Meeting Abstract: Abstracts From the American Heart Association's Vascular Discovery: From Genes to Medicine 2021 Scientific Sessions
ABSTRACT
Originally Published 2 May 2022
Free Access

Abstract MP03: Histone-mediated Platelet Activation And Microvesicle-induced Thrombin Generation In COVID-19

Alicia S Eustes, Jagadish Swamy, melissa jensen, Katina M Wilson, Shibani M Kudchadkar, Usha Perepu, Francis J Miller, Steven R Lentz, and Sanjana Dayal**AUTHOR INFO & AFFILIATIONS**
Arteriosclerosis, Thrombosis, and Vascular Biology
Volume 41, Number Suppl_1
https://doi.org/10.1161/atvb.41.suppl_1.MP03

Abstract

Background: Severe COVID-19 leads to inflammation and coagulopathy with progression to multiple organ failure. Several prothrombotic mechanisms have been proposed, including NETosis with release of citrullinated histones, platelet hyperactivation, and generation of procoagulant microvesicles.
Aims: We hypothesized that histones derived from NETosis promote platelet activation and release of microvesicles that mechanistically contribute to thrombin generation and thrombosis in COVID-19.
Methods: Platelet poor plasma (PPP) was prepared from 136 COVID-19 patients enrolled in a multicenter randomized clinical trial comparing standard prophylactic dose to intermediate dose enoxaparin in hospitalized patients with COVID-19 (NCT04360824). We also prepared PPP and washed platelets from 53 healthy subjects. We measured citrullinated histone H3 (H3Cit) by ELISA, microvesicles by flow cytometry, and thrombin generation using the Calibrated Automated Thrombogram. *Ex vivo* platelet adhesion and thrombus growth on collagen was measured in a microfluidic chamber.
Results: Compared to healthy subjects, COVID-19 patients had elevated plasma levels of H3Cit and platelet-derived microvesicles. When PPP was triggered with exogenous tissue factor and phospholipids, higher endogenous thrombin potential, peak thrombin, and velocity index were observed in COVID-19 patients compared to healthy subjects. Increased thrombin generation with COVID-19

PPP was evident even when triggered without added phospholipids, suggesting the presence of procoagulant microvesicles in COVID-19 plasma. Enhanced thrombin generation also was observed after transfer of microvesicles isolated from COVID-19 patient plasma to control PPP. Incubation of control platelets with PPP from COVID-19 patients but not healthy subjects caused increased platelet-dependent thrombin generation and larger platelet-thrombi under venous shear stress. These effects of COVID-19 plasma on platelet-dependent thrombin generation and platelet-thrombi formation were inhibited by a histone aptamer.
Conclusions: We conclude that histone-mediated platelet activation promotes thrombosis in COVID-19 in part via increased thrombin generation driven by microvesicles.