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RESEARCH LETTER

Neutrophil Activation 24 Hours After an Endovascular Therapy–Treated Acute Ischemic Stroke Is Associated With 3-Month Clinical Outcome

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Despite high recanalization rates achieved by endovascular therapy (EVT) in cases of acute ischemic stroke (AIS) related to a large-vessel occlusion, ≈50% of the treated patients do not reach functional independence at 3 months.

A potential explanation for this finding is the occurrence of both local[1] and systemic[2] inflammation triggered by the AIS, which appears to be driven by neutrophils, a hypothesis supported by the identification of neutrophil count[3] as a prognostic marker of unfavorable clinical outcome (CO) after an AIS.

Myeloperoxidase is predominantly, but not exclusively, secreted by activated neutrophils after an AIS and serves both as a biomarker of neutrophil activation (NA) and an effector of inflammation, partly through its association with neutrophil extracellular traps (NETs),[4] playing a role in local and systemic inflammation after an AIS.

With emerging treatments targeting NA, our objective was to identify whether NA 24 hours after an AIS is still associated with unfavorable CO.

Patients treated with EVT at the Rothschild Foundation Hospital between April 2016 and April 2020 for an AIS associated with a large-vessel occlusion of the anterior circulation, for whom blood samples taken before EVT and 24 hours after the onset of the AIS were available, were included in this study. The local ethics committee validated this research protocol (CPP Ile de France VII, ID-RCB number: 2015-A01856-43), and an informed consent was obtained from the patient or a close relative before inclusion. Blood was collected in EDTA after brachial venipuncture before and 24 hours after EVT. Myeloperoxidase was quantified using commercially available ELISA kits (Hycult Biotechnologies). As the main analysis, we compared the myeloperoxidase levels measured before and 24 hours after EVT according to favorable or unfavorable CO status. Unfavorable CO was defined as a 3-month modified Rankin Scale score between 3 and 6. A multivariable logistic model was performed by considering the following prespecified confounders: age, pretreatment National Institutes of Health Stroke Scale and Alberta Stroke Program Early Computed Tomography scores, and use of intravenous thrombolysis (and pretreatment myeloperoxidase values for the association with

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24-hour myeloperoxidase values). Database supporting the results may be obtained upon reasonable request.

Overall, 163 patients were included from April 2016 to April 2020. Median age was 72 years, and 50.9% were men. Median National Institutes of Health Stroke Scale at admission was 16, and most patients had a prestroke modified Rankin Scale score ≤2 (144/161 [89.4%]). Overall, 56% of patients had an M1 occlusion, 25% an M2 occlusion, and 17.9% an internal carotid artery occlusion. A total of 38.7% had a stroke of unknown onset, with no statistical difference between groups. Eighty-five of 163 benefited from intravenous thrombolysis injection. Seventy-four (45%) patients experienced favorable CO at 3 months. The following characteristics were unbalanced between favorable and unfavorable CO and therefore integrated into the multivariate analysis: age, hypertension, initial National Institutes of Health Stroke Scale score, and number of device pass.

Patients who experienced favorable CO had lower myeloperoxidase levels 24 hours after EVT (median, 24 ng/mL; interquartile range, 18–34) than patients who experienced unfavorable CO (median, 30 ng/mL [interquartile range, 24–44]; $P<0.001$; Figure). No such difference was found in myeloperoxidase levels before EVT (27 ng/mL versus 30 ng/mL; $P=0.26$).

After adjustment, myeloperoxidase levels 24 hours after EVT remained associated with a lower likelihood of favorable CO (adjusted odds ratio, 0.61 [95% CI, 0.38–0.97]).

We found no significant heterogeneity in the association between CO and 24-hour myeloperoxidase levels according to recanalization grade (phet, 0.12) or hemorrhagic transformation occurrence (phet, 0.65) although the association was greater in patients with incomplete recanalization (adjusted odds ratio, 0.30 [95% CI, 0.10–0.85]).

There was no significant correlation of myeloperoxidase levels 24 hours after EVT with pretreatment Alberta Stroke Program Early Computed Tomography score or neutrophils counts. Myeloperoxidase levels and Alberta Stroke Program Early Computed Tomography score at 24 hours were not significantly correlated after prespecified adjustment ($r=-0.11$ [95% CI, −0.27 to 0.045]), using partial Spearman's rank correlation.

