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Basic Science – Cardiac Diseases, Arrhythmias

Metabolomics and frailty: a "from bench to bedside" approach to atrial fibrillation in older patients

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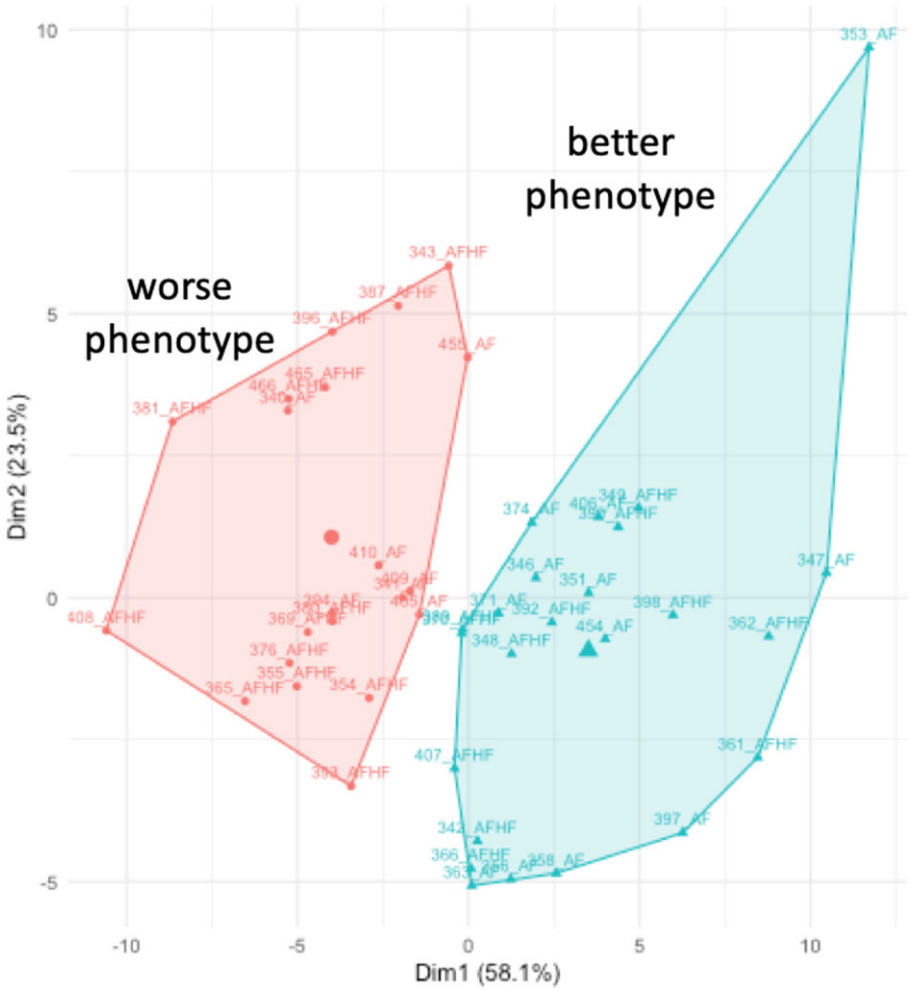
Background: Atrial fibrillation (AF) is the most common sustained arrhythmia diagnosed at an advanced age. The most important complications of AF are stroke, heart failure and dementia. The pathophysiology of the arrhythmia is complex and multifaceted and several aspects are still not completely understood.

Purpose: Our project aimed at exploring the molecular characteristics of AF in older patients using an untargeted metabolomics approach, an analytical technique that provides an insight of the global metabolic profile at an individual level. As secondary endpoints, we evaluated the association between metabolomics and acylcarnitines, which are mediators of myocyte electrical instability, and difference in metabolomics profile between healthy controls (C) and AF patients (AF-P).

Method: We evaluated 50 consecutive older AF-P with persistent AF, waiting to be treated with elective electrical cardioversion of the arrhythmia, and 22 healthy controls (C). In all patients, the cardiological evaluation was integrated with tools of the Geriatric Multidimensional Assessment (GMA) to describe neurocognitive function (Mini-Mental State Examination, MMSE), depressive symptoms (15-item Geriatric Depression Scale, GDS), and physical performance (Short Physical Performance Battery, SPPB). Interleukin-6 (IL-6), a marker of low-grade inflammation, was measured with ELISA assays. Metabolomics analysis and acylcarnitine measurements were carried out using gas chromatography coupled with mass spectrometry (GC-MS).

Results: AF-P and C did not differ by age (76 $\pm$ 6 vs. 70 $\pm$ 14 years, $p = 0.055$); patients had a lower proportion of women (AF-P: 32% vs. C: 64%, $p = 0.012$). Cluster analysis applied to metabolomic data in all population identified two subset of subjects, characterized by a different body mass index (BMI; 23.57 vs. 32.53 Kg/m², $p = 0.046$). When studying only the AF-P group, the simultaneous presence of a higher CHA2DS2-VASc score (4.17 $\pm$ 1.32 vs. 2.88 $\pm$ 1.83, $p = 0.007$), a lower physical function (SPPB; 8.97$\pm$ 2.22 vs. 10.75 $\pm$ 1.13, $p = 0.009$), and higher IL-6 levels (4.42 vs. 2.39 pg/mL, $p = 0.002$) described the cluster with a worse clinical phenotype and a specific metabolomics pattern. Furthermore, an association between IL-6 and medium- long-chain acylcarnitines emerged (acylcarnitine 12:1, $\beta = 31.7 \pm 9.4$, $R = 0.446$, $p = 0.001$).

Conclusions: Present analysis demonstrated that a specific metabolomics profile was characteristic of older AF patients with a frail phenotype, identified by higher CHA2DS2-VASc score and IL-6 concentration, and lower physical performance. Future studies are needed to reveal the single molecular pathways responsible of these behaviour, potentially useful to guide a targeted therapy. Last, inflammation per se could contribute to electrical instability in AF, while body mass index, a surrogate measure of undernutrition, could identify different metabolic pathways in controls and in patients with the arrhythmia.



Single circles/triangles identify the metabolomic profile of each patient.

Metabolomics by clinical phenotypes