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Angel Contreras-García, Maxime Desgagné, D'Elia Noelia, Charles-Hubert Lafantaisie-Favreau, Juan Carlos Ruiz, Georges-Etienne Rivard, Michael R. Wertheimer, Paula Messina, Caroline D. Hoemann

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EVENT ABSTRACT

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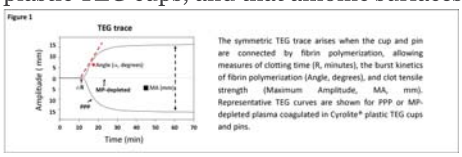
Anionic surfaces with minimal charge density can restore burst coagulation of microparticle/exosome-depleted blood plasma

Angel Contreras-Garcia[1], Desgagné Maxime[2], D'Elia L. Noelia[3], Charles-Hubert Lafantaisie-Favreau[4], Juan Carlos Ruiz[5], Georges-Etienne Rivard[6], Wertheimer Michel[1], Paula Messina[3] and Caroline D. Hoemann[2, 4]

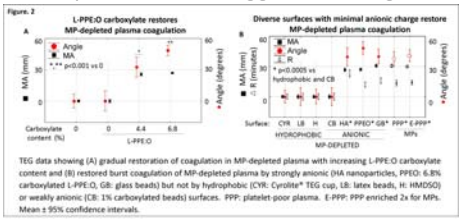
[1] Ecole Polytechnique, Engineering Physics, Canada
[2] Ecole Polytechnique, Chemical Engineering, Canada
[3] Universidad Nacional del Sur, Chemistry, Argentina
[4] Ecole Polytechnique, Institute of Biomedical Engineering, Canada
[5] Universidad Autónoma Metropolitana-Iztapalapa, Basic Sciences and Engineering, Chemical Engineering, Mexico
[6] Hôpital Sainte Justine, Division of Hematology-Oncology, Canada

Introduction: Blood contains microparticles (MP) and exosomes derived from a variety of cell types including activated platelets. MPs are procoagulant because their surfaces can express tissue factor and/or calcium-binding sites for coagulation factors that cooperate to induce burst thrombin activation [1]. Platelet-poor plasma (PPP) contains low levels of MPs and can be induced to coagulate after contact with both hydrophilic and hydrophobic surfaces [2]. In a standard thromboelastography (TEG) assay with plastic cups and pins, PPP undergoes spontaneous burst coagulation, as revealed in the TEG trace by a variable clotting time (10 to 26 minutes), a low Angle (~33°) and reproducible low clot tensile strength or Maximum Amplitude (MA ~28 mm) [3] (Fig. 1). PPP coagulates faster and more reproducibly in TEG cups and pins coated with anionic carboxylate-rich nanolayers suggesting FXII activation [2], however the role of MPs is unclear. This study tested the hypothesis that MPs are necessary for PPP burst coagulation in plastic TEG cups, and that anionic surfaces are sufficient to restore burst coagulation of MP-depleted plasma.



Materials and Methods: Plastic Cyrolite® TEG cups and pins (Hemoscope, IN, USA) were modified by plasma-enhanced chemical vapor deposition to make hydrophobic (PP-HMDSO, poly(hexamethyldisiloxane) or variable anionic (L-PPE:O, 0, 4.4% or 6.8% carboxylate functional group content) nanocoatings [3]. Coagulation in the TEG cup was initiated by combining i) human citrated PPP (Precision Biologics, NS, Canada), ii) MP-depleted plasma (by ultracentrifugation 150,000xg, 30 min) or iii) PPP 2xenriched for MP, with 20 µL of 200 mM $CaCl_2$ containing 2.5 mg/mL 10 µm diameter beads (latex, borosilicate glass, carboxylated plastic), or 0.25 to 25 mg/mL hydroxyapatite (HA) nanoparticles (2.03 Ca/P ratio) [4]. Bead composition was analyzed by XPS. Statistical tests used ANOVA (Statistica).

Results: Glass beads with 9% Si and 4% Ca content triggered the fastest PPP clotting time ($p<0.05$ vs all hydrophobic surfaces). PPP burst coagulation was enhanced by glass beads, L-PPE:O (6.8% carboxylate), and HA nanoparticles, as shown by the Angle increasing from 36° to >55°. HA nanoparticles accelerated PPP burst coagulation in a dose-dependent manner ($p=0.004$). MP-depleted plasma failed to clot in plastic TEG cups (Fig. 1), and burst coagulation was progressively restored by L-PPE:O with 4.4 to 6.8% carboxylate content ($p<0.001$, Fig. 2A). MP-depleted plasma coagulation was also induced by 2.5 mg/mL glass beads and 25 mg/mL HA nanoparticles but not by Latex beads, HMDSO, or 1% carboxylated beads (Fig. 2B). In MP-depleted plasma, L-PPE:O with 6.8% carboxylate content triggered the highest Angle (50°) with a clot tensile strength similar to PPP and MP-enriched PPP (Fig.2B).



Discussion: Glass beads, >4.4% carboxylated surfaces and HA were effective MP biomimetics that restored burst coagulation. These results suggest that inorganic anionic surfaces can serve as functional binding sites for the calcium-binding gla domain of factors

FIXa, FXa and prothrombin. This study is consistent with the notion that tenase and prothrombinase form side-by-side on the same anionic surface [1].

Conclusions: A minimal 6.8% anionic charge group density is required to bring tenase and prothrombinase in close physical proximity for optimal cooperative behavior.

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