

Functional Effects of Platelet Manufacturing Methods

An Interim Analysis of the Chilled Platelet Study *in vitro* (CHIPSiv)

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on behalf of the CHIPSiv Study Team

Background

- Platelets in the U.S. are majority apheresis
- 3 apheresis machines are in use
- Platelets are stored in plasma or PAS
- **Despite this, platelets are treated as a ubiquitous product**
- Unclear how storage temperature +/- manufacturing method impacts function

Cold Stored Platelet Program

- Goal to license cold stored platelets for US Army, Navy, Air Force
 - Potential 21-day storage duration
 - Funded by US DOD/USAMMDA
- Program PI – Spinella
 - Clinical Trial PI – Spinella
 - RCT of CSP vs RTP in CT Surgery Patients
 - Adaptive trial design, increasing storage duration based on trial data
 - Over 250 of 1000 enrolled
 - Estimated Trial Completion – 25 Jan 2025
 - **CHIPS *in vitro* (CHIPSiv) Study** PI – Shea
 - Data to complement trial data in effort to license 7 apheresis platforms

CHIPSiv Study Design

- RT tested d0 and d7, CS tested d0, d7, d14, d21
 - RT agitated, CS unagitated (Shea, Spinella, Thomas 2022; PMID:35898113)
- Two study sites, N=20 total per group
- Seven study groups: Amicus PAS (AI) and plasma (AP), Trima PAS (TI) and plasma (TP), Haemonetics (MCS) in plasma, PRT Amicus PAS, and PRT Trima plasma
- Intrinsic product function assessed

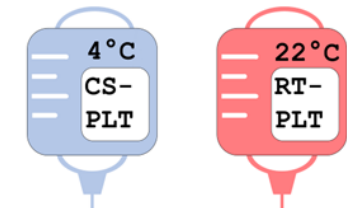
Study Groups by Manufacturing Method

- A. Trima in Plasma
- B. Trima in Isolate
- C. Amicus in Plasma
- D. Amicus in Intersol
- E. Haemonetics in Plasma
- F. PRT-Trima in Plasma
- G. PRT-Amicus in Intersol

10 donors per group X
5 study groups X
2 study sites =
100 donors

Platelet Donations, Storage Temperatures, and Storage Sampling Days

1st Donation 2nd Donation



N=100

N=100

Assay Days
0, 7, 14, 21

Assay Days
0, 7

Perform Assays

Compare Metrics:

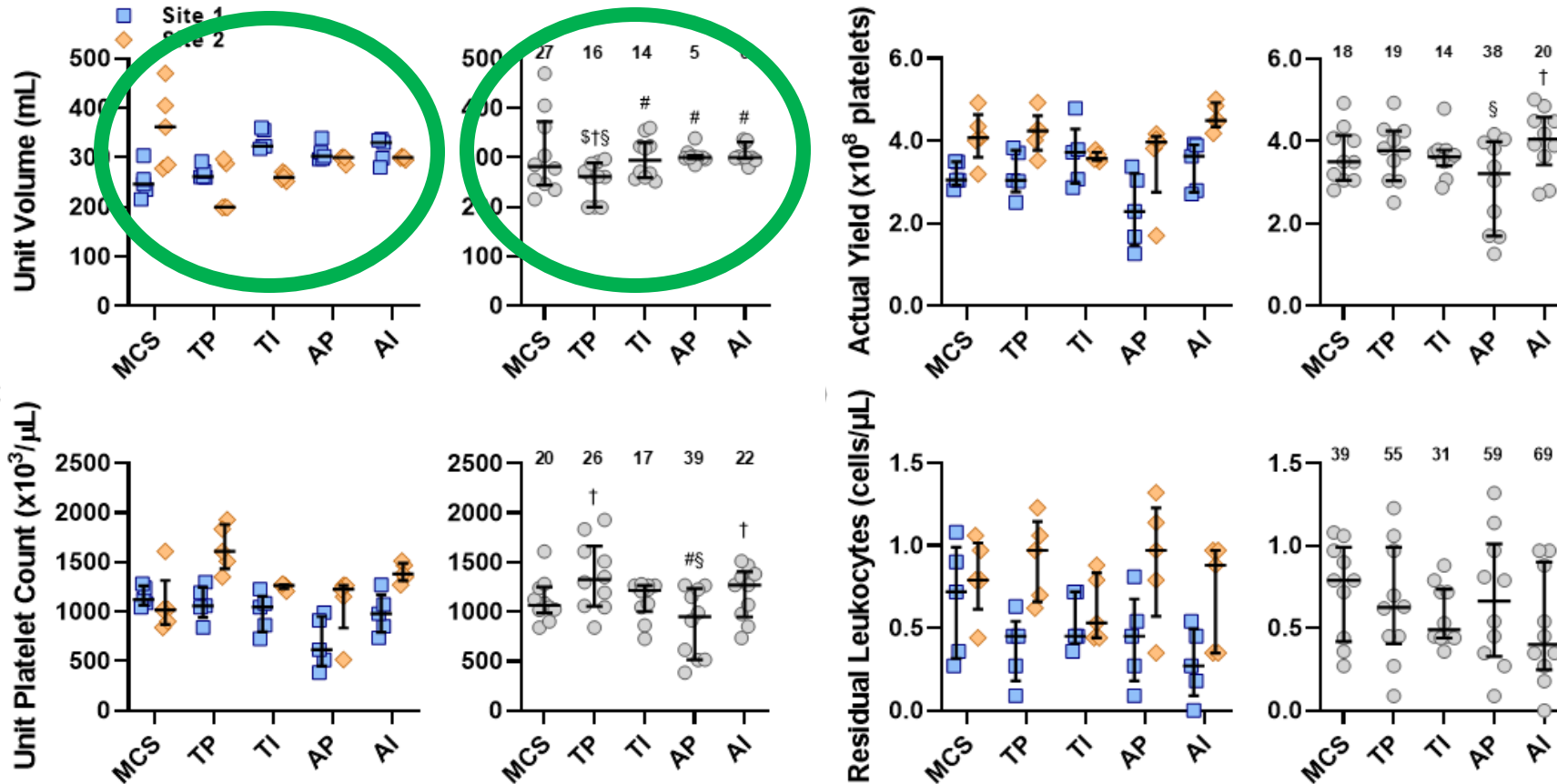
- 4°C D7 vs 22°C D7 in each study group
- 4°C D0, 7, 14, 21 in each study group
- 22°C D0 vs 22°C D7 in each study group
- % change from D0 for each time point across all study groups and temperatures



Validation Study

- Validation study completed N=5 per site MCS, TP, TI, AP, AI (Thomas et al. 2023; PMID: 37070399)

■ Site 1
◆ Site 2



Methodology

- GMP study
- Yield ≥ 3.0
- Platelets aseptically serially sampled
 - RT: d0, d7
 - CS: d0, d7, d14, d21
- Traditional and exploratory metrics
 - Biochemistry, **count**, **aggregometry**, **thrombin generation (PRP)**, **ROTEM**, **microfluidics**, **microparticles**, clot retraction
- Both sites currently have Trima Plasma (TP) and PAS (TI) and Amicus Plasma (AP) and PAS (AI) in progress
- Data presented is from one site and is an interim analysis using raw data

Donor Characteristics

Total N=24 (48 PLT)

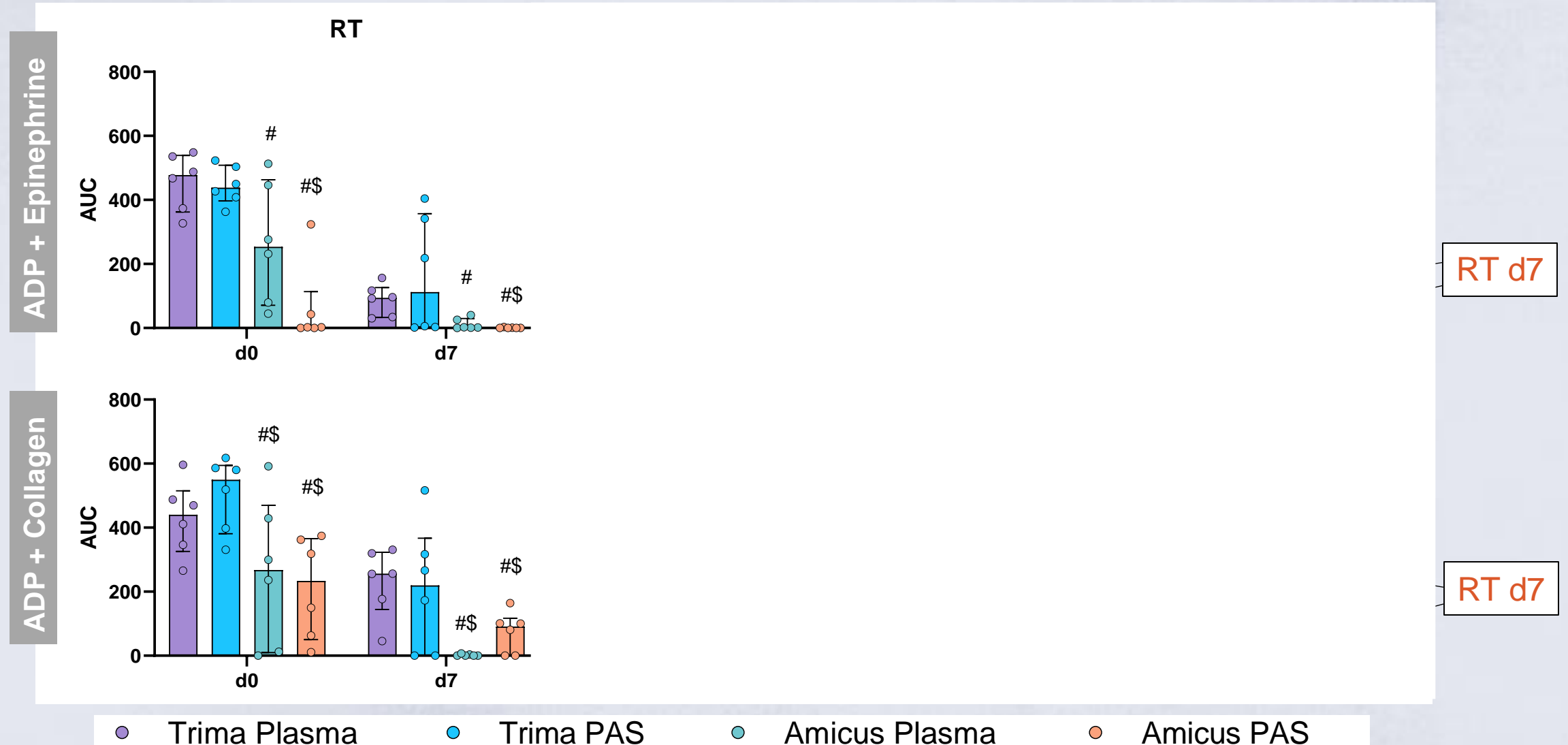
Biological Sex	[N (%)]
Female	12 (50%)
Male	12 (50%)

Age [median (IQR)] 29 (25-50)

Race & Ethnicity	[N (%)]
Asian	2 (8%)
Black	0 (0%)
White	22 (92%)
Other	0 (0%)
Hispanic	1 (4%)

