

Impaired Pattern of Endothelial Derived Microparticles in Heart Failure Patients

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Abstract

Chronic heart failure (CHF) remains a leading cause of cardiovascular morbidity and mortality worldwide that is characterized pandemic features. Metabolic diseases, neurohumoral state, and systemic inflammatory response are considered the origin of microvascular endothelial cell inflammation that leads to development of CHF and supporting cardiac remodelling and vascular dysfunction. Endothelial-derived microparticles (EMPs) are considered a novel biological marker of endothelial injury and vascular tone disorders. Biological effect of EMPs realizes through supporting of cell-to-cell cross-talking mediated by transport microRNA, active molecules, hormones, peptides, regulator proteins, etc. EMPs derived from activated endothelial cells may play a pivotal role in the vascular remodelling and endothelial reparation. In opposite, EMPs originated from apoptotic endothelial cells are considered a direct trigger of vascular injury. The review is addressed to discussion of one of possible mechanism of effect realizing of endothelial-derived microparticles different origin in heart failure affected endogenous reparation and tissue injury.

Keywords: Endothelial-derived microparticles; Heart failure; Cardiovascular remodelling; Tissue repair

Introduction

Chronic heart failure (CHF) remains a global medical problem strongly associated with cardiovascular morbidity and mortality worldwide [1]. Pathogenesis of CHF appears to be in-depth sophisticated and still not completely understood, because various molecular mechanisms affected worsening of cardiac failure is still under recognized [2]. Patients with CHF present with increased sympathetic nerve activity, depression in negative feedback sensory control mechanisms regarding vascular tone and cardiac rhythm, changes of neurohumoral and inflammatory markers in circulation, as well as increased coagulation and oxidative stress [3]. All these findings are reflected several faces of pathogenesis of CHF and they are associated with the development of endothelial dysfunction, tissue injury, cardiovascular remodelling that is suitable for CHF [4]. Therefore, metabolic comorbidities, such as obesity, diabetes, insulin resistance, and aging may negatively affect tissue reparation via involving various intracellular metabolic pathways, stress responses, lipotoxicity, cytoskeletal rearrangement, angiogenesis, as well as apoptotic signalling, cell-to-cell cooperation, and other functions of targeting cells [5-7]. Microparticles as derivatives of cellular membrane are discussed powerful paracrine regulators of target cell functions affected growth of tissue, reparation, vasculogenesis, inflammation, and apoptosis [8]. Microparticles originated from different cells (endothelial cells, mononuclears, platelets) play a pivotal role in intercellular information exchange through transfer of active molecules, microRNA (), peptides, hormones, inflammatory factors, growth factors, etc. [9-12]. Although elevated level of apoptotic-derived endothelial microparticles (EMPs) have demonstrated their prediction for CHF development and clinical outcomes [13,14], the role of activated endothelial cell derived microparticles is still not clear. Here they are hypothesized that CHF development is the result of both

disease-specific and traditional cardiovascular risk factors contributed in imbalance between apoptotic-derived EMPs and activated EMPs forming impaired phenotype. The review is addressed to discussion of one of possible mechanism of effect realizing of EMPs different origin in heart failure affected endogenous reparation and tissue injury.

Definition of endothelial-derived microparticles

EMPs are defined a heterogeneous population of vesicles (diameter 100-1000 nm) that are released by cellular vesiculation and fission of the membrane of endothelial cells [15]. This mechanism affects genome and may mediate by some triggers. It is well known that EMPs appear to be found into circulation in response to many situational changes (physiological conditions, stress) microenvironmental stimulation, coagulation / thrombosis, endotoxemia, endothelial shear stress, activated cells or those undergoing apoptosis, ischemic injury, hypoxia, and malignancy [16-20].