Briefly, we report that (1) NA is associated with worse CO 24 hours after EVT, and (2) this effect seems more pronounced in patients with incomplete recanalization, but (3) myeloperoxidase concentration at 24 hours is not associated with infarct volume or hemorrhagic transformation.

Our results could be explained by both local and systemic NA. On the one hand, neutrophils are activated in situ, yielding to a proinflammatory milieu with NET production[5] during the same time window; on the other hand, recent studies suggest that neutrophils exert their detrimental effects on outcome by decreasing humoral immunity through the secretion of NETs,[2] potentially increasing the mortality rate related to severe infections. Besides the limited sensitivity of Alberta Stroke Program Early Computed Tomography score, these last findings may clarify how NA influences prognosis without directly affecting final infarct volume in our series.

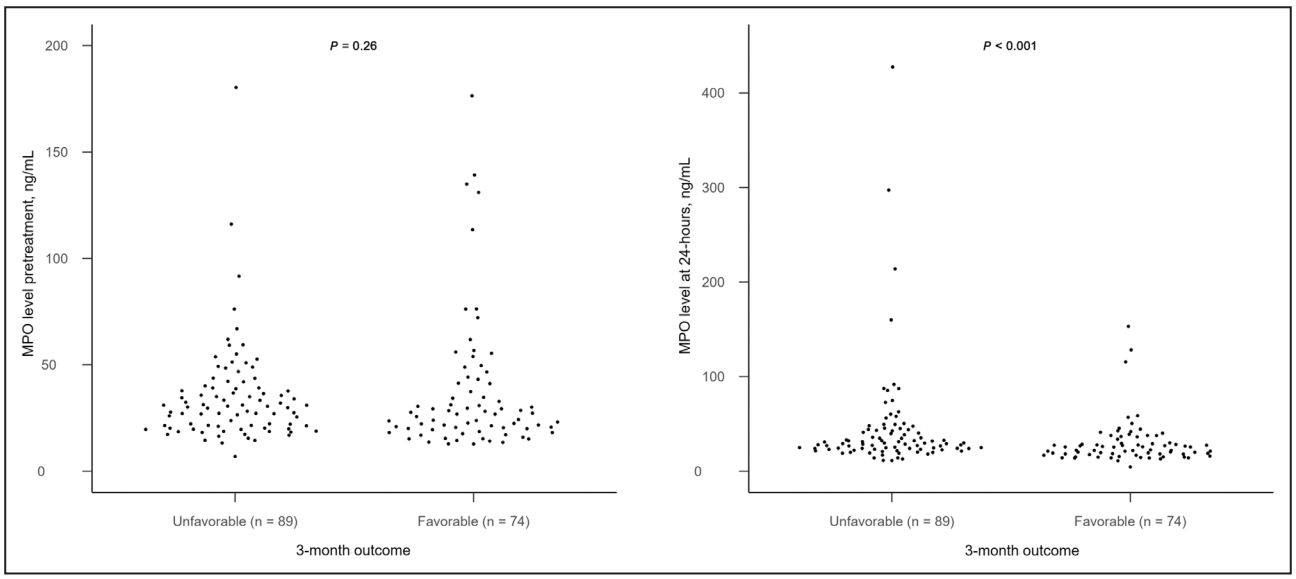

Figure. Comparison of myeloperoxidase concentration levels assessed before and 24 hours after endovascular treatment according to 3-month favorable clinical outcome.
P values calculated from Mann–Whitney *U* test are reported. Three-month favorable outcome is defined as 3-month mRS 0 to 2 or equal to prestroke mRS. MPO indicates myeloperoxidase; and mRS, modified Rankin scale.

Despite several limitations related to the small sample size, the retrospective design, the absence of non–large-vessel occlusion AIS, the lack of information on the EVT technique or coexisting infection, and the limited time points of blood samples, the present results support future efforts toward developing strategies targeting subacute NA during an AIS, while ongoing RCTs are focusing on the acute stage of an AIS by targeting NA, either through Toll-like receptor 4 (APRIL [Phase Ib/IIa Clinical Study of ApTOLL for the Treatment of Acute Ischemic Stroke], NCT04734548) or NET production (NETs-Target [Efficacy of Pulmozyme on Arterial Recanalization in Post-Thrombectomy Patients Managed for Ischemic Stroke], NCT04785066; or ReSCInD [Reduction of Systemic Inflammation After Ischemic Stroke by Intravenous DNase Administration], NCT05880524).

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Disclosures

None.

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