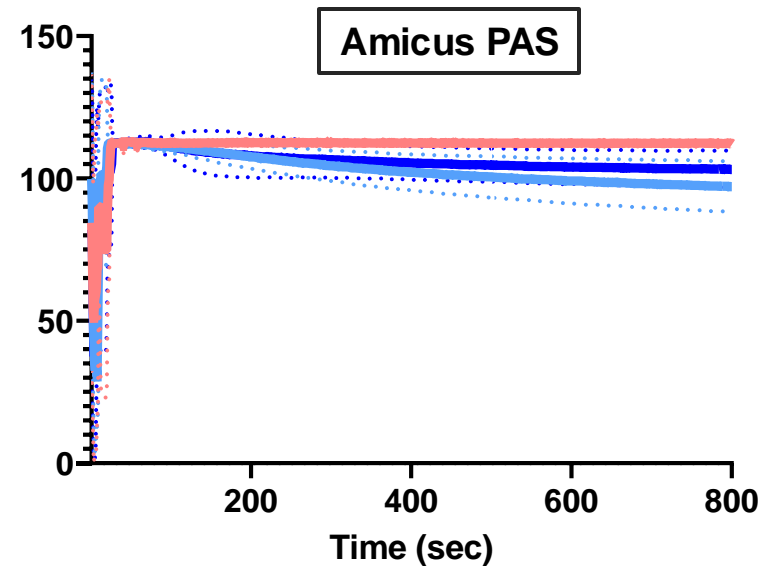
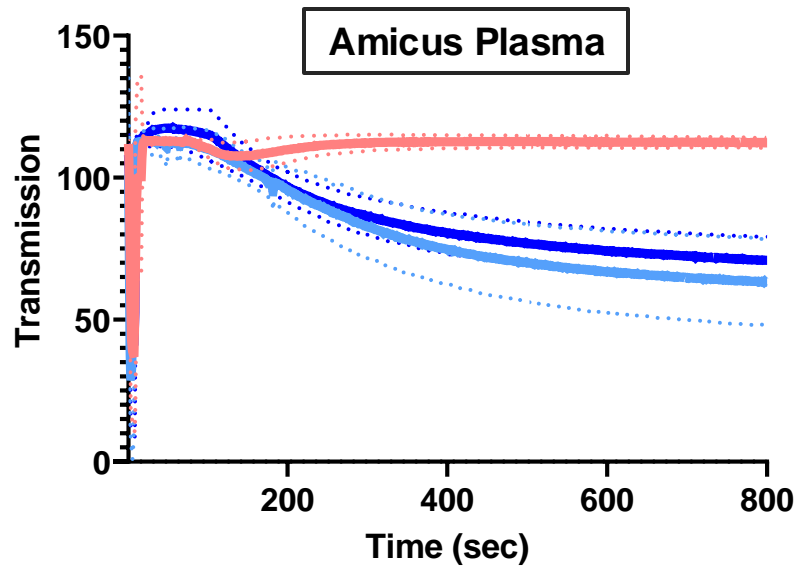
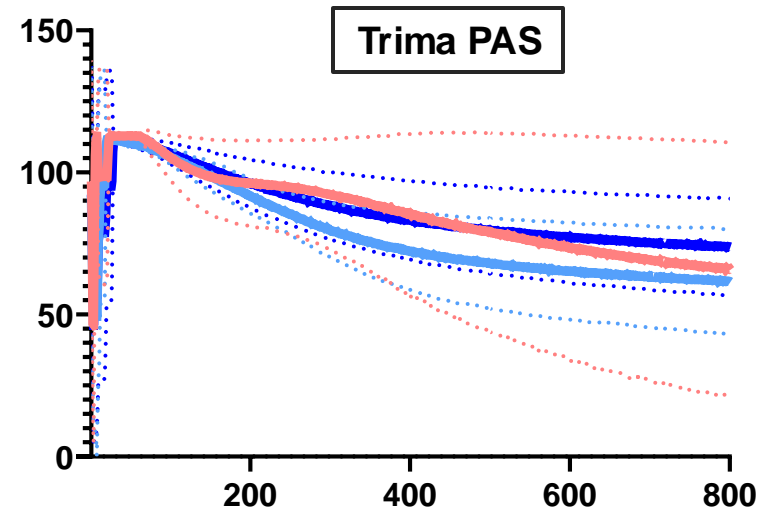
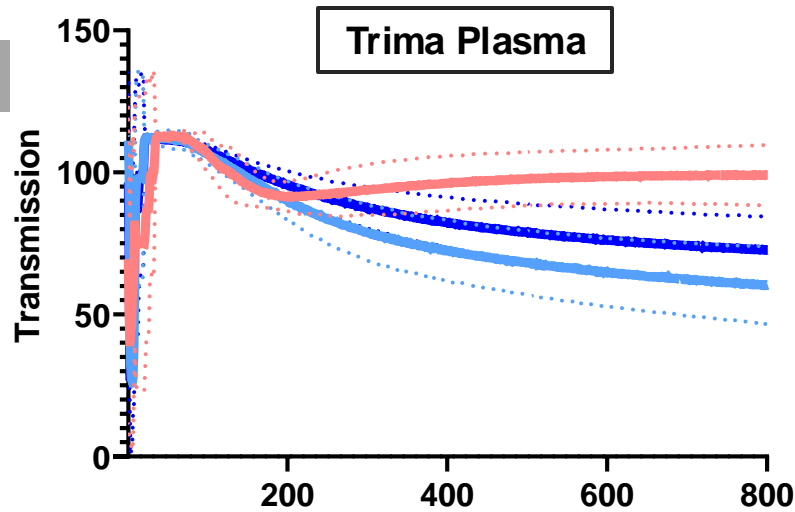
Blood Type	[N (%)]
A	8 (33%)
B	5 (21%)
AB	2 (8%)
O	9 (38%)

Aggregation Ability is Heavily Platform Dependent



CS at least retains PLT aggregation ability out to d21...

