Abstract: 3057

Relation of atrial remodeling to circulating biomarkers of myocardial fibrosis and apoptotic microparticles in patients with atrial fibrillation and heart failure with preserved ejection fraction

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Topic(s):
Atrial Stressors Causing Atrial Fibrillation

Citation:
ESC Research Grant, EHRA Academic Research Fellowship Programme

Introduction: Left atrial (LA) remodeling is a mainstay for atrial fibrillation (AF) occurrence. AF further promotes structural changes in LA, as fibrosis and stretching, followed by AF progression to its permanent form. Many profibrotic pathways have been studied, and circulating microparticles (MPs) may have a role. MPs are extracellular submicron anucleoid phospholipid vesicles released from different cells. Annexin V-binding (AnV+) MPs were suggested as a marker of apoptosis.

Purpose: To evaluate association of circulating biomarkers of myocardial fibrosis and MPs subsets with LA remodeling in patients with AF and heart failure with preserved ejection fraction.

Methods: We studied 274 patients (median age 62 years, 37% females). Paroxysmal AF was diagnosed in 150 patients (55%) and non-paroxysmal AF (persistent or permanent) in 124 (45%). Median CHA2DS2-VASc score was 3 in males and 4 in females. Patients with valvular AF, recent (<6 months) thromboembolic or hemorrhagic event, advanced chronic kidney or hepatic dysfunction, malignancy or active inflammatory disorders were excluded.

Transthoracic echocardiography was performed. LA maximum volume index (LAVi) was measured as an index of LA structural remodeling in AF. Average values from ten consecutive cardiac cycles were calculated.

Blood levels of galectin 3, interleukin-1 receptor-like 1 (ST2), transforming growth factor beta 1 (TGF-ß1), procollagen type III aminoterminal propeptide (PIIINP), matrix metalloproteinase 9 (MMP-9), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), angiotensin II and aldosterone were assayed as surrogate biomarkers of myocardial fibrosis with ELISA.

Using microflow cytometry (Figure), numbers of platelet-derived (CD42b+), monocyte-derived (CD14+), endothelial (CD144+), and apoptotic MPs (AnV+) were quantified in plasma samples.

Linear regression was used to reveal parameters associated with LAVi. Raw data were normalized with Box-Cox transformation.

Results: Median LAVi in studied patients was 48 (39-59) ml/m² and increased from patients with paroxysmal AF (42 [35-51] ml/m²) to persistent AF (53 [43-62] ml/m²) and permanent AF (57 [46-69] ml/m²), p<0.001. On univariate analysis male gender (ß=0.11, p=0.04); history of hypertension (ß=0.18, p=0.03); AF type, i.e. progression from paroxysmal to permanent (ß=0.38, p<0.001); AnV+ MPs (ß=0.19, p=0.005); ST2 (ß=0.15, p=0.02); and early mitral inflow velocity (E) / early mitral annular diastolic velocity (E′) averaged for LV septal and lateral basal regions (ß=0.18, p=0.005) were associated with LAVi.

Using stepwise multivariate regression AnV+ MPs (ß=0.14, p=0.03); AF type (ß=0.35, p<0.001); and E/E′ ratio (ß=0.11, p=0.04) remained significant predictors of LAVi (adjusted for age and gender).

Conclusion: Level of circulating apoptotic MPs is associated with LAVi in AF patients with HFpEF, and may be involved in remodeling process or could represent surrogate markers of myocardial damage in AF.
Abstract: The relation of atrial remodeling to circulating biomarkers of myocardial fibrosis and apoptotic microparticles in patients with atrial fibrillation and heart failure with preserved ejection fraction.

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