A Compartmentalized Monocyte Trafficking Program Defines Early Vascular Immune Remodeling After Pulmonary Thromboendarterectomy

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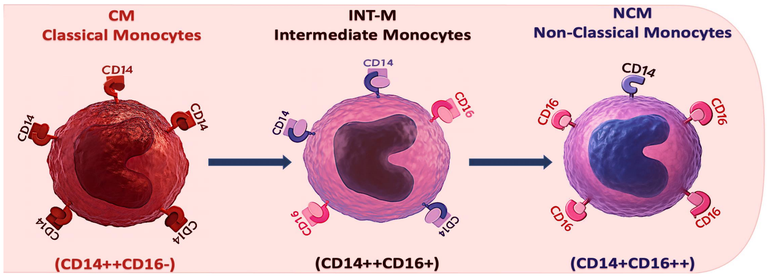
20 YEARS OF CLINICAL EXCELLENCE

Background

Pulmonary thromboendarterectomy (PTE) is a definitive therapy for chronic thromboembolic pulmonary hypertension (CTEPH),yet the mechanisms underlying vessel recovery after removal of long-standing thrombo-inflammatory fibrotic tissue remains unknown. Here, we seek to describe the early innate immune response in the pulmonary vascular bed to PTE

Monocytes are typically divided into three subtypes:

- **Classical monocytes (CM)** which are inflammatory and rapidly recruited to sites of injury. These cells rely on C-C Chemokine Receptor Type 2 (CCR2), a chemokine receptor that enables their mobilization from the bone marrow into the bloodstream.
- **Intermediate monocytes (INT-M)** are active responders releasing both inflammatory(TNF-α, IL-1β) and anti-inflammatory cytokines(IL-10). It also acts as a potent antigen presentation (HLA-DR).
- **Non-classical monocytes (NCM)**, which patrol the endothelium and are involved in tissue repair and remodeling. Their development depends on the transcription factor Nuclear Receptor Subfamily 4 Group A Member 1 (NR4A1).



Does PTE trigger a compartmentalized monocyte trafficking program that links reperfusion, clot chronicity, and early vascular immune remodeling in CTEPH?

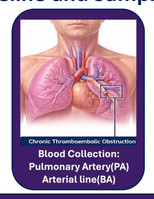
Methods

Study Population
Prospective single-center cohort
N = 23 patients with CTEPH undergoing PTE

Sample Sources
Pulmonary artery (PA) and systemic circulation (BA)

Monocyte Subsets (Flow Cytometry)
- **CM** (Classical): CD14++ CD16-
- **INT-M** (Intermediate): CD14++ CD16+
- **NCM** (Non-Classical): CD14+ CD16++

Study Timeline and Sample Collection



Pre Incision (Pre-Cx) → Post Clamp Off (Post-Cx) → POD-1 → POD-2

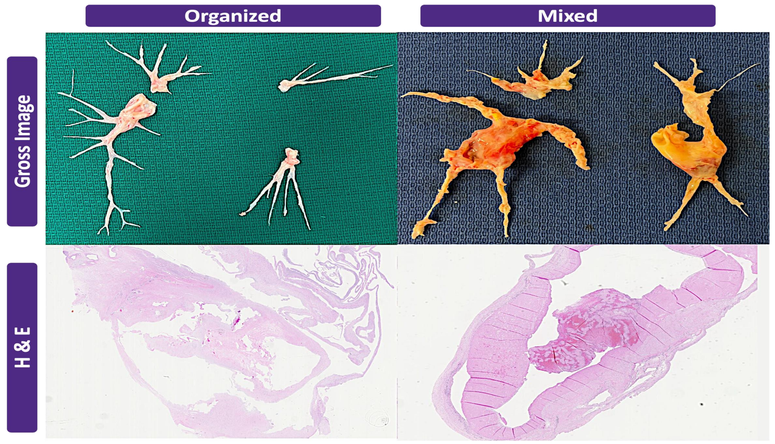
Serum banking
PBMC banking
Flow analysis