ADP + Epinephrine

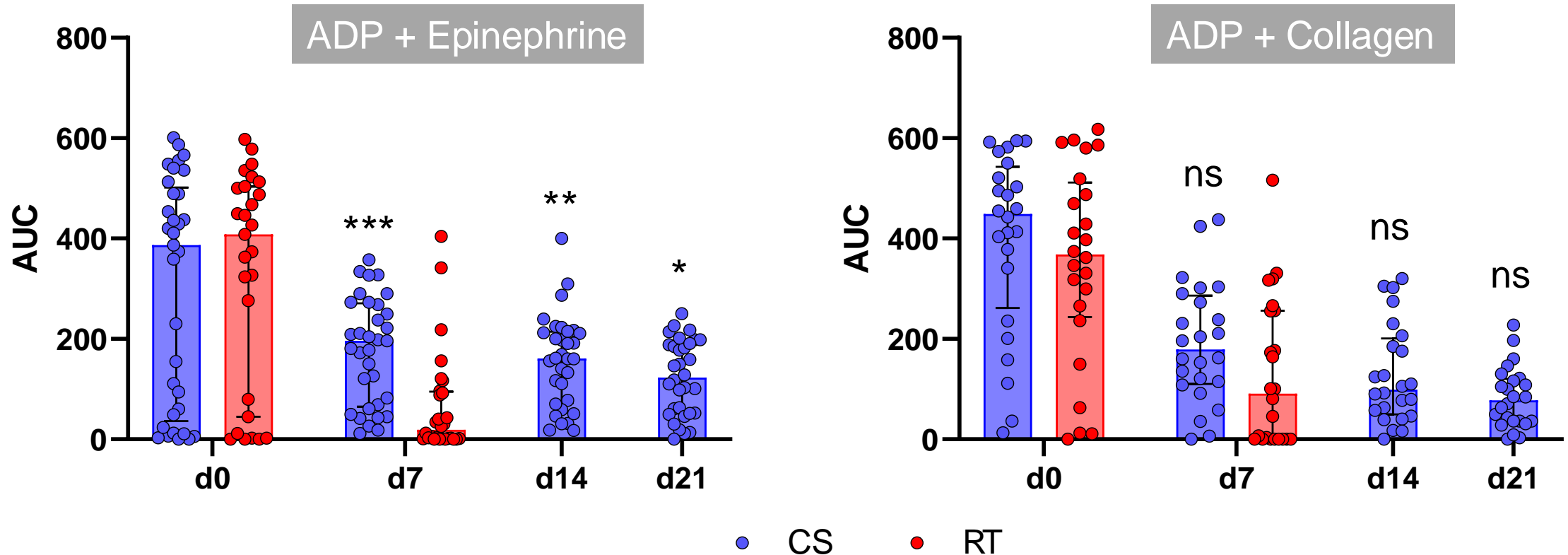


more aggregation



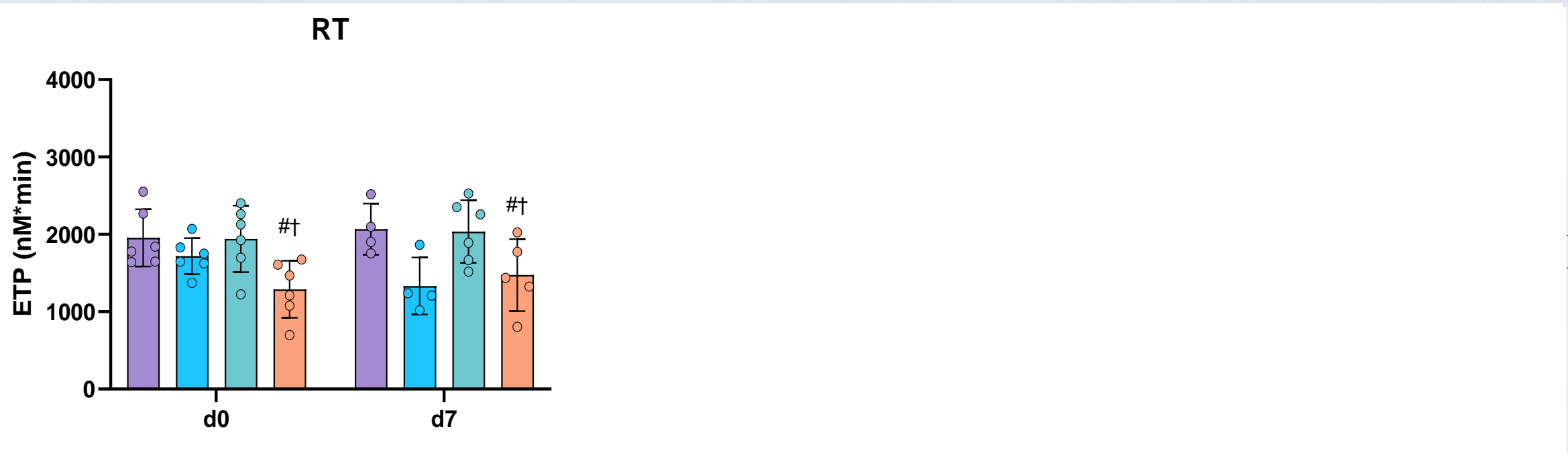
RT D7 CS D14 CS D21

... and perhaps even improves aggregation



ns: not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. RT d7

Thrombin Generation is also Platform Dependent

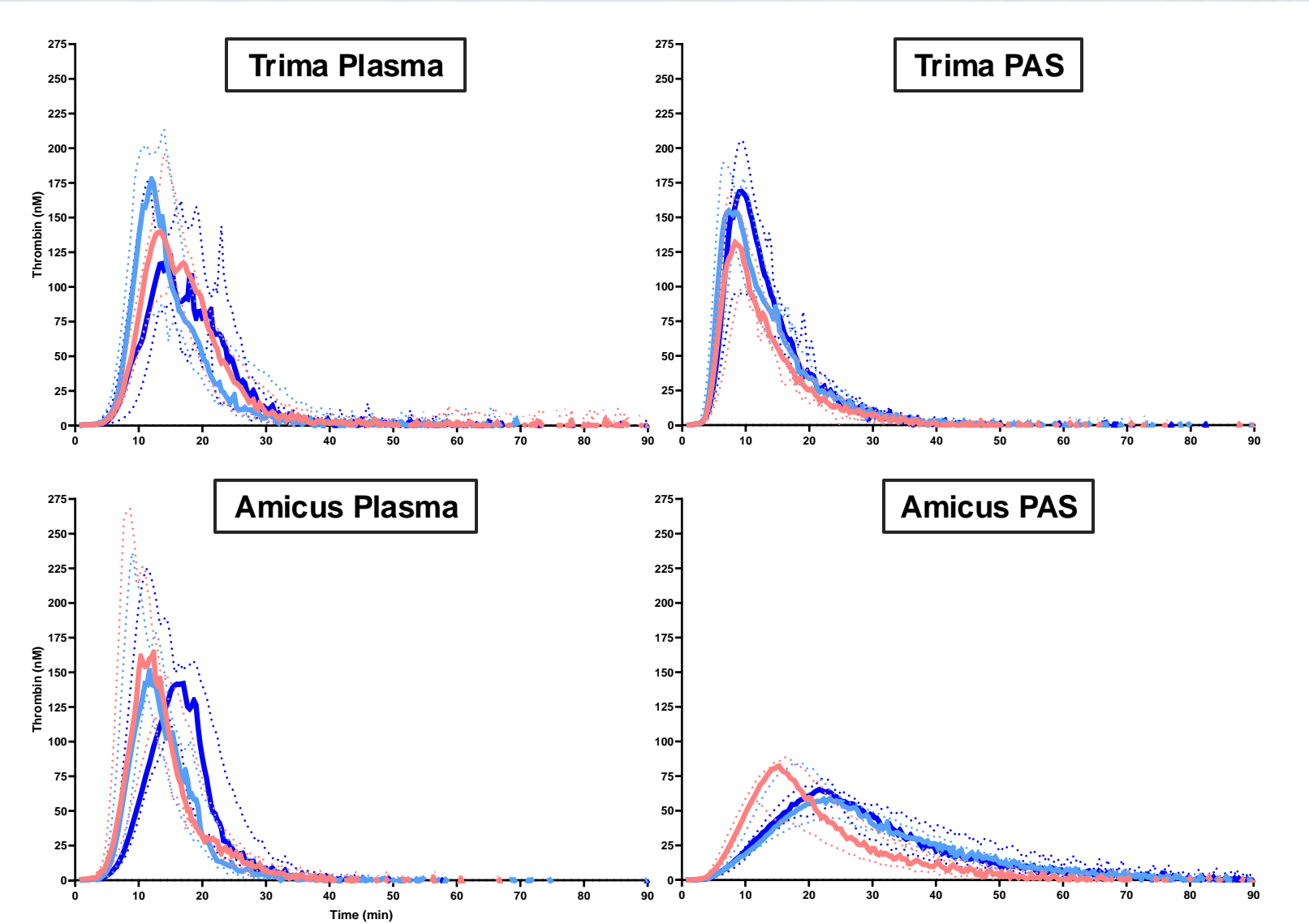


RT d7

● Trima Plasma ● Trima PAS ● Amicus Plasma ● Amicus PAS

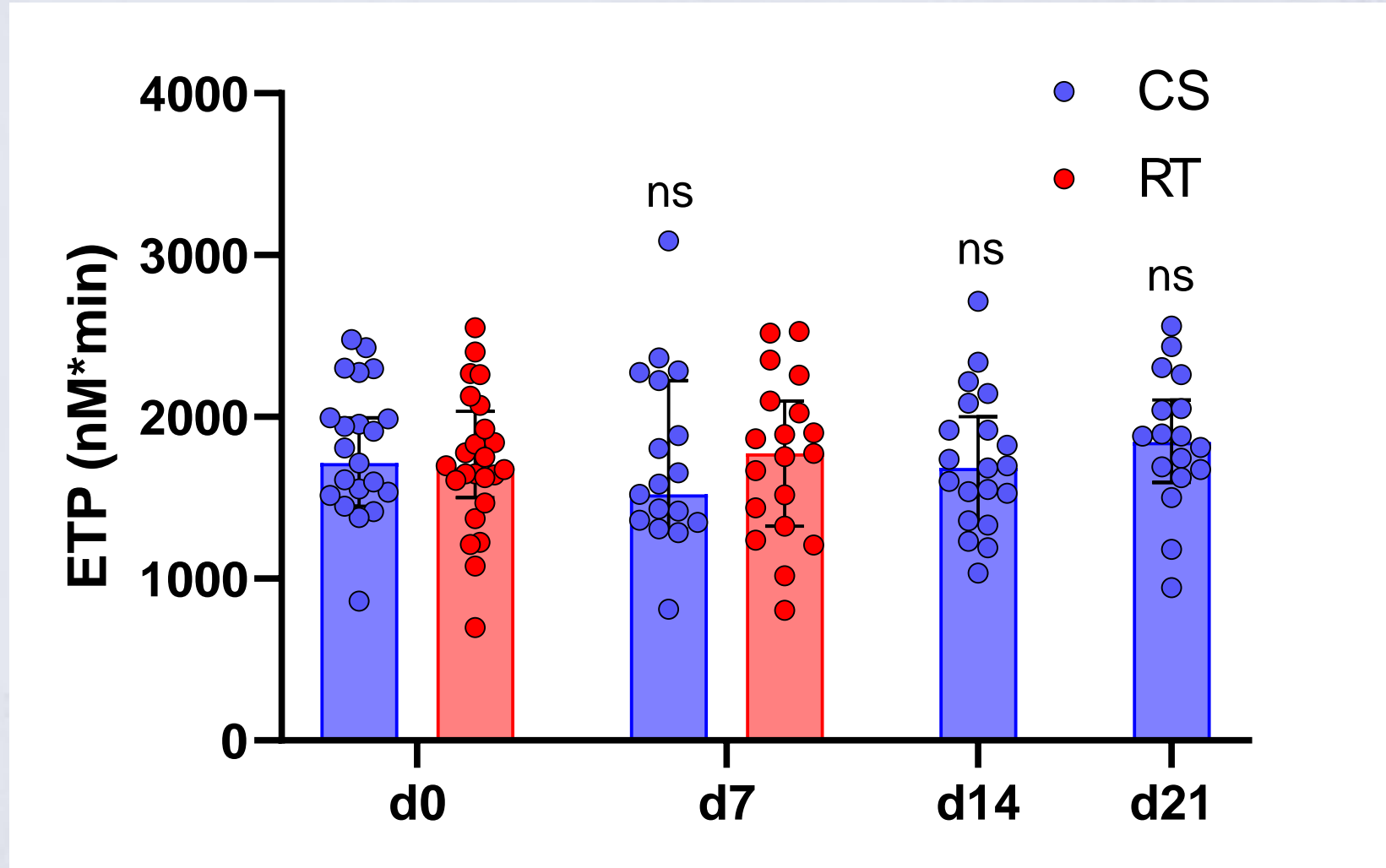
significantly different from Trima Plasma; \$ Trima PAS; † Amicus Plasma; § Amicus PAS

CS Retains Thrombin Generation Capacity



RT D7 CS D14 CS D21

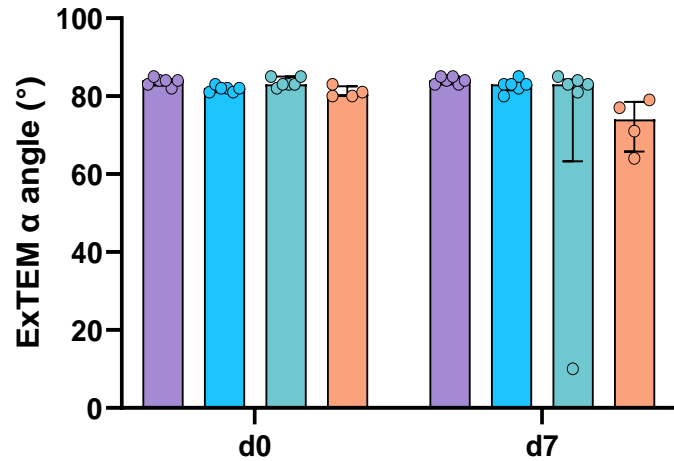
CS Retains Thrombin Generation Capacity



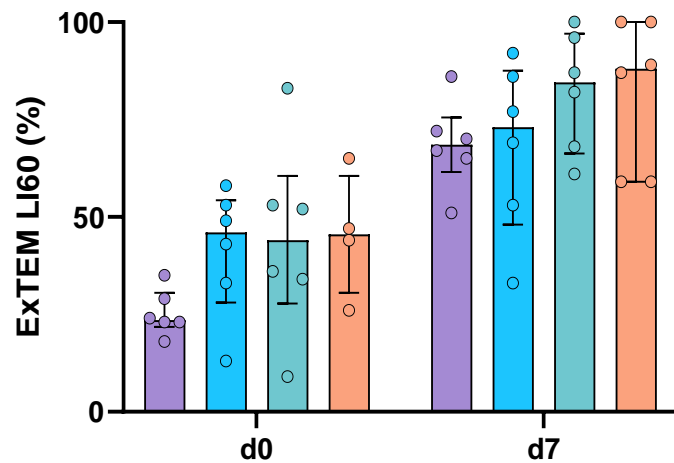
ns: not significant, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. RT d7

