.e. during arteriosclerotic plaque development, specially the antioxidant, antithrombotic and anti-inflammatory properties of the high-density lipoprotein-cholesterol (HDL-C) protect against atherogenesis [6, 7]. It is believed that the anti-inflammatory nature of HDL-C could also be beneficial in other inflammatory diseases as sepsis or rheumatoid arthritis [8, 9].

Inflammatory processes precede or develop at cerebral death of the donor and follow the graft in subsequent phases of conservation and surgery during lung transplantation [10–12]. We have previously shown that pretransplant dyslipidaemia determines outcome in lung transplant recipients [13], but up to now, the role of lipids in lung patients has been poorly investigated. In particular, we still lack data on whether preoperative dyslipidaemia affects the incidence of PGD.

In view of these circumstances, we hypothesized that preoperative dyslipidaemia may influence the incidence of PGD after lung transplantation.

## MATERIALS AND METHODS

The study was approved by the local ethics committee (KEK-Nr.: 2014-0195). A systematic chart review of all consecutive lung transplantations performed between 1 March 2000 and 31 October 2013 at the University Hospital Zurich was carried out. Since 1 March 2000, our centre has adopted and exclusively used low-potassium dextran organ preservation solution.

We collected clinical and demographic data of 264 consecutive patients over 13 years of age, receiving their first bilateral lung transplant. Lipid profiles at transplantation assessment or just before transplantation (baseline) were documented in a standardized fashion, including total cholesterol (Chol; normal value <5 mmol/l), triglycerides (TGs; normal value <2 mmol/l), HDL-C (normal value >1 mmol/l) and cholesterol/HDL-C ratio (normal value <5). Dyslipidaemia was defined as any of the parameters to be out of range. At the time of transplantation, none of our patients received statins. Immunosuppression consisted of induction therapy with basiliximab, and maintenance therapy included steroids, cyclosporine A and anti-metabolites (azathioprine or mycophenolate mofetil) as previously described [14].

PGD grade 3 was diagnosed according to the ISHLT criteria [2]. Chest radiographs were obtained after transplantation and then generally daily for 3 days. The $Pa_{O_2}/FI_{O_2}$ ratio was measured several times daily.

We further assessed currently known risk factors for PGD such as body mass index (BMI), blood transfusion >1000 ml during transplantation and the need of cardiopulmonary bypass (CPB) or intraoperative extracorporeal membrane oxygenation (ECMO) as well as the recipients' underlying conditions.

At last, we analysed possible donor's risk factors for PGD including age, female sex and history of tobacco, as recently described by Grimm *et al.* [15].

### Data analysis

Descriptive statistics were presented as arithmetic means with standard deviation (SD) for quantitative data and as absolute numbers with percentages for qualitative data. Comparisons of continuous variables between patients with PGD grade 3 and those without were performed with Student's *t*-test, whereas proportions were compared with the $\chi^2$ test or Fisher's exact test as appropriate. To identify PGD grade 3 risk factors, a logistic regression model was used. PGD grade 3 was taken as the primary endpoint (outcome variable). The following potential predictor variables were selected and introduced in the logistic regression model in order to assess the association with graft dysfunction: pretransplant dyslipidaemia (yes versus no); intraoperative use of CPB or ECMO (yes versus no); intraoperative blood transfusions >1000 ml (yes versus no) and recipient BMI. Odds ratios (ORs) with the corresponding 95% confidence intervals were then calculated. A *P*-value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics (version 22, IBM Corp., Armonk, NY, USA).

## RESULTS

There were 264 consecutive first bilateral adult lung transplantations performed at the University Hospital Zurich during the study period. The mean patient age was 47 ± 15 years, with 44% female recipients (*n* = 115). Patients' clinical characteristics are presented in Table 1.

Of these, 63 subjects (24%) developed PGD grade 3. Blood transfusions during surgery were required in 96 recipients (36%). CPB or intraoperative ECMO were used in 112 recipients (42%), both statistically more frequent in recipients with PGD. With regard to the underlying condition, patients with chronic obstructive pulmonary disease (7 vs 77, $P < 0.0005$) and cystic fibrosis (13 vs 67, $P < 0.005$) were significantly less likely to develop PGD. Patients with PGD had significantly longer ischaemic time

**Table 1:** Demographic features and PGD risk factors

| | PGD (*N* = 63) | No PGD (*N* = 201) | *P*-value |
|---|---|---|---|
| Age (years) [mean ± SD] | 48 ± 15 | 47 ± 15 | 0.71 |
| Male, *n* (%) | 33 (52) | 106 (53) | 0.96 |
| BMI [mean ± SD] | 23.4 ± 5.1 | 21.5 ± 4.3 | 0.0025 |
| Diagnosis, *n* (%) | | | |
| COPD | 7 (11) | 77 (38) | 0.15 |
| Other ILD | 43 (68) | 57 (28) | <0.001 |
| CF | 13 (21) | 67 (33) | 0.39 |
| CPB or ECMO | 43 (68.3) | 69 (34.3) | <0.001 |
| Ischaemic time (min) [mean ± SD] | 350 ± 89 | 322 ± 91 | 0.017 |
| Blood transfusion >1000 ml, *n* (%) | 35 (55.5) | 61 (30.3) | <0.001 |
| Dyslipidaemia, *n* (%) | 45 (71.4) | 108 (57.3) | 0.013 |

PGD: primary graft dysfunction; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CF: cystic fibrosis; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation.

