

Circulating Microparticles in Heart Failure: Relation to Comorbidities and Aging

***Alexander E. Berezin**

Chief of Cardiology Unit, Internal Medicine Department, State Medical University, Zaporozhye, Ukraine

Abstract

Development of Heart Failure (HF) associates with endothelial dysfunction that considered a key cause for tissue injury, and target organ damage. Endothelial Microparticles (EMPs) are small membrane vesicles that originate from activated or apoptotic endothelial cells and play a pivotal role in cell-to-cell communication, cellular fusion, and transport of biological active molecules. EMPs contribute in different types of biological effects depending on their origin. EMPs derived from activated endothelial cells may mediate tissue and vascular repair; induce angiogenesis, neovascularization, and cell differentiation. EMPs originated from apoptotic particles support inflammation, oxidative injury, reprogramming, intercellular communication of the target cells. Balance between both phenotypes of microparticles in circulation is frequently mediated by HF stage, aging, as well as comorbidity states. The review is depicted the role of several phenotypes of EMPs in realize of comorbidity state effects on endothelial function among HF patients.

Keywords: Chronic heart failure; Circulating endothelial-derived microparticles; Cardiovascular remodelling; Tissue repair

***Corresponding Author:** Alexander E. Berezin, Chief of Cardiology Unit, Internal Medicine Department, State Medical University, Zaporozhye, Ukraine; fax/phone: +380612894585; E-mail: dr_berezin@mail.ru

Introduction

Heart Failure (HF) remains a broadly spreading cardiovascular disease with high incidences of morbidity and mortality that has been demonstrated continuous arise worldwide [1, 2]. The innate mechanisms mediated a nature evolution of HF are actively investigated, while several phases of molecular interplaying in this settings are under recognized [3]. As known, endothelial dysfunction is considered a key cause for vascular tone disorders, tissue injury, and target organ damage that are suitable for HF and closely associates with clinical outcomes and prognosis [4]. Various autocrine and paracrine mechanisms are involved in the pathogenesis of endothelial dysfunction [5]. One of them is realize of Endothelial-Derived Microparticles (EMPs) contributed in cell-to-cell interaction, cellular fusion, and transport of active molecules, regulator peptides, miRNA, hormones, proinflammatory cytokines, and they therefore play a pivotal role in endothelial communication, angiogenesis, neovascularization, tissue reparation, and vascular tone mediating [6-8]. It has been suggested that various comorbidities, such as metabolic disorders, inflammatory and autoimmune state, infections, stress, and pregnancy, may induce endothelial dysfunction and provoke tissue damage through mediating of EMP secretion several originated and their effect of target cells [9]. However, the causative role of imbalance between different phenotypes of EMPs that is forming with comorbidities in evolution of HF is still unclear. The review is depicted the role of several phenotypes of EMPs in realize of comorbidity state effects on endothelial function among HF patients.

Biological function of endothelial-derived microparticles

EMPs are membrane small vesicles derived from endothelial cell in response to injury, activation or apoptosis [10, 11]. A wide spectrum of triggers (eg, inflammatory cytokines, hypoxia, thrombin, shear stress, direct cytotoxic agents) leads to endothelial cell activation via intracellular Ca^{2+} overload and phosphatidylserine accumulation, which induce the specific disruption of the cell membrane [12]. As result in this process membrane of endothelial cells appears to be asymmetrical and subsequently lead to an invagination of inner cell surface and forming microvesicles from endothelial cell membrane fragments. Overall, the mechanisms involved in the remodeling of the plasma membrane are complex, and affects cytoskeleton of the endothelial cells with switching genome mechanisms [13].

Microparticles are defined as small microvesicles (diameter 100-1000 nm) derived from activated and apoptotic endothelial cells [14]. Although knowledge on EMPs is sufficiently limited due to their sub-micrometer size and to intrinsic limitations in methods applied for their determination [15], it has been suggested that EMPs are powerful regulator of several biological processes, i.e. reparation, angiogenesis, neovascularization, immunity, thrombosis, inflammation [16, 17]. As known, circulating EMPs are considered a storage pool of bioactive vascular effectors because contain regulating proteins, peptides, active molecules, mRNA, miRNA, hormones, growth factors (transforming growth factor beta and vascular endothelial growth factor), inflammatory components (matrix metalloproteinases) [18-20]. Depending their origin (activated endothelial cells or apoptotic particles) EMPs contribute in different types of biological effects. It has been postulated that activated phenotype of circulating EMPs mediates tissue and vascular repair, angiogenesis, neovascularization, cell differentiation and growth, but apoptotic phenotype of EMPs support inflammation, oxidative injury, reprogramming, intercellular communication and phenotype modification of the target cells (mononuclears, endothelial cells, dendritic cells,), thrombosis, and direct

endothelial damage [21]. Interestingly, the resulting biological effect of circulating EMPs depends on balance between both phenotypes of microparticles in circulation [22, 23]. Recent clinical investigations allow us to suggest that comorbidities coexisted with cardiac failure worse endothelial function through imbalance between proangiogenic and apoptotic EMPs, while exact molecular mechanism of these effects is still incompletely understood and is required further studies [24-27].

Circulating endothelial-derived microparticles and heart failure

Recent studies have shown an elevation of circulating EMPs in heart failure [28, 29], while etiology of this setting does not effect of the number of EMPs [30]. Although concentration of circulating EMPs is considered a possible marker of endothelial damage in HF, the apoptotic EMPs to activated EMPs ration or apoptotic EMPs to circulating endothelial progenitor cell ratio have the most predictive value for HF patients [25, 26, 31]. Therefore, diabetes mellitus, inflammation state, atherosclerosis and uric acid may contribute in elevation of apoptotic-derived EMPs and decrease in activated-derived EMPs [32]. Aging is discussed as powerful risk factor of HF in general population. In fact, increased procoagulant activity in elderly subjects may probably relate with level of circulating microparticles [33]. Moreover, EMPs are components of the angiogenic response that is altered with age and mediates endothelial dysfunction development and vascular aging [34]. In this setting deficiency of circulating endothelial progenitor cells and increased apoptotic EMPs are obviously key players in HF among senior population [35, 36]. Metabolic diseases, such as diabetes mellitus, hyperuricemia, insulin resistance, may negatively effect on mobbing and differentiation of endothelial progenitor cells with angiogenic capacity and therefore potentiate secretion of apoptotic-derived EMPs that leads to altered profile of EMPs [37, 38]. In this context, imbalance between different phenotypes of EMPs is able to support endothelial injury and affect the progression of HF [39, 40]. Although this hypothesis appears to be attractive, it is required to confirmation in large clinical investigations.

In conclusion, circulating EMPs are cellular markers of endothelial damage, vascular integrity disorders, inflammatory activity, hypercoagulation, and worsening of vascular reparation in HF with possible predictive value. Imbalance between apoptotic- and activated-derived EMPs that is suitable for HF may relate to comorbidities. The altered profile of EMPs may be considered a diagnostic tool for risk stratification among HF subjects.

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