Preservation of ROTEM is Platform Dependent

RT



RT d7



RT d7

more lysis
↓

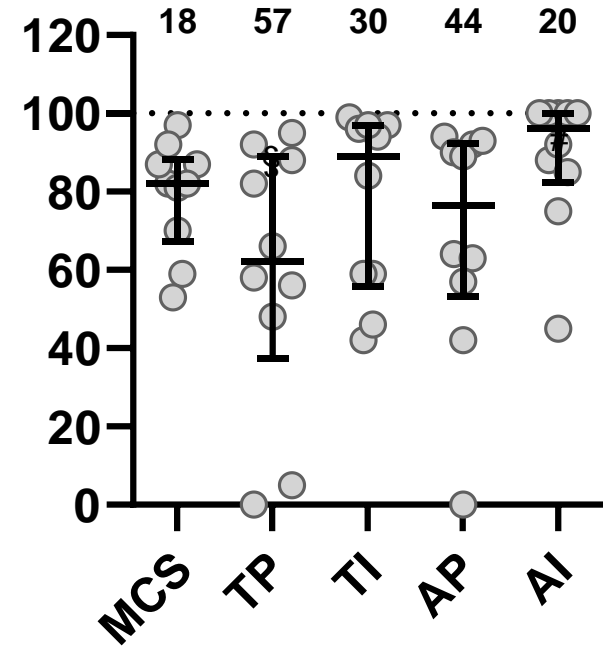
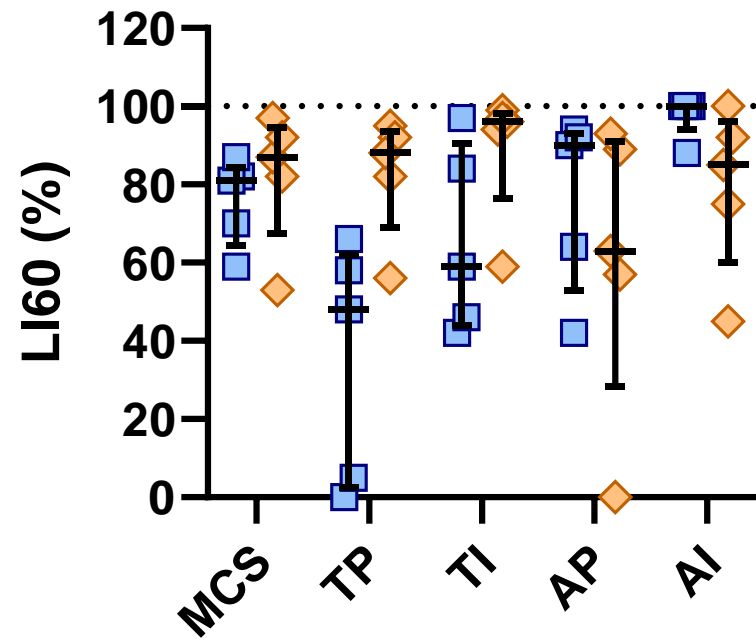
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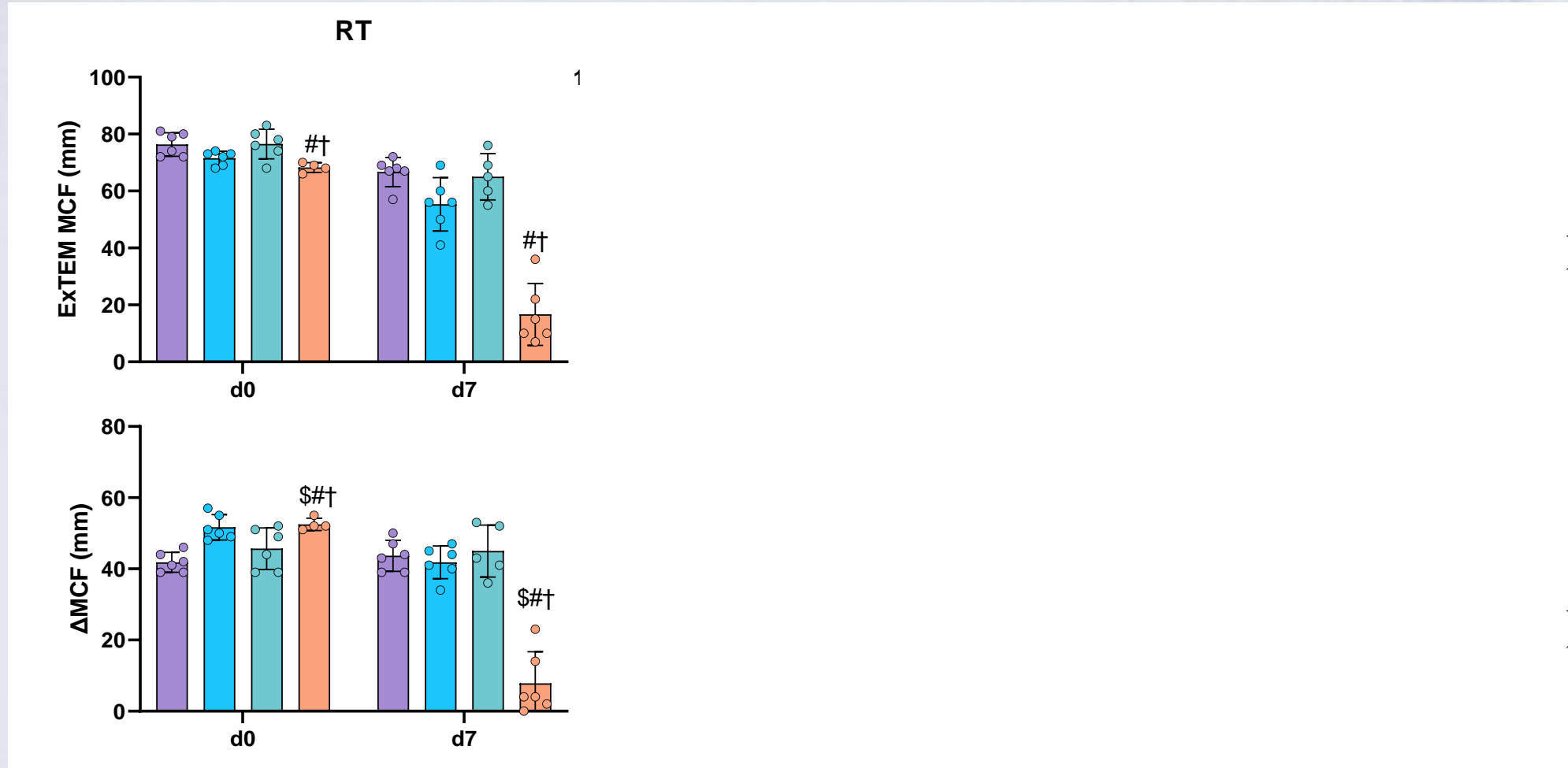
Lysis Signal Consistent Across Sites in Validation Study



