



## Endothelial Progenitor Cell Number to Apoptotic Endothelial Cell-Derived Micro Particles Ratio in Chronic Heart Failure Phenotypes

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### Abstract

Heart failure (HF) remains a leading cause of cardiovascular (CV) mortality and morbidity worldwide. Endothelium is considered a target organ that is involved in the pathogenesis of HF at the earliest stages and corresponds to CV risk factors, CV diseases and different phenotypes of HF. Endothelial progenitor cells (EPCs) with pro-angiogenic phenotypes and apoptotic endothelial cell-derived microparticles (EMPs) may reflect the severity of endothelial dysfunction and predict HF phenotypes. Moreover, apoptotic EMPs and EPCs are involved in the function of endogenous endothelial repair system, which contributes in the pathogenesis of HF across all stages. The short communication is dedicated the predictive role of altered ration between both biomarker of HF in the way to individualize the contemporary predictive score.

**Keywords:** Chronic heart failure; Biomarkers; Endothelial progenitor cells; Endothelial cell-derived microparticles; Prediction

### Introduction

Heart failure (HF) is a leading cause of cardiovascular (CV) morbidity and mortality worldwide [1]. Although HF pathogenesis is investigated deep enough, there are some chains of nature evolution of cardiac dysfunction, which require to be explained in detail. Endothelium is considered a target organ that is involved in the pathogenesis of HF at the earliest stages and corresponds to CV risk factors, CV diseases and different phenotypes of HF [2]. The endothelial dysfunction plays a pivotal role in several vascular complications of HF including accelerating atherosclerosis, ischemia, arrhythmias, thrombosis, myopathy, kidney dysfunction, and stroke [3]. In this context, reparation of endothelial injury is pretty important biological process, which mediates endothelium integrity, vasomotion, and control for microvascular inflammation. It has been postulated that the endogenous repair system based on mobbing and differentiation of endothelial progenitor cell is under regulation of appropriate cell-to-cell cooperation *via* specific signaling system [4]. Endothelial cells are able to produce and actively release microparticles due to cell activation and apoptosis [5]. These microparticles incorporate into process of transferring biological signals to target cells and mediate several responses supporting differentiation of endothelial precursors [6,7]. Thus, adequate functionality of endogenous endothelial repair system is based on balance between co-regulator producing (microparticles) and number/survival of endothelial progenitor cells.

Recent preclinical and clinical studies have shown that the apoptotic endothelial cell-derived microparticles (EMPs) may play a pivotal role in cell homeostasis, cell-to-cell cooperation, immune response, blood coagulation, restoring impaired reparative capacity of endothelium [8,9]. Apoptotic EMPs are released from the injured endothelial cells contributing in transfer of some biological information because of containing chromatin derivate (DNAs, micro-RNAs). Nevertheless,

they may directly injure an endothelial cell and worse vascular integrity [3]. There is a large body of evidence regarding that the circulating EMPs through transporting coagulants, peptides, active molecules, hormones, lipids [4-6]. Interestingly, apoptotic EMPs may directly injury endothelium, whereas EMPs received from activated endothelial cells may be a trigger of cytoprotective effects on vasculature [7,8]. There is evidence regarding an association between increased circulating number of apoptotic EMPs and neurohumoral/inflammatory activation, CV events and HF-related outcomes [9-12].

There is a large body of evidence regarding active participation of angiogenic endothelial progenitor cells (EPCs) with classic (CD45-CD34+CD309+CD144+) and non-classic (CD45-CD14+CD309+ and CD45-CD14+CD309+ Tie-2+) phenotypes in regulation of cardiac regeneration and endothelial function [13]. Moreover, lowered number of EPCs defined as CD34+ CD309+ associated positively with CV risk factors, HF etiology, age or gender of the HF patients, left ventricular hypertrophy and altered cardiac function [14,15]. Previously we reported that patients with HF with preserved left ventricular ejection fraction (HFpEF) have exhibited lowered CD31+/annexin V+ EMPs to CD14+CD309+ cells ratio and CD31+/annexin V+EMPs to CD14+CD309+Tie-2+ cells ratio in comparison with patients with reduced left ventricular ejection fraction (HFrEF). Interestingly, in euvoletic individuals with chronic HF this ration predicted HFrEF more sensitivity and specificity than traditional cardiac biomarkers, i.e. natriuretic peptides, galectin-3 and highly sensitive C-reactive protein [9]. In this context, it would be optimal to compare the predictive value of the ration for survival in patients with different HF phenotypes. If it has been suggesting that CD31+/annexin V+ EMPs to CD14+CD309+ cell number ratio would have elucidated reparative ability of endothelium, the role of this ration in predicting CV events and HF-related events might have clinically significant value [16]. Novel biomarker-based predictive score has shown that adding CD31+/annexin V+ EMPs to CD14+CD309+ cell number ratio to clinical and biochemical biomarker may sufficiently improve a predictive value of entire score [17]. Large clinical studies are required to elucidate the

role of impaired ratio between apoptotic EMPCs and pro-angiogenic phenotypes of EPCs in HF individuals.

## Conclusion

CD31+/annexin V+ EMPs to CD14+CD309+ cells ratio might be a strong predictor of HF phenotypes and probably much more accurate predict HF-related outcomes than traditional cardiac biomarkers. However, there are needed much more clinical investigations to clear this aspect of individualized predictive approach.

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