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Impaired Pattern of Endothelial Cell-Derived Microparticles in Heart Failure Patients with Preserved and Reduced Left Ventricular Ejection Fraction

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Abstract

The prevalence of heart failure with preserved left ventricular ejection fraction (HFpEF) rises consequently within past decades. Both phenotypes of HF, i.e. HFpEF and HF with reduced EF (HFrEF), have exhibited similar cardiovascular mortality rates and admission rates, while development and progression of HFpEF and HFrEF associate with different co-morbidities. Understanding of the pathophysiological mechanisms of the two phenotypes of HF is essential for discovery of future new treatments. Biomarkers reflecting several stages of failing heart evolution and different pathophysiological faces of HF (N-terminal pro brain natriuretic peptide, high-sensitivity troponin T, and galectin-3) have been implemented into routine clinical practice to increase diagnostic and predictive capabilities of clinical-based stratification models. Recent clinical studies have shown that development of endothelial dysfunction in HF could relate to activation and/or apoptosis of endothelial cells. Worsening endothelium integrity and function relate to release of newly detectable circulating biomarkers called endothelial cell derived microparticles (EMPs). The commentary is discussed the role of impaired immune pattern of circulating EMPs associated with elevated number of apoptotic endothelial cell-derived microparticles in prediction of HFpEF development.

Keywords: Heart failure; HFpEF; HFrEF; Endothelial dysfunction; Microparticles

Introduction

Heart failure (HF) with preserved left ventricular ejection fraction (HFpEF) exhibits dramatically increase worldwide especially in the developed countries remaining one of leading cause of cardiovascular (CV) mortality and morbidity [1,2]. The increased prevalence of hypertension, diabetes, atrial fibrillation in various aging patients, as well as improve longevity of the subjects with known CV disease relates to HFpEF epidemic [3]. Unless HFpEF, HF with reduced left ventricular ejection fraction (HFrEF) has been developed rather due to ischemia / inflammatory cardiomyopathies, myocardial infarction than in result of hypertension and cardiac hypertrophy. Understanding of the pathophysiological mechanisms of the two phenotypes of HF is essential for discovery of future treatments.

Within past decade contemporary medical strategy of HFpEF treatment has been exhibited serious benefit in prevention CV events and HF-related outcomes [4,5]. Obviously, effective prevention of co-morbidities evolution in HFpEF might be a clue of improving survival and decrease disability [6]. In this context, early stratification of asymptomatic patients at risk for HFpEF development and patients with known cardiac dysfunction at risk of HF advance is essential for decrease of CV events and HF-related morbidity and mortality [7].

Biomarkers reflecting several stages of failing heart evolution and different pathophysiological faces of HF (N-terminal pro brain natriuretic peptide, higher-sensitivity troponin T, and galectin-3) have been implemented into routine clinical practice to improve of diagnostic and predictive capabilities of clinical-based stratification models [8-12]. Probably similar approach might merge of contemporary medical care efficacy [13,14]. However, several co-morbidities seem to influence the response to biomarker-guided therapy and might explain the lower efficacy of care in HFpEF patients [15]. Therefore, there is no evidence regarding possibilities to use of several biomarkers for predicting HFpEF development in general population with higher statistical power.

Endothelial dysfunction (ED) is common risk factor for HF development beyond etiology [16]. Recent studies have revealed closely association between development of ED and activation/apoptosis of endothelial cells [17-19]. Worsening endothelium integrity and function relate to release of newly detectable circulating biomarkers called endothelial cell-derived microparticles (EMPs) [20].

Microparticles are defined as heterogeneous in size (0.1-1 μm) small membrane vesicles (0.1-1 μm) that are produced as result in activation, injury or apoptosis of endothelial cells. They are considered a source of important information on the status of endothelial cells and vascular function. It is well known that EMPs are up-regulated through several inflammatory stimuli, including tumor necrosis factor-α, interleukins, chemokines, chemo-attractants, and components of oxidative stress and mediated by activation of nuclear factor-κB in a time-dependent manner. EMPs play a sufficient role in vascular function by altering the processes of inflammation, coagulation, cell activation/apoptosis, and angiogenesis [21]. Furthermore, EMPs could provide valuable information regarding not only damage of endothelium, but also about endothelial repair system activation [22]. Indeed, circulating levels of EMPs are thought to reflect a balance between cell stimulation, proliferation, apoptosis, and cell death.

It has found that HF development has closely associated with decreased number of EMPs that released from activated endothelial cells and increased EMP number related to apoptosis of endothelial cells [23]. To improve our knowledge the predictive role of classic phenotype of EMPs (CD31+/CD41-, CD62e+, CD144+) in HFpEF

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has not yet obviously defined [24-26], whereas in HFrEF the increased number of circulating apoptotic EMPs has associated with merged 3-year HF-related death rate, all-cause mortality rate, and a risk of recurrent admission to the hospital [27,28]. In contrast, apoptosis-related Annexin V-binding EMPs have elevated at early stage of HFpEF associated with co-morbidities, such as insulin resistance, obesity, diabetes, and merited to clinical outcomes [29-30].

Although detailed interrelationship between the pattern of circulating EMPs (i.e. numerous of annexin V microparticles), features of cardiac remodeling and HF-related outcomes were not defined, it is needed to establish the predictive role of apoptotic EMPs in HFpEF subjects in large prospective study in the future. Such information might be essential to understanding whether the tested pathways could produce clinically relevant therapeutic targets.

In conclusion, impaired immune pattern of circulating EMPs associated with elevated number of apoptotic endothelial cell-derived particles might be useful for predicting HFpEF in patients at higher risk of HF development. More clinical studies are needed to explain the decrimental role of EMPs signature among HFpEF versus HFrEF.

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