more lysis



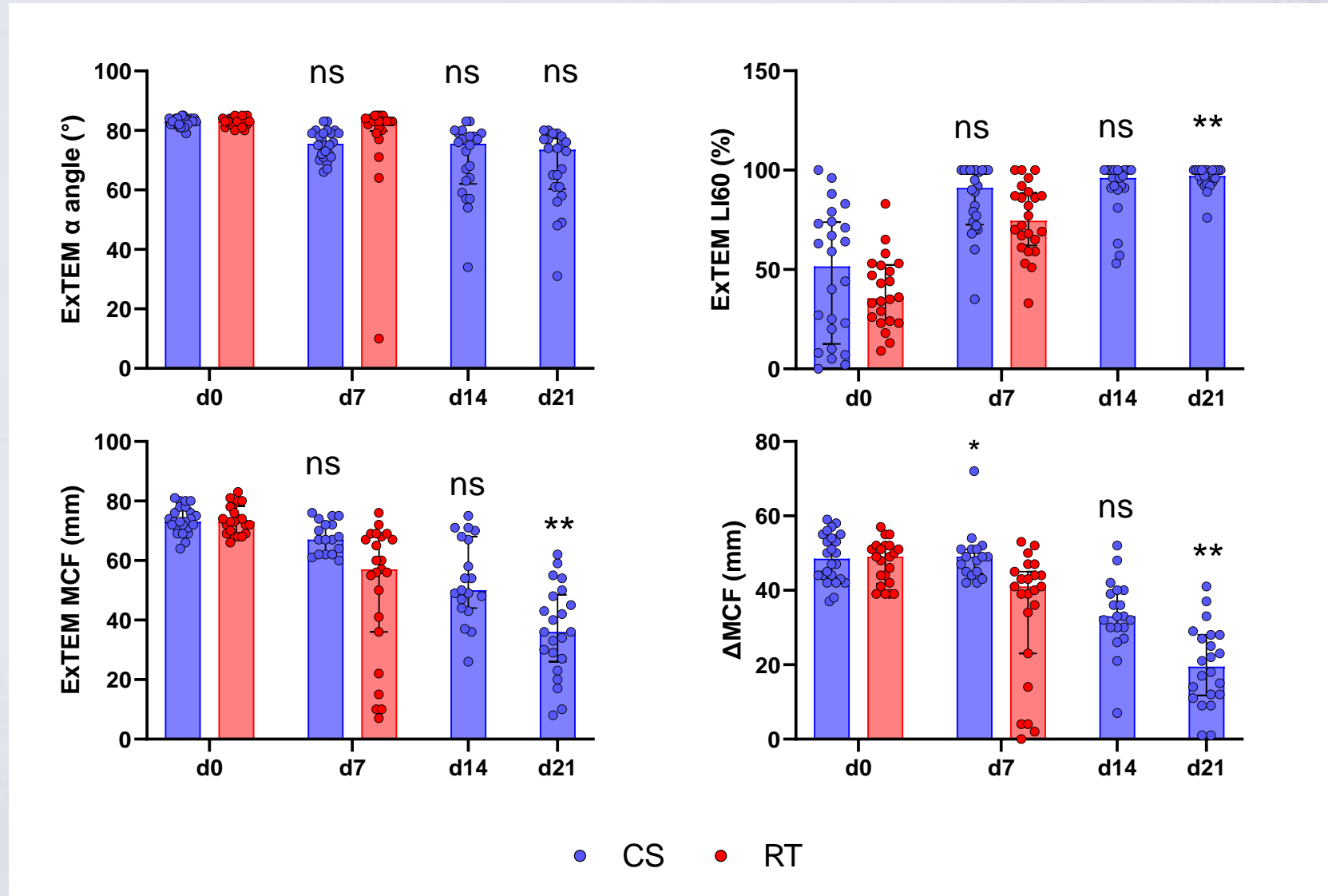
ROTEM MCF is Platform Dependent



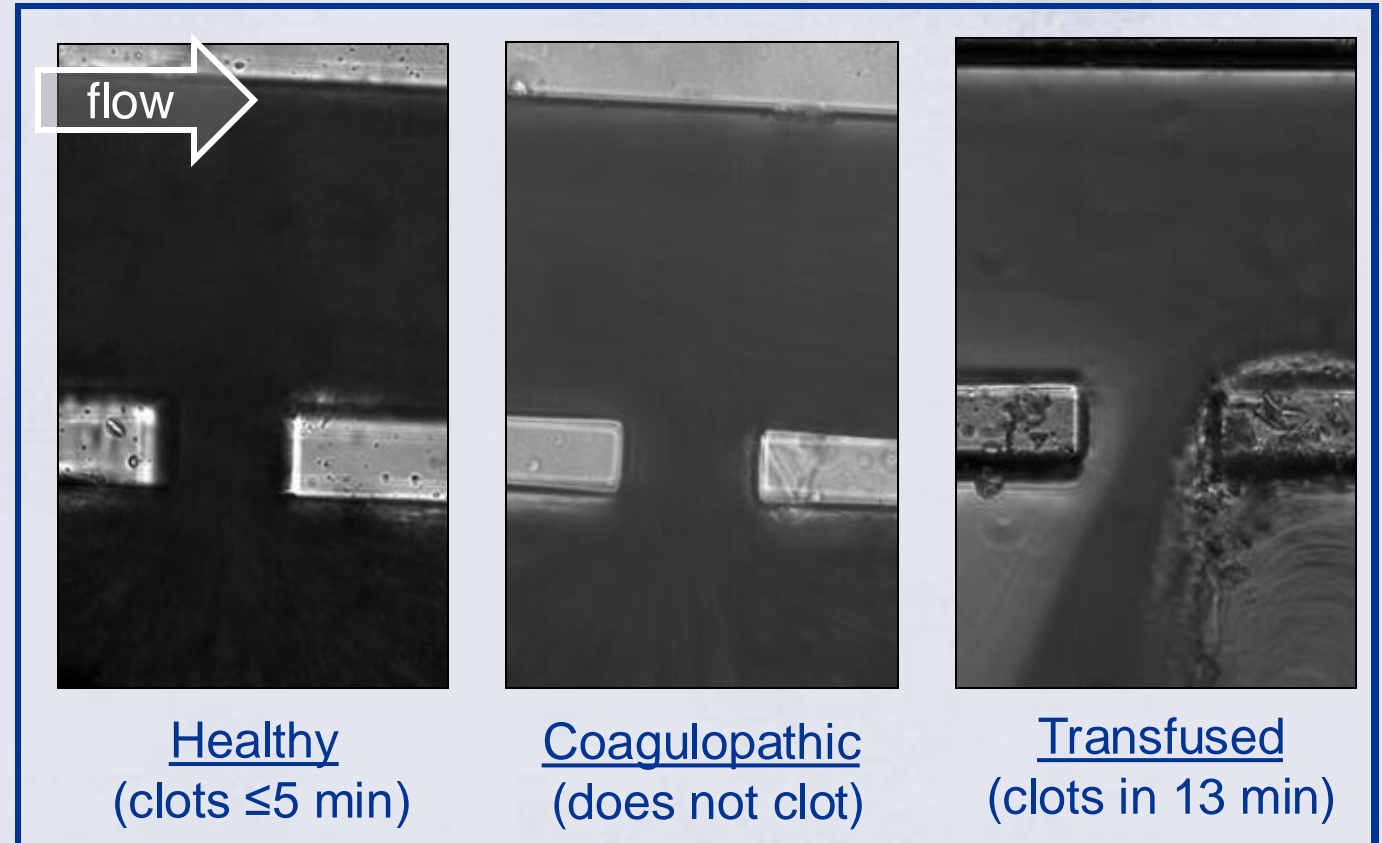
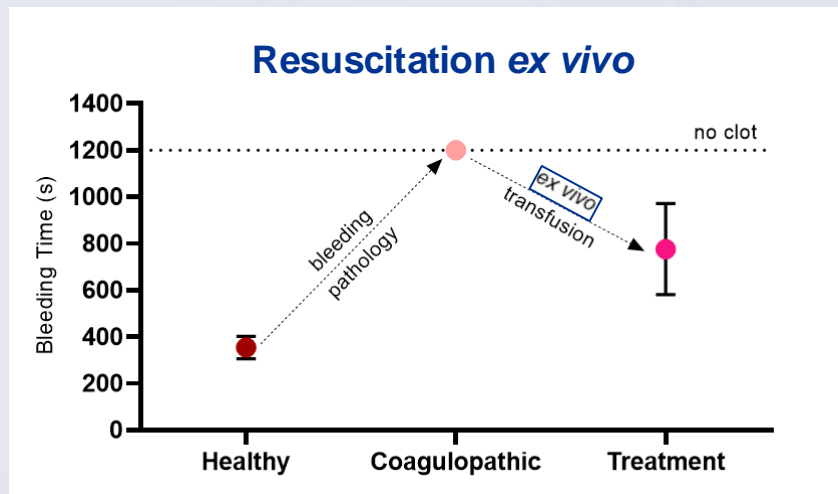
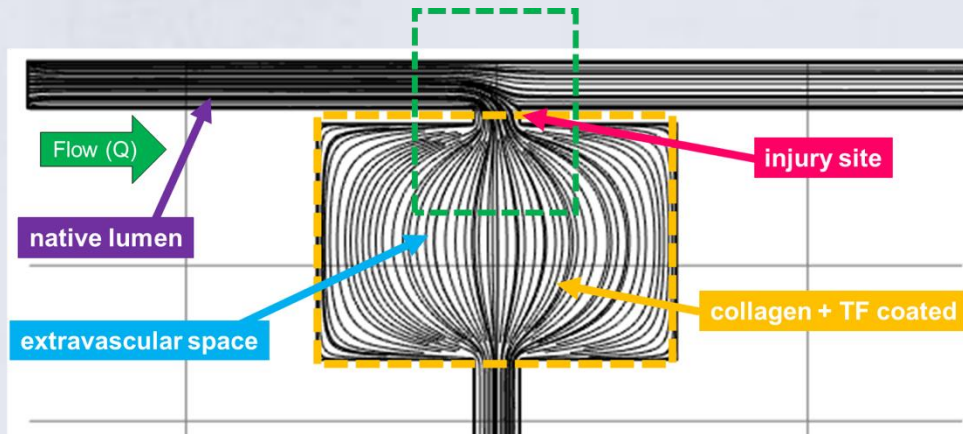
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Preservation Differences per Parameter

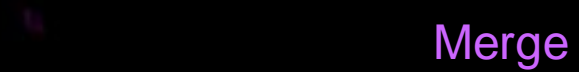
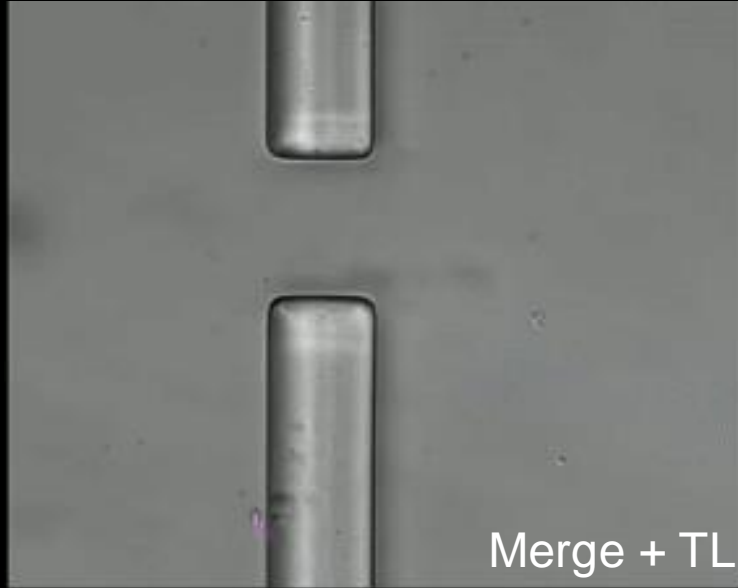
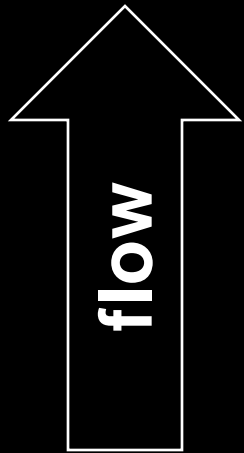


