Abstract: P3789
Circulating biomarkers of myocardial fibrosis and cellular apoptosis in patients with atrial fibrillation and heart failure with preserved ejection fraction

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Topic(s):
Mechanisms for Heart Failure and Cardiac Complications in Atrial Fibrillation

Citation:
European Heart Journal (2019) 40 (Supplement), 2381

Introduction: Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) commonly coexist. AF is associated with left atrial (LA) and ventricular (LV) myocardial fibrosis, contributing to diastolic dysfunction in HFpEF. Many profibrotic pathways have been studied in AF and HFpEF, but scarce data are available on the role of circulating microparticles (MPs).

Purpose: To evaluate association of circulating biomarkers of fibrosis and MPs subsets with Doppler-derived parameters of diastolic function in AF and HFpEF.

Methods: We studied 274 patients with non-valvular AF and HFpEF (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. Transthoracic echocardiography was performed to assess LV diastolic function, including early mitral inflow velocity (E), E/A velocities ratio (on sinus rhythm), early mitral annular diastolic velocity (E') for LV septal and lateral basal regions, E/E' ratio, LA maximum volume index (LAVi), E-wave velocity deceleration time (DT), flow propagation velocity (Vp). Average values from ten consecutive cardiac cycles were calculated. E/E' ratio was chosen as valid and reproducible index of diastolic function in AF patients for regression analysis. Blood levels of galectin 3, interleukin-1 receptor-like 1 (ST2), transforming growth factor beta 1 (TGF-β1), procollagen type III aminoterminal propeptide (PIIINP), matrix metalloproteinase 9 (MMP-9), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), angiotensin II and aldosterone level were assayed as surrogate biomarkers of myocardial fibrosis and profibrotic signaling. Using microflow cytometry, numbers of platelet-derived (CD42b+), monocyte-derived (CD14+), endothelial (CD144+), and apoptotic MPs (Annexin V+) were quantified in plasma samples. Linear regression was used to reveal parameters associated with diastolic function assessed as E/E' ratio. Data were normalized with Box-Cox transformation.

Results: Grade I diastolic dysfunction was found in 149 (54%); 94 (34%), and 31 (11%) patients had grade II and grade III diastolic dysfunction, respectively. On univariate analysis, age (β=0.23, p=0.0001); male gender (β=−0.19, p=0.02); history of hypertension (β=0.15, p=0.02); AF type, i.e. progression from paroxysmal to permanent (β=0.14, p=0.02); AnV+ MPs (β=0.19, p=0.01); angiotensin II (β=0.13, p=0.04); ST2 (β=0.1, p=0.04); and TIMP-1 (β=0.13, p=0.03) were associated with E/E' ratio. Using stepwise multivariate regression, AnV+ MPs (β=0.15, p=0.01) and TIMP-1 (β=0.3, p=0.04) remained significant predictors of E/E' ratio, adjusted for age, gender, hypertension and AF type.

Conclusion: Apoptotic (AnV+) MPs and TIMP-1 were independently associated with diastolic dysfunction in AF and HFpEF. These may contribute to the pathophysiology of AF and HFpEF, and complications related to the presence of both.
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We studied 274 patients with non-valvular AF and HFpEF (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. Transthoracic echocardiography was performed to assess LV diastolic function, including early mitral inflow velocity (E), E/A velocities ratio (on sinus rhythm), early mitral annular diastolic velocity (E') for LV septal and lateral basal regions, E/E' ratio, LA maximum volume index (LAVi), E-wave velocity deceleration time (DT), flow propagation velocity (Vp). Average values from ten consecutive cardiac cycles were calculated. E/E' ratio was chosen as valid and reproducible index of diastolic function in AF patients for regression analysis. Blood levels of galectin 3, interleukin-receptor-like 1 (ST2), transforming growth factor beta 1 (TGF-β1), procollagen type III aminoterminal propeptide (PIIINP), matrix metalloproteinase 9 (MMP-9), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), angiotensin II and aldosterone level were assayed as surrogate biomarkers of myocardial fibrosis and profibrotic signaling. Using microflow cytometry, numbers of platelet-derived (CD42b+), monocyte-derived (CD14+), endothelial (CD144+), and apoptotic MPs (Annexin V+) were quantified in plasma samples. Linear regression was used to reveal parameters associated with diastolic function assessed as E/E' ratio. Data were normalized with Box-Cox transformation.

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**Conclusion:**

Apoptotic (AnV+) MPs and TIMP-1 were independently associated with diastolic dysfunction in AF and HFpEF. These may contribute to the pathophysiology of AF and HFpEF, and complications related to the presence of both.

**Relation of E/E' to TIMP-1 and AnV+ MPs**

![Graph showing the relation of E/E' to TIMP-1 and AnV+ MPs](image-url)