PLASMA METABOLOMIC PROFILING IDENTIFIES PLATELET-RELATED METABOLIC CHANGES AFTER PFO CLOSURE IN MIGRAINE WITH AURA

F. Marincola[1], N. Zuddas[1], F. Cannas[1], A. Becchetti[2], L.V. Renna[3], M. Brambilla[2], R. Cardani[3], M. Conti[2], K. Nallio[2], M. Chessa[3], D. Trabattoni[2], V. Fanos[4], M. Camera[2|5]

[1]Università degli Studi di Cagliari, Cagliari, Italy; [2]Centro Cardiologico Monzino IRCCS, Milano, Italy; [3]IRCCS Policlinico San Donato, San Donato, Milano, Italy; [4]University Hospital of Cagliari, Cagliari, Italy; [5]Università degli Studi di Milano, Department of Pharmaceutical Sciences, Milano, Italy

Background and Aims. Patent foramen ovale (PFO) is frequently observed in patients with migraine with aura (MA), although the biological mechanisms linking the two conditions remain incompletely understood. Beyond paradoxical embolism, increasing evidence suggests that PFO may be associated with systemic platelet activation, enhanced thrombin-generating potential and oxidative stress imbalance. These processes are closely interconnected with mitochondrial function and energy metabolism, supporting the concept that a circulating prothrombotic and redox-sensitive milieu may contribute to PFO-associated migraine pathophysiology. Plasma metabolomics offers a systems-level approach to investigate these mechanisms by identifying molecular signatures associated with thrombo-inflammatory activation, oxidative stress and altered metabolic homeostasis. In this context, the longitudinal metabolic profiling before and after percutaneous PFO closure may provide insight into potentially reversible biological pathways involved in the PFO–-MA phenotype. The aim of this study was therefore to characterize the plasma metabolomic profile of patients with MA and PFO before and at 6-month post-PFO closure, with particular focus on pathways related to energy metabolism, lipid utilization and oxidative balance.

Methods. In this prospective study, 120 patients with MA and PFO undergoing percutaneous closure were enrolled. Plasma samples were collected before the procedure and at 6-month follow-up. Untargeted metabolomic analysis was performed using high-resolution proton nuclear magnetic resonance spectroscopy (^{1}H-NMR). Spectral data were processed to identify metabolites and pathway-level changes associated with PFO closure.

Results. NMR-based metabolomic profiling revealed consistent modulation of metabolites involved in glycolysis, lipid β-oxidation, ketone body metabolism, and the tricarboxylic acid cycle following PFO closure. At baseline, the metabolic profile was characterized by increased reliance on lipid-derived substrates, as indicated by elevated ketone bodies and lipid-related metabolites, alongside reduced levels of glycolysis-related metabolites such as lactate and alanine. At 6 months, a metabolic reprogramming was observed, with increased levels of lactate and alanine and reduced ketone bodies, indicating a shift toward glucose-based energy metabolism. Overall, these changes suggest improved metabolic flexibility and a reduction in lipid-driven energy reliance, consistent with a lower systemic metabolic stress burden.

Conclusions. In patients with MA and PFO, plasma metabolomics identified a baseline metabolic signature consistent with a systemic redox-sensitive and prothrombotic environment, in line with previously reported platelet activation and oxidative imbalance. The observed post-closure metabolic shift toward glucose utilization supports the hypothesis that PFO contributes to a metabolically dysregulated state that may be, at least partially, reversible after closure (Figure 1). These findings highlight metabolomics as a valuable tool to investigate the molecular mechanisms underlying the PFO–migraine association and to link metabolic reprogramming with platelet-driven thrombo-inflammatory processes.

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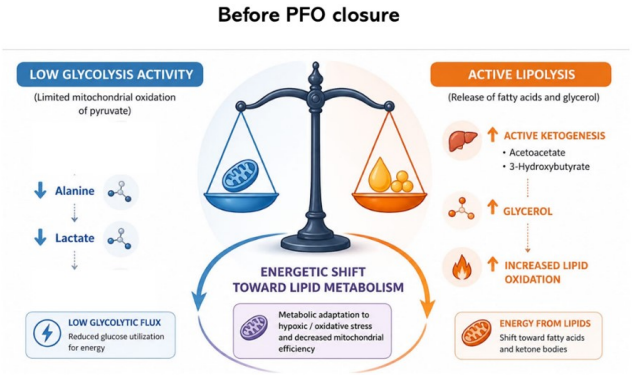


Figure 1. Metabolic shift toward lipid-based energy metabolism in PFO patients.