Microfluidic Model of Transfusion



CHIPSiv: Induction of Dilution or P2Y12 inhibition + study product

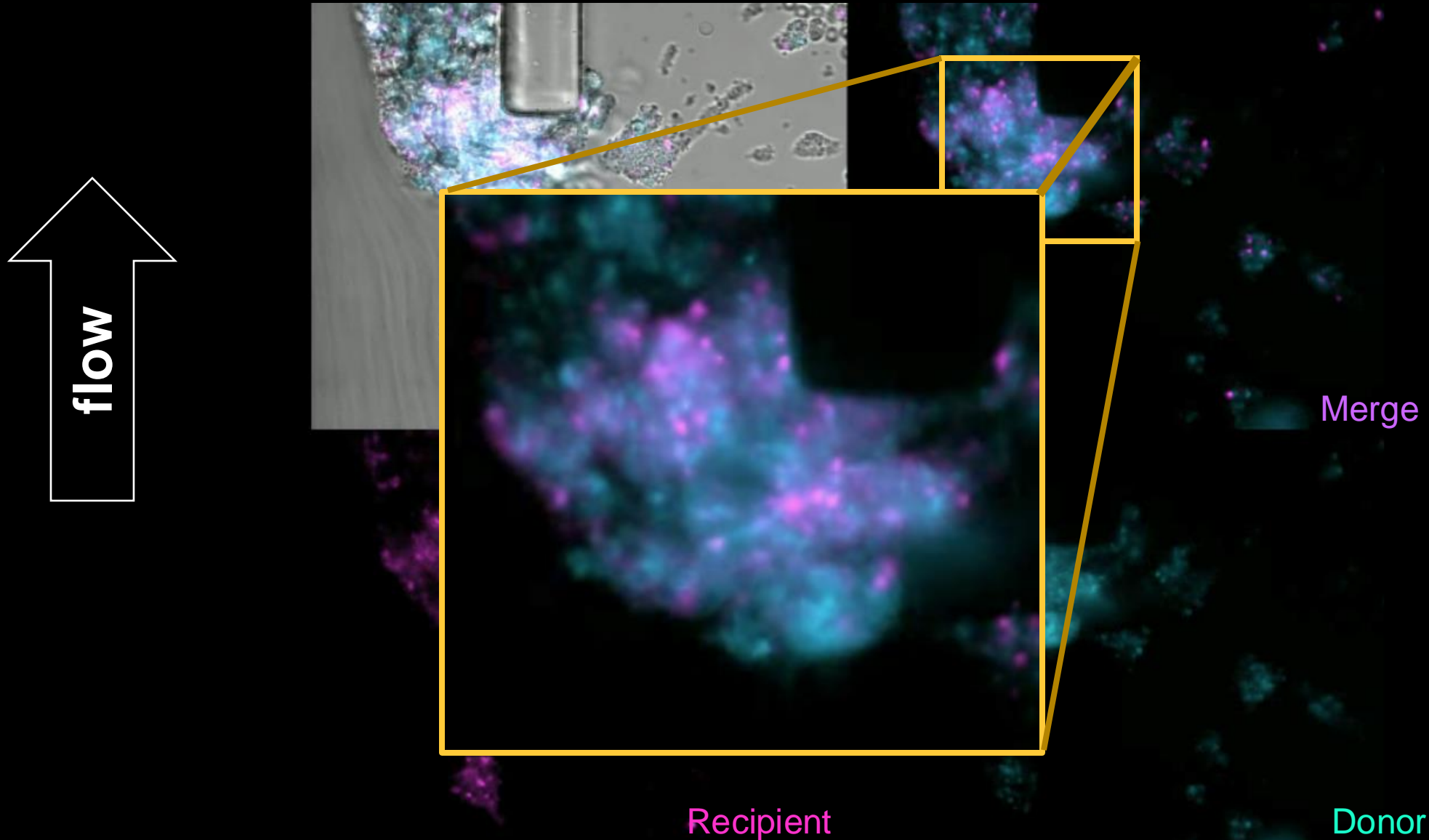
Recipient and Donor Platelets Synergize



Recipient

Donor

Recipient and Donor Platelets Synergize

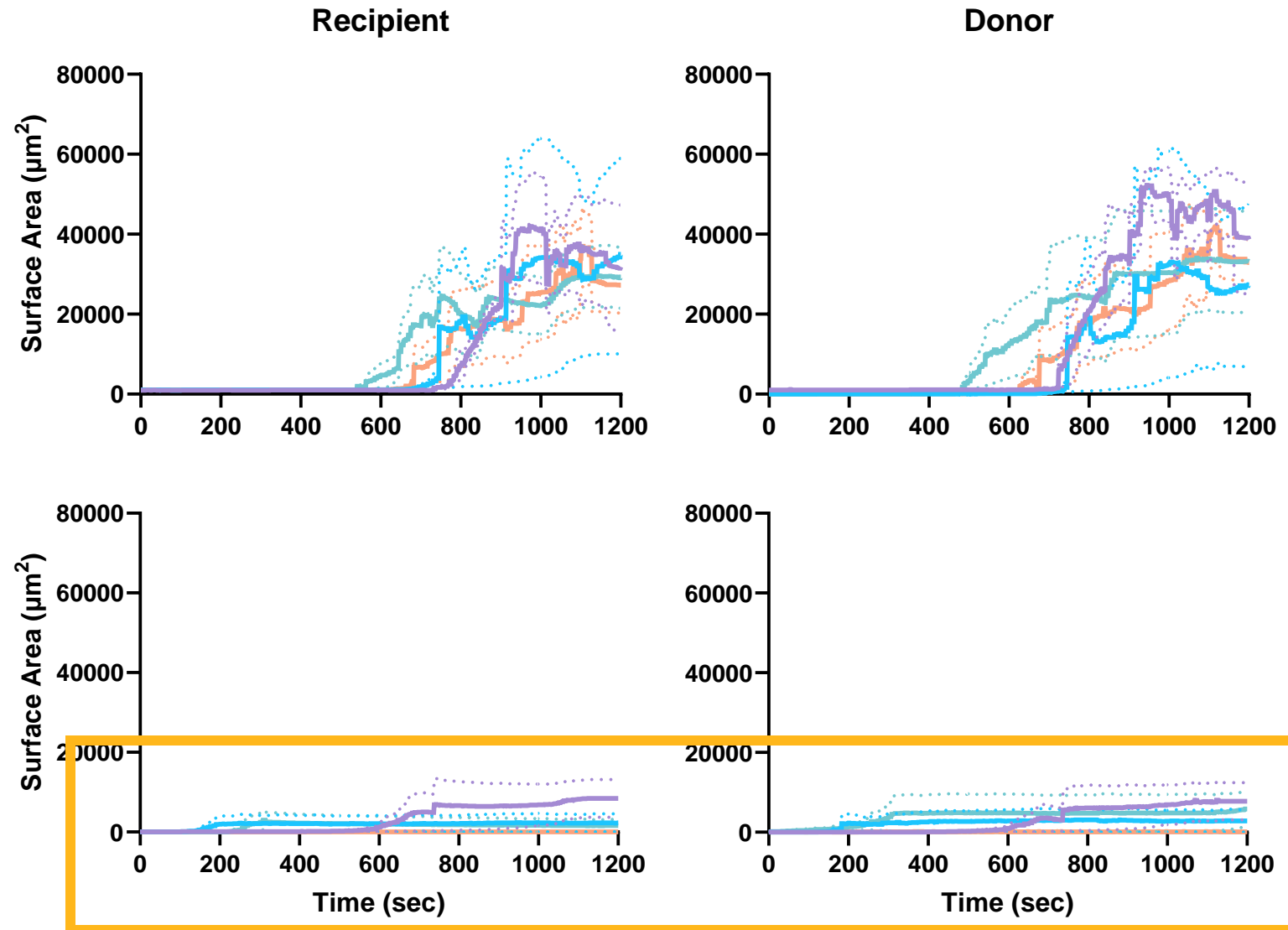


Resuscitation Capacity of PLT is Shear-Dependent

Arterial Shear

Dilution

Venous Shear

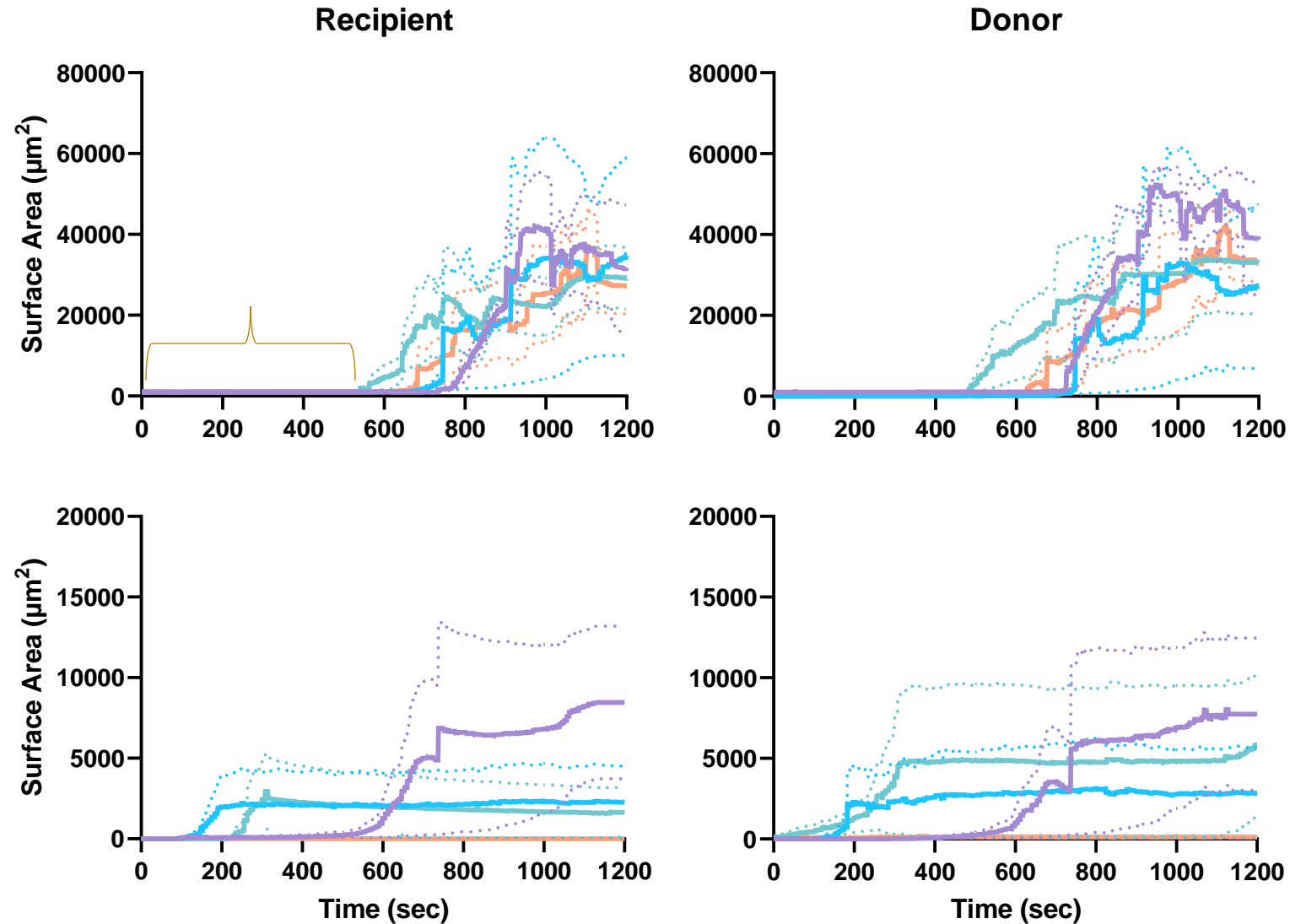


Resuscitation Capacity of PLT is Shear-Dependent

Arterial Shear

Dilution

Venous Shear



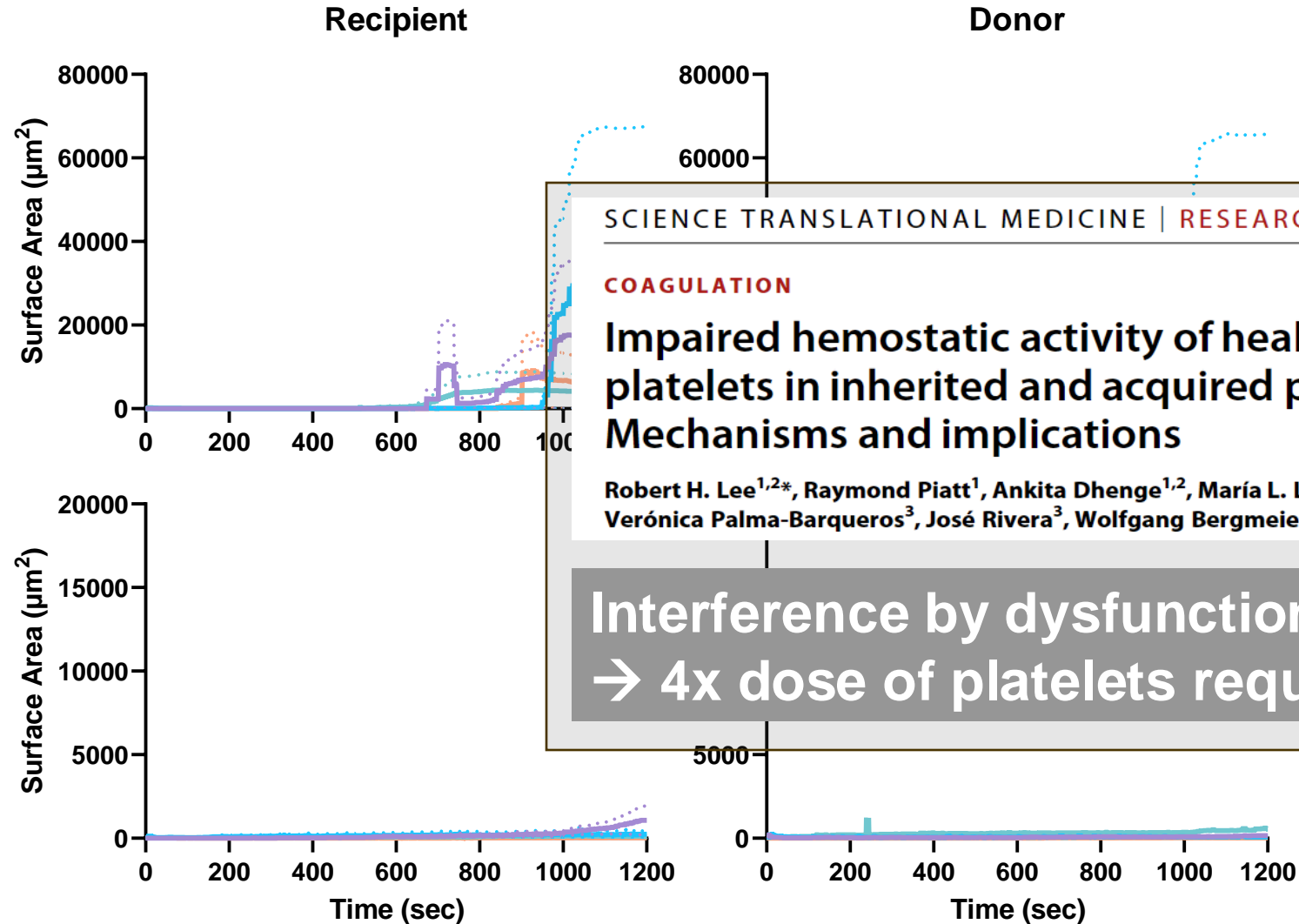
