Metabolomics to characterise adaptations in cellular metabolism for the stages of atrial fibrillation

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Background: Atrial fibrillation (AF) is a highly prevalent, progressive cardiac arrhythmia associated with high cardiovascular comorbidity. Current treatments targeting electropathophysiology have high recurrence rates, prompting researchers to uncover alternative molecular mechanisms underlying AF, aiming to find novel targets for diagnostics and treatment. Highly relevant to several cardiovascular diseases, adaptations in cellular metabolism have gained interest in AF. However, changes in the metabolome across various AF stages have not yet been studied.

Aim: The study aims to identify leads for potential biomarkers and treatment targets by gaining more insight in metabolic adaptation and mechanisms in atrial fibrillation.

Methods: From the HALT&REVERSE biobank, 60 atrial appendage samples were selected [controls (SR=21), paroxysmal (ParAF=16), persistent (PerAF=11) and longstanding-persistent AF (Ls-PerAF=12)]. Metabolomics, a large-scale semi-quantitative method based on mass-spectrometry, was performed. Comparisons were made SR vs. AF, and SR vs. AF stages by Mann-Whitney U and Kruskal Wallis statistical tests with a Benjamini-Hochberg correction (FDR=0.10) for multiple testing.

Results: Comparing SR and AF, fructose-1,6-diphosphate (F1,6DP) was decreased (p<0.001), whilst CDP (p<0.001) and UMP were increased (p<0.01). Comparing the AF stages, in SR vs. ParAF CDP was significantly increased. Regarding the AF stages, SR and LsperAF show the biggest differences in metabolites, presenting as decreases glycolysis and nicotinamide metabolites. Overall, metabolites associated with the glycolysis, nicotinamide, and carnitine metabolism show decreases in AF patients, whilst metabolites involved with pyrimidine metabolism are increased AF patients.

Conclusion: CDP, F1,6DP and UMP were strongly correlated with AF samples in univariate analyses and therefore should be further investigated in serum for their biomarker potential, specifically CDP which was already strongly increased in ParAF. F1,6DP and similar energy metabolites in the glycolysis and nicotinamide pathways are decreased in AF and therefore could be as a therapeutic target through supplementation. Leads from this analysis should be validated and further investigated in mechanistic studies of these metabolic pathways.