

Biologia vascolare

CHRONIC ERYTHROCYTE REMODELING AND IMPAIRED RHEOLOGICAL FUNCTION IN PATIENTS WITH PATENT FORAMEN OVALE

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Background and Aims. Patent foramen ovale (PFO) is associated with migraine with aura, cryptogenic stroke, and a prothrombotic phenotype. While the contribution of platelet activation and endothelial dysfunction is recognized, the impact of chronic abnormal intracardiac flow on erythrocyte biology remains poorly explored. Red blood cells (RBCs) are sensitive to mechanical and oxidative stress, which can alter their morphology, deformability, and aggregability, thus affecting microcirculatory flow and thrombogenicity. We previously observed increased erythrocyte oxidative stress and reduced hematological parameters in PFO patients, suggesting chronic RBC remodeling associated with PFO. We aimed to characterize erythrocyte morphology and rheological properties in patients with PFO before and after percutaneous closure.

Methods. Sixty-seven patients with PFO were evaluated before closure (T0) and at 6-month follow-up after closure (T1), and compared with 28 healthy subjects (HS). Standard hematological parameters, including erythrocyte count and red cell distribution width (RDW-CV), were assessed by automated blood count. Erythrocyte ultrastructure was evaluated by scanning electron microscopy (SEM). Functional erythrocyte properties, including deformability under shear stress and aggregation behavior, were analyzed using LoRRca.

Results. Patients with PFO displayed evidence of erythrocyte structural remodeling. RDW-CV was significantly increased compared with HS (13.43% ± 1.36 vs 12.44% ± 0.53; p = 0.0011), indicating greater heterogeneity in erythrocyte size, and remained elevated at 6-month follow-up after closure (13.82% ± 1.75), suggesting persistence of long-lived structural alterations. SEM revealed morphological heterogeneity in PFO patients. In addition to biconcave RBCs, a “shield-shaped” erythrocyte phenotype was observed in PFO samples but not in HS, identifying a previously undescribed RBC morphological signature associated with PFO (Figure). Functional analysis showed that in PFO patients RBC deformability under prolonged shear stress was significantly reduced at baseline compared with post-closure values, indicating increased membrane rigidity and reduced mechanical resilience (elongation index 0.18 ± 0.03 vs 0.20 ± 0.04; p=0.019). Conversely, erythrocyte aggregability was significantly increased before PFO closure and improved after closure (amplitude 36.45 ± 3.66 vs 34.07 ± 3.36; p=0.0002), suggesting partial restoration of physiological rheological behavior after elimination of abnormal intracardiac flow. These findings are consistent with a model of chronic mechanical conditioning of erythrocytes in PFO, resulting in persistent structural remodeling and altered functional behavior.

Conclusions. PFO is associated with a distinct erythrocyte phenotype characterized by structural heterogeneity, abnormal morphology, impaired deformability, and increased aggregability. These alterations are consistent with chronic erythrocyte remodeling induced by prolonged exposure to abnormal hemodynamic stress. Partial recovery after PFO closure supports a causal relationship between PFO-related flow disturbance and erythrocyte dysfunction. Given the role of RBC rheology in vascular homeostasis and thrombosis, erythrocyte alterations may represent an additional contributor to the thromboinflammatory burden associated with PFO. Funding: M6C2I2.1_PNRR_NEXT_GENERATION_EU, PNRR-MAD-2022-12376277, CUP-B43C22001110008 Clinical trial: NCT06046508

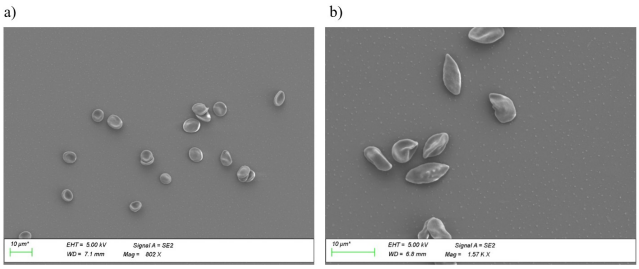


Figure. Ultrastructural analysis of erythrocytes in a) healthy subject and b) patient with patent foramen ovale.