...and Model Dependent

Arterial Shear

P2Y12
Inhibition

6.4 μ M ticagrelor

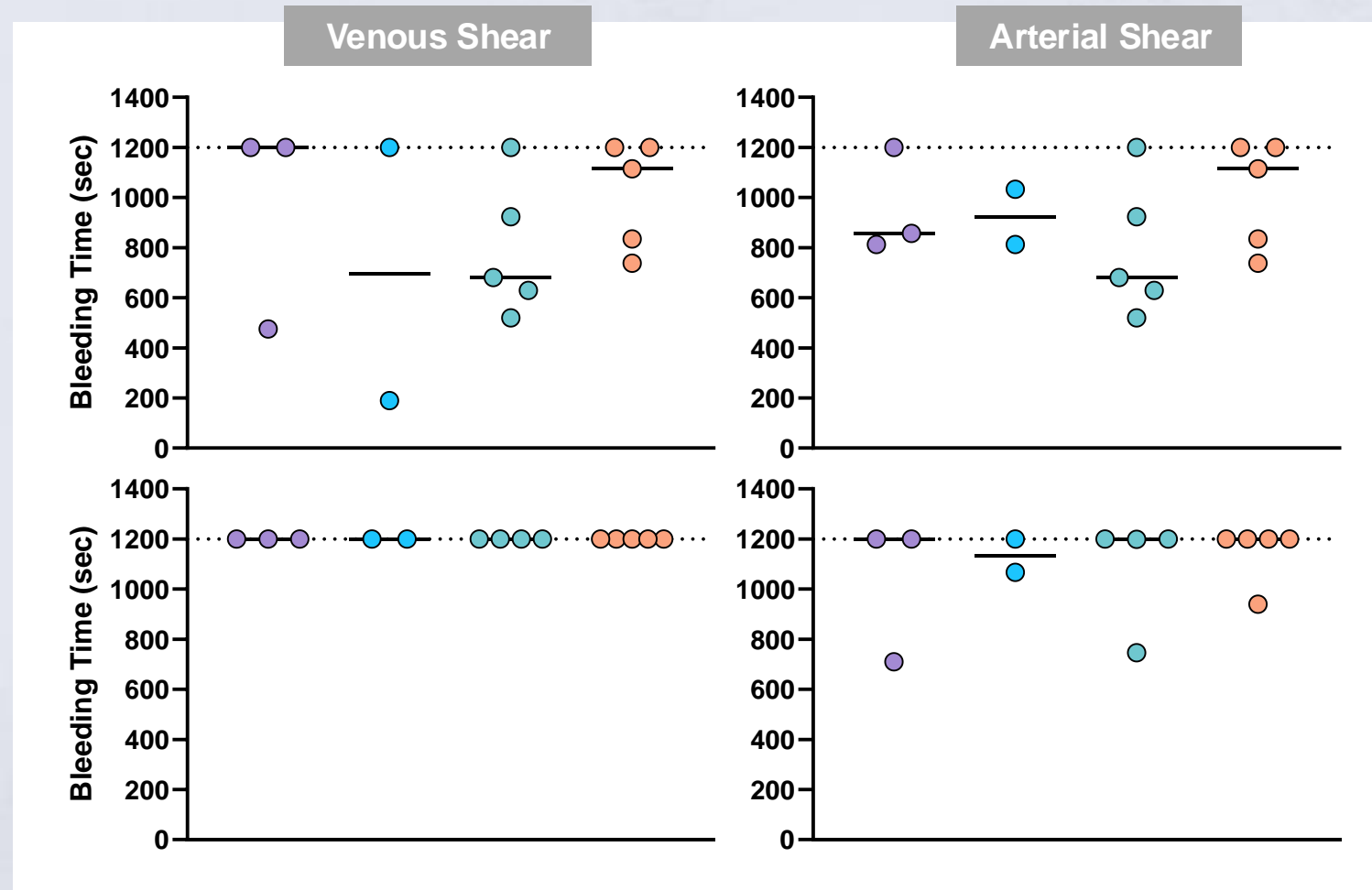
Venous Shear



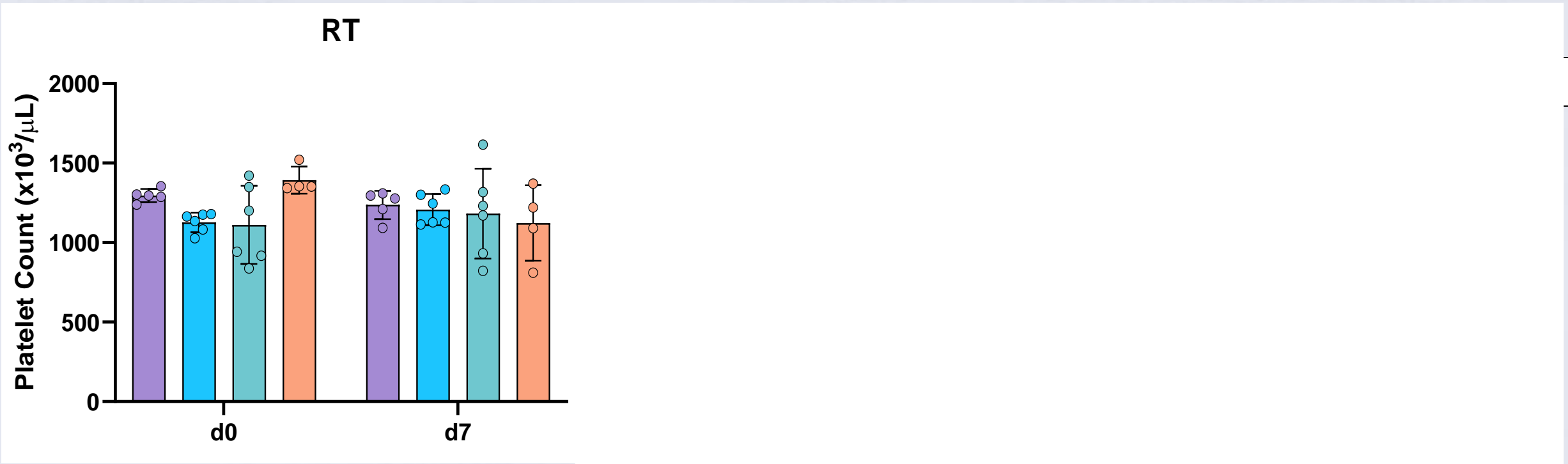
Differences Reflected in Microfluidic Hemostasis Times

Dilution

P2Y12 Inhibition



Platelet Count is Highest in Amicus PAS

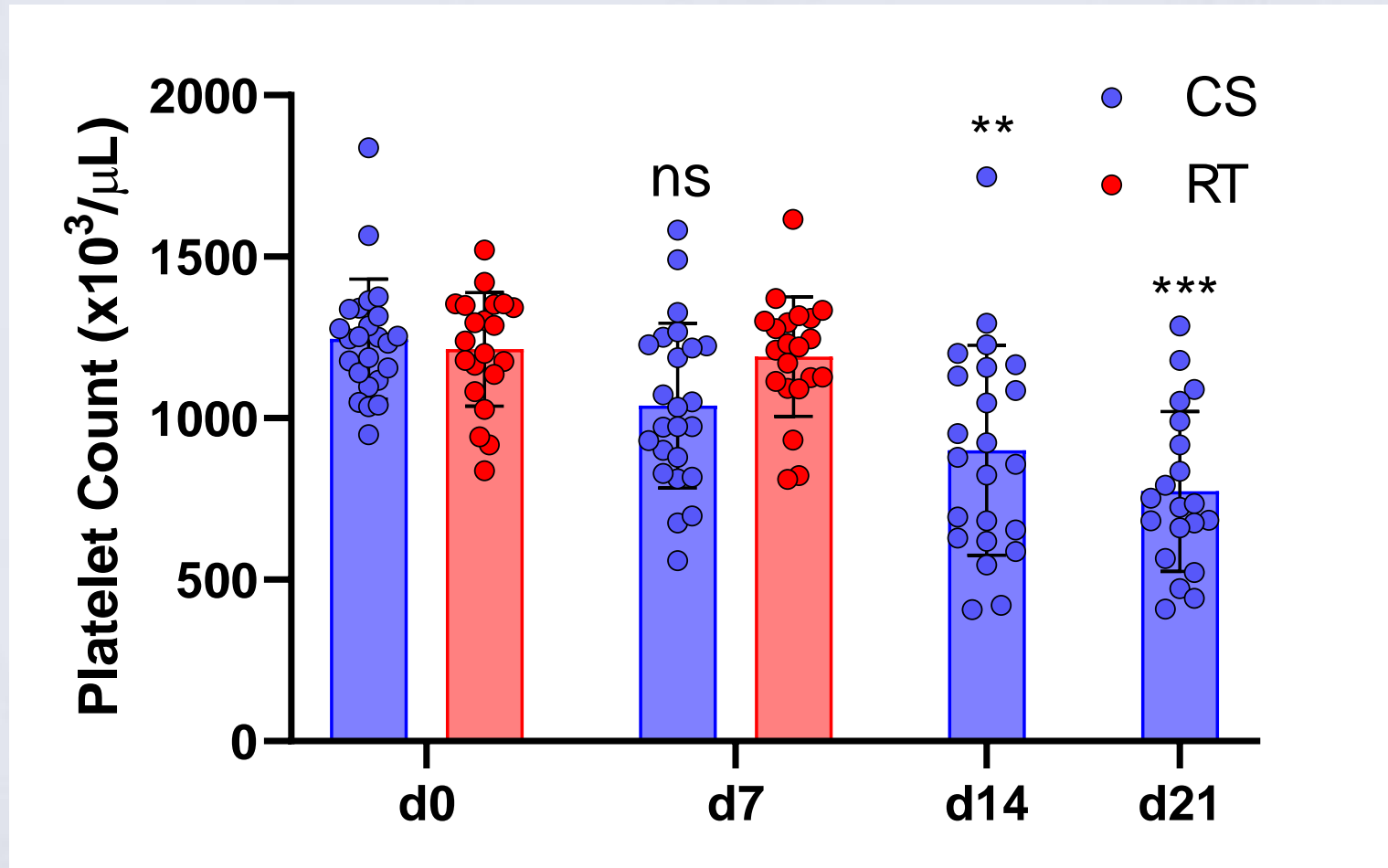


d7

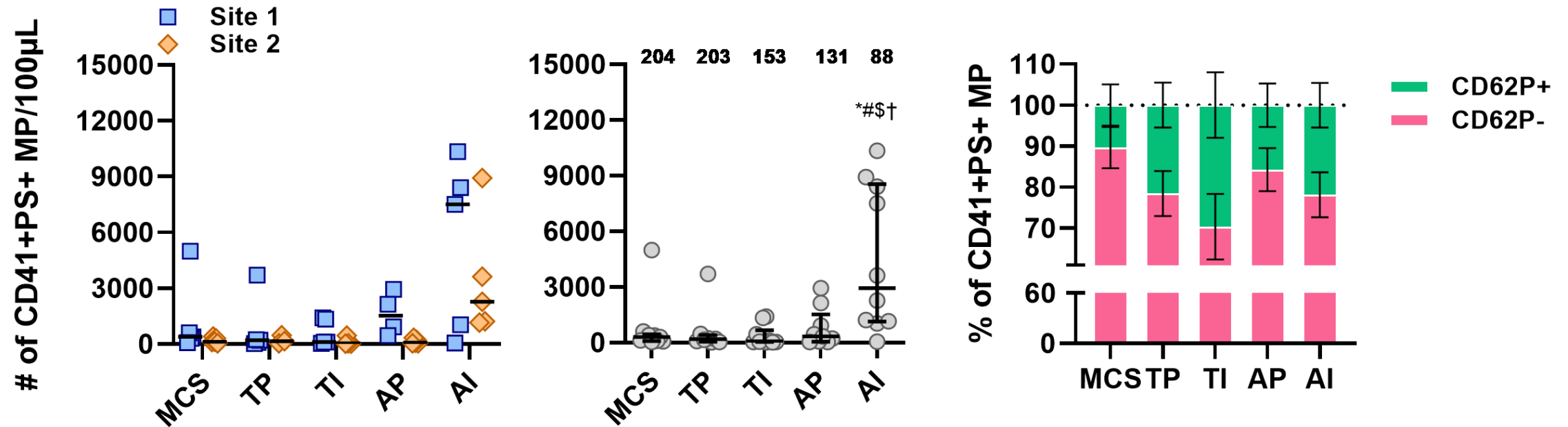
● Trima Plasma ● Trima PAS ● Amicus Plasma ● Amicus PAS

significantly different from Trima Plasma; \$ Trima PAS; † Amicus Plasma; § Amicus PAS

