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Activated amyloid-beta pathways in patients with atrial fibrillation and heart failure, a pathway analysis in BIOSTAT

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Background. Atrial fibrillation (AF) and heart failure (HF) are two growing epidemics that frequently co-exist, share clinical risk factors, and predispose to each other. There is limited understanding of the underlying pathophysiology of the combination of both conditions.

Purpose. To perform pathway analyses of circulating plasma proteins and evaluate whether patients with both HF and AF have different activated pathways compared to those with HF without AF.

Methods. We performed pathway overrepresentation analyses of differentially expressed plasma proteins in HF, with reduced (HFrEF) and preserved (HFpEF) ejection fraction, with AF versus sinus rhythm on ECG at enrolment in BIOSTAT-CHF, using 92 cardiovascular biomarkers. Pathway analyses were performed based on existing knowledge using Gene Ontology, REACTOME, and KEGG, to study underlying activated biological pathways. Resulting pathways were corrected by Bonferroni method.

Results. We studied 2,839 patients with HF irrespective of their ejection fraction of whom 1,116 (39%) had AF and 1,723 (61%) were in sinus rhythm. HF patients with AF were older (76 ± 10 vs. 70 ± 12, p < 0.001), were less women (28% vs. 34%, p < 0.001), had history of stroke (16% vs. 10%, p < 0.001), renal disease (39% vs. 31%, p < 0.001) and less history of coronary artery disease (40% vs. 53%, p < 0.001). There were no significant differences in patients with hypertension (62% vs. 60 %, p = 0.22), diabetes (32% vs. 31%, p = 0.51) and COPD (18% vs. 16%, p = 0.20). A total of 1,661 (59%) had HFrEF and 432 (15%) had HFpEF. Pathway overrepresentation analyses revealed three amyloid-related pathways statically significant in total HF group, and in HFrEF and HFpEF respectively, with AF compared with those in sinus rhythm: amyloid-beta formation (p < 4.0E-4, p < 7.4E-6), amyloid-beta metabolic process (p < 1.0E-3, p < 1.9E-5), and amyloid precursor protein catabolic process (p < 9.1E-4, p < 1.6E-5). The key proteins related to these processes were spondin-1 (SPON-1), insulin-like growth factor binding protein 1 (IGFBP-1) and 7 (IGFBP-7). After adjusting for sex and age and correcting for multiple testing with fall discovery rate (FDR), SPON-1 (FDR < 6.3E-6), IGFBP-1 (FDR < 6.6E-3) and IGFBP-7 (FDR < 2.5E-9) remained statically significant in HFrEF patients with AF vs. sinus rhythm; whereas only SPON-1 (FDR < 7.3 E-3) and IGFBP-7 (FDR < 1.9E-3) remained in HFpEF patients with AF vs. sinus rhythm.

Conclusion. Pathway analyses revealed activation of amyloid-beta pathways in HF patients with AF versus sinus rhythm with SPON-1, IGFBP-1 and IGFBP-7 overrepresented proteins. Amyloid-beta pathways may play a role in the pathophysiology of the combination of HF and AF, which needs to be replicated and validated in additional cohorts.

Figure. Pathway analysis of activated proteins in patients with HF, HFrEF (A) and HFpEF (B) and AF versus sinus rhythm. Proteins are represented as dots and pathways as circumferences.

Abstract Figure. Pathway overrepresentation analysis