PATIENT CHARACTERISTICS	Total (N=23)
DEMOGRAPHICS	
Age at PTE, yrs	51.4 ± 17.9
Sex, n (%)	23 (100%)
Female, n (%)	12 (52%)
Male, n (%)	11 (48%)
BMI, kg/m²	36.0 ± 10.7
COMORBIDITIES	
PE, n (%)	16 (70%)
DVT, n (%)	7 (30%)
CLOT CHARACTERISTICS	
Chronicity – Organizing, n (%)	2 (9%)
Chronicity – Organized/Fibrotic, n (%)	13 (57%)
Chronicity – Mixed acute-on-chronic, n (%)	8 (35%)
Duration Dx→Sx, days	704 ± 1044
HOSPITAL COURSE	
ICU LOS, days	9.0 ± 10.7
Post-op hospital LOS, days	12.7 ± 13.1

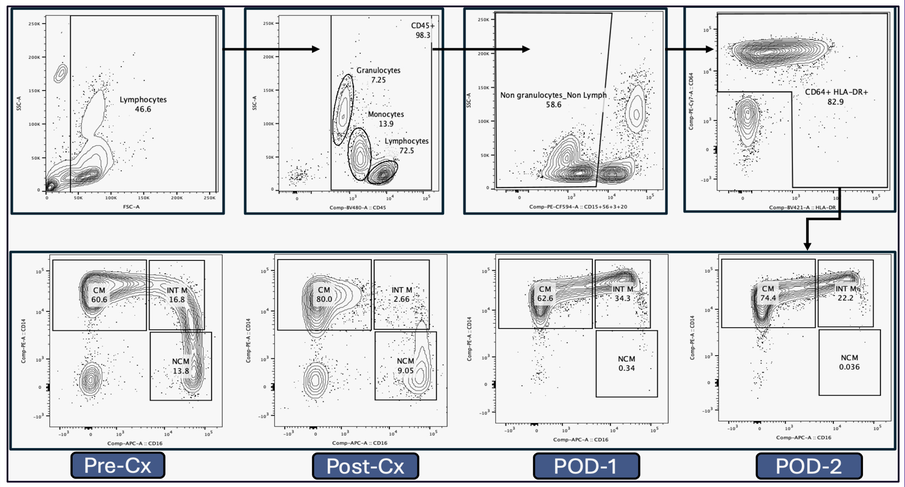
HEMODYNAMICS (PRE-PTE)	
6MWD, m	351.2 ± 97.5
NYHA III–IV, n (%)	18 (80)
PVR, dynes·s·cm⁻⁵	431.2 ± 269.5
Pre-op mRAP, mmHg	8.6 ± 5.9
Pre-op mPAP, mmHg	37.9 ± 12.2
Pre-op PCWP, mmHg	11.6 ± 5.0
Pre-op CI, L/min/m²	2.9 ± 1.1
Pre-op SvO_2, %	67.6 ± 9.2
Creatinine, mg/dL	0.9 ± 0.1
LVEF, %	59.5 ± 7.5

Methods

Histopathologic Stratification by Thrombus Chronicity



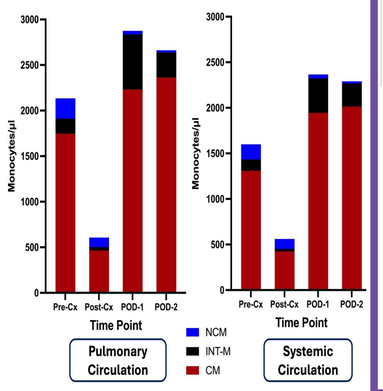
Flow Cytometry Gating Strategy at Perioperative Time-points