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**Table 2:** Blood lipid profiles

| | PGD ($N$ = 63) | No PGD ($N$ = 201) | $P$-value |
|---|---|---|---|
| Cholesterol (mmol/l) | 4.27 ± 1.58 | 4.46 ± 1.55 | 0.39 |
| HDL-C (mmol/l) | 1.25 ± 0.55 | 1.55 ± 0.63 | <0.001 |
| Triglyceride (mmol/l) | 1.42 ± 0.78 | 1.17 ± 0.66 | 0.015 |
| LDL-C (mmol/l) | 2.40 ± 1.07 | 2.42 ± 1.14 | 0.94 |
| Cholesterol/HDL-C | 3.81 ± 2.02 | 3.10 ± 1.17 | <0.001 |

HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; Cholesterol/HDL-C: cholesterol/high-density lipoprotein-cholesterol.

**Table 3:** Predictor variables associated with the development of PGD grade 3 in multivariable logistic regression analysis

| Variable | OR | 95% CI | $P$-value |
|---|---|---|---|
| Dyslipidaemia (no dyslipidaemia as reference) | 1.932 | 1.004–3.719 | 0.049 |
| CPB or ECMO (no CPB or ECMO as reference) | 2.783 | 1.402–5.525 | 0.003 |
| Recipient BMI (per 1 kg/m$^2$) | 1.099 | 1.019–1.163 | 0.011 |
| Red cell transfusion >1000 ml (red cell transfusion ≤1000 ml as reference) | 2.051 | 1.036–4.059 | 0.039 |

OR: odds ratio for the development of primary graft dysfunction; 95% CI: 95% confidence interval; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; BMI: body mass index.

(350 ± 89 vs 322 ± 91, $P$ = 0.017) and higher BMI (23 ± 5 vs 21 ± 4.4, $P$ < 0.007). Dyslipidaemia was present in 153 recipients (58%). Among subjects with PGD, dyslipidaemia was more prevalent (45 vs 108, $P$ = 0.023). Patients developing PGD had higher TG levels (1.41 ± 0.78 vs 1.16 ± 0.78, $P$ < 0.012), lower HDL-C concentrations (1.24 ± 0.55 vs 1.57 ± 0.7163, $P$ < 0.0005) and higher cholesterol/HDL-C values (3.80 ± 2.02 vs 3.00 ± 0.92, $P$ < 0.0005; Table 2).

To test for the importance of the individual risk factors of dyslipidaemia, requirement for CPB or ECMO therapy, elevated recipient's BMI and transfusion of >1000 ml of red cells, a logistic regression model was generated. We found the requirements for ECMO and red cell transfusion to be the strongest risk factors with an OR of >2, pretransplant dyslipidaemia to be of intermediate risk (OR 1.9) and an increased BMI to be a minor risk factor (OR 1.1; Table 3).

None of the cited donor risk factors were found to be statistically significant.

## DISCUSSION

Our findings suggest dyslipidaemia to be an independent risk factor for the development of the PGD after lung transplantation, with low circulating levels of HDL-C and hypertriglyceridaemia increasing the incidence of PGD. In the univariate analysis, decreased levels of HDL-C showed the stronger association with PGD, which may support our hypothesis of a possible modulation of the inflammatory pathway modulated by the lipid status. The protective effect of HDL-C in cardiovascular and inflammatory diseases is the result of several beneficial functions [16]. There is growing evidence that HDL-C can be modified and become dysfunctional during acute or chronic inflammatory states [17].

Among the few studies that have investigated the context of lipids and inflammation in lung transplant recipients, Allen *et al.* [18] demonstrated that lung transplant recipients with PGD grade >2 had elevated pretransplant levels of pro-inflammatory cytokines. In recipients with pulmonary arterial hypertension, Heresi *et al.* observed a higher mortality and clinical deterioration associated with depleted levels of HDL-C; however, none of these patients underwent lung transplantation [19].

The limitations of our study are the retrospective character and the limited number of recipients; nevertheless, this is the largest cohort to date available, and thus, our data are important to initiate further trials.

Even though the exact mechanism linking dyslipidaemia and PGD cannot be explained, it seems suggestive in view of research performed in other inflammatory diseases [6–9]. Thus, our data are a valuable addition to the existing knowledge and could trigger further research.

The documented association in our study was independent of adjustment from multiple known confounding variables, and was strongest with lower serum levels of HDL-C, fulfilling the concept of linearity (i.e. stronger effect with a more pronounced risk factor). Similar to other study populations, longer ischaemic time, blood transfusions and the use of CPB or intraoperative ECMO represent independent risk factors for PGD after transplantation [3].

Even if HDL-C levels are difficult to alter today [20], TG and cholesterol levels can be addressed therapeutically and may have a positive influence on the development of PGD. These circumstances and possible further understanding of the complex mechanism of HDL-C would encourage further work in this area.

In summary, we identified dyslipidaemia, and especially low HDL-C, as a risk factor for the development of PGD grade 3 after lung transplantation in our study population.

**Conflict of interest:** none declared.

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