

TROMBOEMBOLISMO VENOSO: ASPETTI CLINICI E
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FLOW-MEDIATED DILATION AND ECFC DERIVED ENDOTHELIAL DYSFUNCTION IN VENOUS THROMBOEMBOLISM

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Background and aims. Venous thromboembolism (VTE) is a major cause of cardiovascular morbidity and mortality worldwide. VTE may develop in the presence of major transient risk factors (provoked VTE, pVTE) or minor predisposing conditions (weakly provoked VTE, wpVTE); nevertheless, nearly 40-50% of events arise without any recognizable trigger (unprovoked VTE, uVTE) and are associated with an increased likelihood of recurrence. Endothelial dysfunction (ED) plays a central role in thrombus formation, and its evaluation may provide important insights into the pathophysiology and recurrence risk of VTE. In this context, flow-mediated dilation (FMD) represents a valuable tool to assess vascular endothelial function. The aim of this study is to evaluate the presence of ED in VTE patients through FMD measurement and to investigate the relationship between FMD and putative markers of constitutive ED identified by studying endothelial colony-forming cells (ECFCs)

Methods. This is a substudy of a wider project on ED, funded by the Italian Ministry of Health (GR-2018-12365520). Three months after the acute event, patients underwent peripheral blood sampling for ECFC isolation. ED was assessed by analyzing (i) platelet deposition and fibrin formation through thrombogenesis assay and (ii) thrombin formation through thrombin generation assay (TGA) on ECFCs, along with additional assays described in the main report. For the purpose of this substudy, patients also underwent FMD assessment on the brachial artery according to standardized methodology. Briefly, after at least 10 minutes of supine rest, baseline brachial artery diameter (BAD) was measured by high-resolution ultrasound. A sphygmomanometer cuff positioned on the forearm was then inflated to supra-systolic pressure for 5 minutes to induce ischemia. After cuff deflation, reactive hyperaemia was obtained and the maximal post-deflation brachial artery diameter was recorded within 60-90 seconds. FMD was expressed as the percentage change from baseline diameter. The relationship between markers of ED, assessed by FMD and by ECFC characterization, was explored through correlation analyses, using Spearman's rho (Sr) coefficients.

Results. A total of 26 patients with VTE—classified as uVTE (n=9), wpVTE (n=11), and pVTE (n=6)—were included in the study. Mean age was 47.7 years (SD 10.2), 15 (57.7%) were male and mean body mass index (BMI) was 26.6 kg/m² (SD 5.3). FMD showed a mean value of 8.2% (SD 6.3), ranging from 2.0% to 25.9%. The mean absolute change in BAD was 0.03 cm (SD 0.02, min 0.01 max 0.09 cm). No statistically significant associations emerged between FMD values and some thrombin generation parameters, including Lag phase (Sr=0.048, p=0.849) and endogenous thrombin potential (Sr=-0.133, p=0.598), whereas an inverse trend was found between FMD and peak thrombin generation (Sr=-0.393, p=0.107). With regards to the thrombogenesis assay, no significant correlation was observed between FMD and platelet volume deposition (Sr= 0.250, p=0.333) or fibrin formation (Sr=-0.076, p= 0.771)

Conclusions. Given the limited sample size, the study was likely underpowered to detect associations. Although the relationship between peak thrombin generation and FMD did not reach statistical significance, it may reflect a biologically plausible link between endothelial dysfunction and a prothrombotic phenotype. These results should be considered hypothesis-generating and warrant confirmation in larger cohorts.