Results

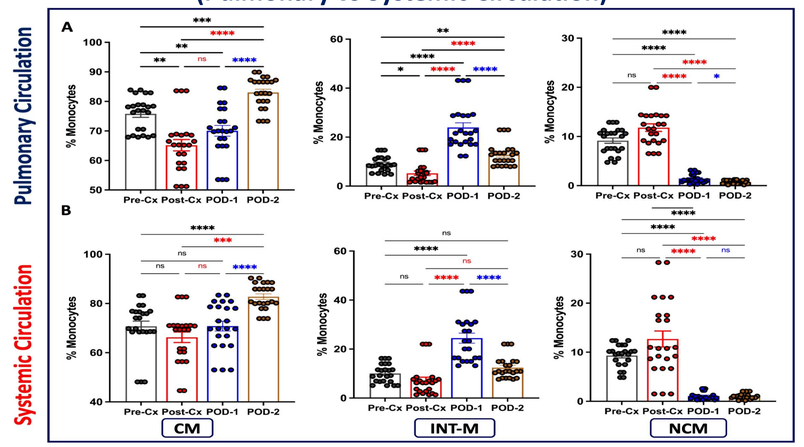
- PTE induced a coordinated tri-phasic monocyte remodeling in both pulmonary and systemic circulations. Total monocytes rose from 1.8 ± 0.7 × 10^3 to 3.0 ± 0.9 × 10^3 cells/μL by POD-2 (p < 0.05), with a parallel shift from vascular surveillance toward an inflammatory phenotype.
- CM and INT-M expanded from 71 ± 8 %(1.3 ± 0.5 × 10^3 cells/μL) to 88 ± 6 % (2.6 ± 0.8 × 10^3 cells/μL) (p = 0.01) and 12 ± 5 % (0.22 ± 0.09 × 10^3 cells/μL) to 22 ± 7 % (0.57 ± 0.18 × 10^3 cells/μL) , (p < 0.01), dominating the POD-1 and POD-2 reperfusion phase.
- NCM declined sharply (14 ± 4 % (0.26 ± 0.11 × 10^3 cells/μL) to 3 ± 2 %(0.09 ± 0.04 × 10^3 cells/μL), p < 0.001).
- The pulmonary bed showed selective immune enrichment. Immediately after reperfusion (Post-Cx and POD-1), PA samples demonstrated significantly higher CM (p = 0.011) and INT-M (p < 0.001) counts than BA — driven by inflammatory subsets, while NCM showed no compartmental gradient (p = 0.99).

Monocyte Dynamics (Cells/Ul) (Pulmonary Vs Systemic Circulation)



Results

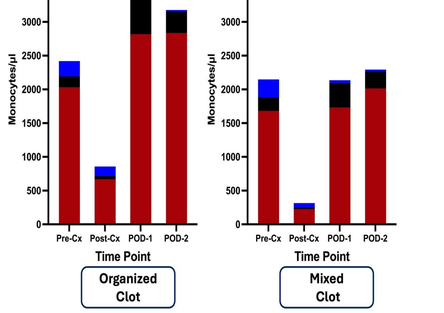
Monocyte Subset Remodeling After PTE Reperfusion (Pulmonary vs Systemic Circulation)



Clot Chronicity Shapes the Post-PTE Monocyte Response

HEMODYNAMIC PARAMETERS *Pre- and Post-Pulmonary Thromboendarterectomy (PTE) (N=10)*			
PARAMETER	PRE-PTE Mean ± SD		POST-PTE Mean ± SD
PVR (*dynes-s-cm⁻⁵*)	431.2 ± 269.5	↓	116.9 ± 49.7
RAP (*mmHg*)	8.6 ± 5.9	↑	10.5 ± 4.4
mPAP (*mmHg*)	37.9 ± 12.2	↓	20.4 ± 5.0
PCWP (*mmHg*)	11.6 ± 5.0	↑	14.5 ± 3.4
CI (*L/min/m²*)	2.9 ± 1.1	↓	2.3 ± 0.4

PVR	mPAP	CI
431.2 → 116.9 dynes·s·cm⁻⁵ (p < 0.01)	37.9 → 20.4 mmHg (p < 0.01)	2.9 → 2.3 L/min/m² (p = 0.08)



- Hemodynamics improved significantly (PVR 431 ± 270 → 117 ± 49 dyn·s·cm^{-5}, p < 0.001).
- Patients with organized, fibrotic clots had longer diagnosis-to-surgery intervals (median 945 vs 420 days, p = 0.06) and greater INT-M peaks (median 0.58 × 10^3 vs 0.24 × 10^3 cells/μL, p = 0.04) than with mixed lesions (p = 0.04).

Conclusions

PTE induces profound dynamic shifts in monocyte subsets in both pulmonary and systemic circulations.

Monocyte remodeling parallels hemodynamic improvement and likely reflects resolution of thromboinflammation.

Intermediate monocytes increase postoperatively, while non-classical monocytes remain low throughout.

- PTE reperfusion induces rapid monocyte remodeling were CM and INT-M expand after reperfusion, while NCM sharply decline.
- Early Pulmonary circulation monocyte enrichment suggests vascular sequestration, followed by systemic redistribution.
- The correlation between clot chronicity and INT-M mobilization indicates diseases severity-specific immune response.

Finding support a compartmentalized innate immune response with systemic activation and transient pulmonary redistribution.

Understanding immune cell trajectories may unveil novel therapeutic targets to optimize recovery in CTEPH.