Low-Density Neutrophils and Monocyte Remodeling Are Associated with Distinct Immune Trajectories of PGD and AKI after Heart Transplantation

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Introduction

- Ischemia-reperfusion injury is a driver of early inflammation after heart transplant. It's unclear what degree its role is in primary graft dysfunction (PGD) and other post-operative outcomes like acute kidney injury (AKI).
- Early inflammation is driven by an innate immune response which includes monocytes and neutrophils.
- Classical monocytes (CM) are rapidly recruited to injured tissue and aid in phagocytosis, debris clearance and the production of reactive oxidative species and cytokines. Intermediate monocytes (IM) are pro-inflammatory antigen-presenting cells that amplify immune signaling. Non-classical monocytes (NCM) play a key role in tissue surveillance, maintenance of endothelial integrity, and the resolution of inflammation and tissue repair.
- Low-density neutrophils (LDN) release inflammatory cytokines, neutrophil extracellular traps, and reactive oxygen species. They also suppress T-cell proliferation and function.

Research Question

What are the kinetics of the early monocyte and low-density neutrophil response and are they indicative of early PGD or AKI?

Methods

- Blood was collected from heart transplant recipients at four time points: pre-clamp (Pre-Cx), post-clamp (Post-Cx), POD-1, and POD-2.
- Peripheral blood mononuclear cells were isolated and then analyzed using multiparametric flow cytometry (CD45, CD15, CD16, CD14, HLA-DR) to quantify LDNs and monocyte subsets.
- Temporal dynamics were assessed using two-way repeated-measures ANOVA with Geisser–Greenhouse correction.

Table 1: Patient Baseline and Operative Characteristics

Variable	N = 12
Demographics	
Age (years)	56.2 ± 10.6
Male Sex	7 (58.3%)
BMI (kg/m²)	25.2 ± 3.8
Donor Type (DBD)	11 (92%)
Transplant Indication	
Ischemic Cardiomyopathy	7 (58.4%)
Non-Ischemic Cardiomyopathy	5 (41.6%)
Multiorgan Transplant (HTx+KTx and HTx+KTx+LTx)	2 (16.7%)
Preoperative Support	
Intra-Aortic Balloon Pump	7 (58.3%)
Inotropes	3 (25.0%)
Durable VAD	1 (8.3%)
None	1 (8.3%)
Operative Parameters	
Total Ischemic Time (min.)	207.2 ± 41.9
CPB Time (min.)	180.3 ± 50
Cross Clamp (min.)	100.6 ± 38
Incidence of PGD	3 (25 %)
Incidence of AKI	9 (75%)

Figure 1 : Monocyte Kinetics for PGD and AKI

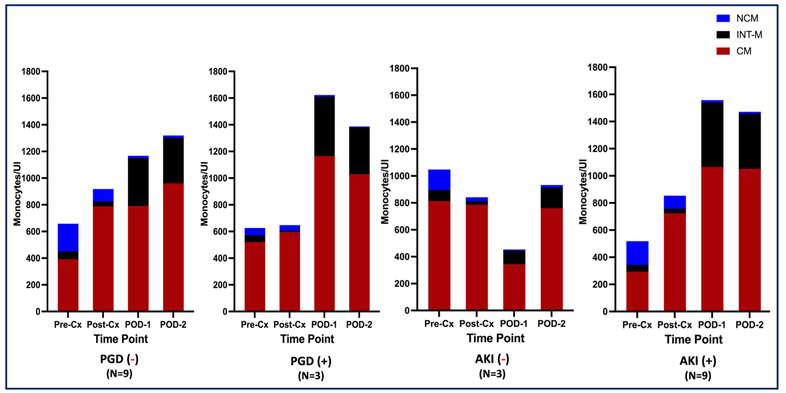


Figure 2: LDN Over Time

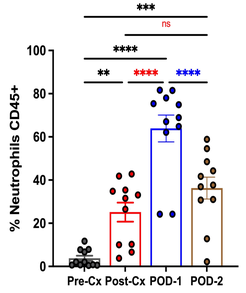


Figure 3: LDN-IM

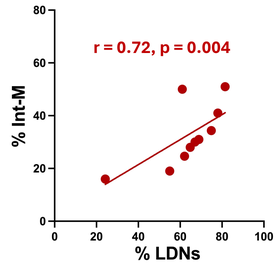
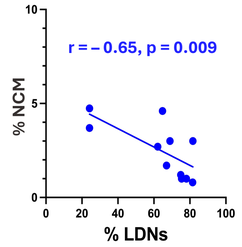


Figure 4: LDN-NCM



Results

- Patients with PGD demonstrated differences across monocyte subsets (p=0.0003) without clear temporal evolution (p=0.150).
- In patients with AKI, monocyte responses demonstrated pronounced temporal remodeling, with significant effects of time (p=0.0007), subset (p<0.0001), and a strong time–subset interaction (p=0.0009), driven by progressive IM expansion and sustained depletion of NCM.
- LDNs were minimal prior to cross clamp but increased sharply following reperfusion, peaking at POD-1 before partially declining by POD-2 (p<0.0001).
- LDN levels correlated positively with IM expansion (r=0.72, p=0.004) and inversely with NCM (r=−0.65, p=0.009).

Conclusions

Heart transplantation is associated with a rapid LDN surge that coincides with INT-M expansion and NCM depletion. Distinct immune trajectories were observed across clinical phenotypes: AKI was characterized by dynamic, evolving immune remodeling, whereas PGD demonstrated a more static profile, potentially reflecting an early-dominant inflammatory state. The association between LDNs and monocyte subset shifts suggests a potential neutrophil–monocyte axis in early post-transplant immune responses and highlights LDNs and monocyte subsets as candidate biomarkers for early risk stratification and future investigation.