Biologic role of endothelial-derived microparticles

Biological effect of EMPs may mediate through supporting of cell-to-cell cross-talking because EMPs transport active molecules, hormones, peptides, regulator proteins, microRNA (small non-coding RNA molecule which functions in RNA silencing and post-transcriptional regulation of gene expression), etc. [12,21]. EMPs are incorporated in endothelial cells by interaction with α_4 - and β_1 - integrins that are expressed on the surface of microparticles. After connection with membrane of the cells EMPs realize their biological effect by directly stimulating target cells or by transferring surface receptors [22]. It has been postulated that the final result depends closely on origin of the EMPs [11,23]. In fact, EMPs derive from activated endothelial cells and may play a pivotal role in the angiogenesis and endothelial reparation [24]. In opposite, EMPs originated from apoptotic endothelial cells are considered a direct trigger of vascular injury [25]. However, many investigators believed that EMPs allow access to usually inaccessible tissues (endothelium,

new small vessels) and understand information changing between target cells aimed personalize vascular aging and reclassify the patients at risk [26-28]. Overall, EMPs are considered a novel biological marker of endothelial injury and vascular tone disorders in general population, cardiovascular patients and subjects with wide spectrum comorbidities including metabolic diseases, autoimmune state, coagulation, etc. [29-30].

Pattern of EMPs in heart failure

Elevated level of apoptotic-derived EMPs was frequently found in aging, cardiovascular diseases including heart failure and it was closely associated with poor clinical outcomes [14,31-33]. Moreover, predominantly increased apoptotic-derived EMPs are related with depletion of potentially angiogenic pool of endothelial progenitor cells and activated endothelial cell derived EMPs [34,35]. It has been suggested that deficiency of proangiogenic microparticles and / or endothelial progenitor cells coexisted elevated apoptotic-derived EMPs might be consider a impaired phenotype of circulating EMPs associated with poor prognosis reflected a change in the apoptotic/ reparative potential, being a putative indicator for vascular remodelling and endothelial dysfunction [33]. Indeed, Nozaki et al. [34] reported that elevated EMP levels were defined an independent predictor of future cardiovascular events in CHF patients, but not for all-cause mortality [34,35]. However, authors concluded that EMPs are a potentially useful biomarker of endothelial dysfunction in CHF risk stratification. Moreover, elevated EMPs might predict cardiovascular events in patients at high risk for coronary heart disease in general population [34,35]. It is important that the assessment of endothelial dysfunction by circulating EMP level may improve prediction of Framingham risk model that allows identifying patients vulnerable to cardiovascular disease [35].

Recent clinical studies have shown that high ratio estimated as apoptotic-derived EMPs to proangiogenic microparticles and / or endothelial progenitor cells predicts CHF-related death, all-cause mortality, and risk of recurrent hospitalization due to stable CHF and acutely decompensated CHF [36,37]. Therefore, prognostic implications and utility for risk stratification of impaired phenotype of circulating EMPs may be even higher when compared with level of apoptotic-derived EMPs and proangiogenic microparticles alone [38,39]. Whether impaired phenotype is useful to predict acute heart failure in patients with hypertension, cardiomyopathies, diabetes mellitus, stable coronary artery disease, asymptomatic atherosclerosis, it is not clear. It has been postulated that exiting apoptotic phenotype of EMPs may discuss a phenotypic marker coexisting other cardiovascular risk factors, such as dyslipidemia, obesity, diabetes, and hypertension. If this assumption is correct, EMP phenotyping is available for the risk stratification among subjects in general population. One of attractive feature of the risk stratification based on measurement of circulating EMPs is relation of impaired phenotype of microparticles of comorbidities that leads to allows you to personalize a global risk and probable measure a response due to treatment or procedure performing. However, microparticle profiles are powerful tool for individual assay of balance between reparative and injury intensity.

Conclusion: Probably impaired pattern of circulating EMPs might be consider a personalized marker of vascular remodelling or vascular aging, while evidence of predictive value of this marker for CHF patients is limited. More clinical trials with higher statistical power are

required to be explaining whether utility of determination of impaired phenotype of EMPs CHF patients is.

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