Count Declines in CS



Microparticles do not seem to be Procoagulant in this Context



significantly different from Trima Plasma (TP); \$ Trima PAS (TI); † Amicus Plasma (AP); § Amicus PAS (AI); * MCS 9000 (MCS)

CS PLT out to d21 have preserved *in vitro* function

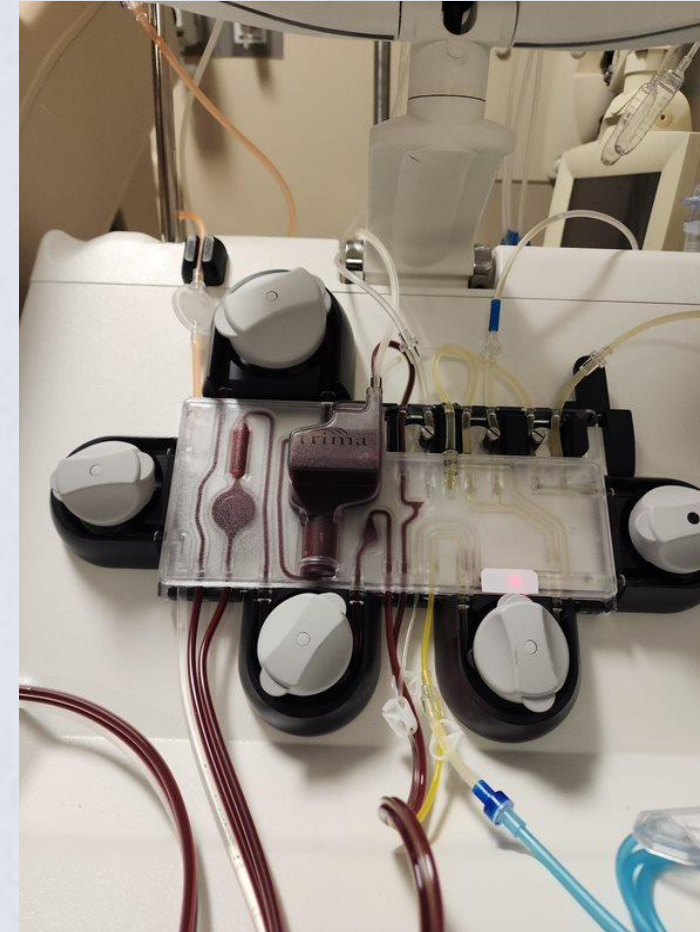
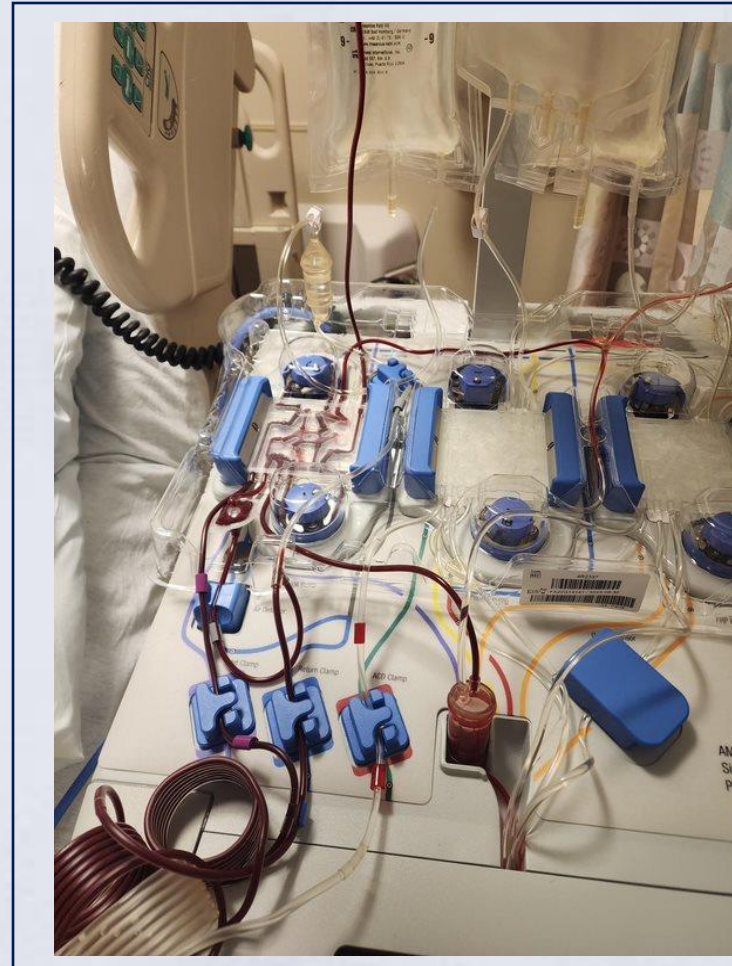
- Aggregate data shows preserved function as measured by aggregometry (*improved*) and thrombin generation (*conserved*)
- Thromboelastometry shows a decline in MCF at d21, yet α conserved, and baseline lysis resolves

- All despite declines in count!

But...

...we can't ignore the machine

- Distinct platform differences that persist through storage
- Different platforms may have different strengths
- ***All platelets are NOT created equal***
 - Clinical data needed, of course
 - Role of *in vitro* for future licensing

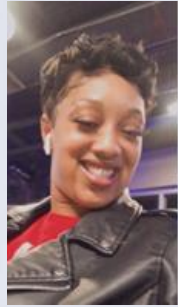


Data In Progress and Future Directions

- Completion of current and future groups
- Distilling these signals into hypotheses + subsequent mechanistic elucidation
- Study will result in 140 unique donors with paired collections at regular intervals
 - Sex differences
 - Donation differences
 - Donor-intrinsic factors
- Inter-site analysis
 - Variability
 - Population
 - Rank-comparisons
- Platform-specific storage performance

CHIPSiv Study Team

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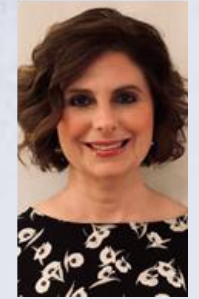
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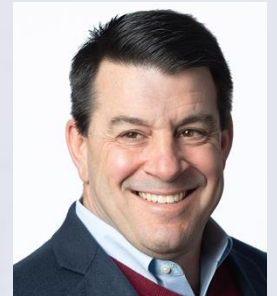
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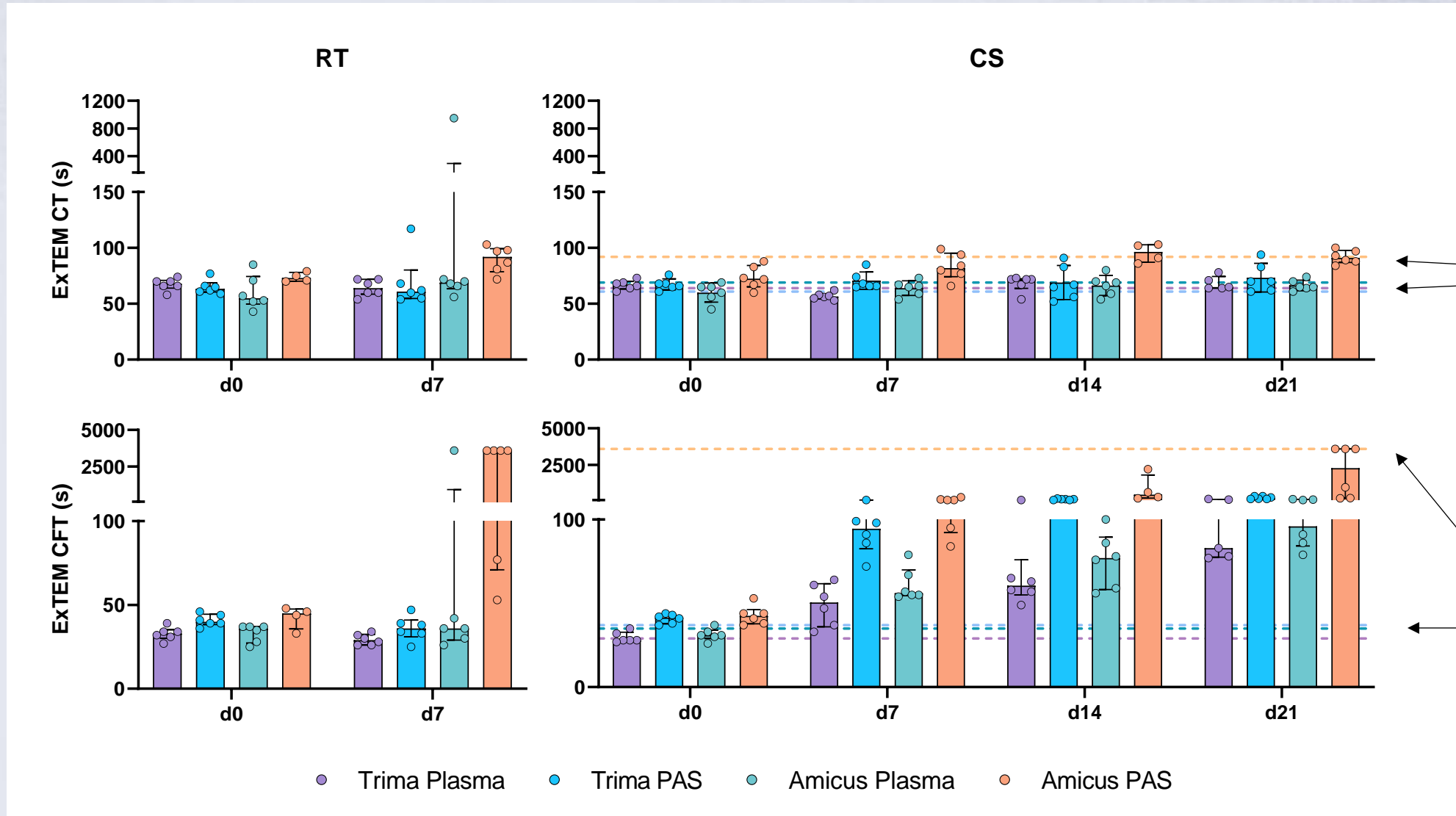
Thank you!



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ROTEM



RT d7

RT d7