Extracellular Vesicles as Novel Delivery Drug System in Heart Failure: From Bench to Bedside?

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Abstract

Heart failure (HF) remains to be a serious public and health problem associated with higher morbidity, mortality and disability. Although there are high-quality developed clinical recommendations regarding prevention and treatment of HF, patients with HF experienced the poor clinical outcomes. Currently transfer of drugs using extracellular vesicles (EVs) into target cells in vivo is promising methods for attenuation of cardiac remodeling and ischemia. The short commentary is presented data confirming the role of specific novel delivery drug systems released wide spectrum of biological active molecules based on EVs’ releasing in HF. The use of EV systems might allow localized and sustained cytokine release and consequently a prolonged biological effect with induction of tissue regeneration and revascularization in HF.

Keywords: heart failure; microparticles; delivery drug systems; therapeutic aspects

Introduction and main results

Heart failure (HF) continues to have a sufficient impact on morbidity, mortality and disability in developed countries [1, 2, 3]. Although improving the management of HF remains a priority for health care services, the outcome of HF patients remains poor despite modern pharmacological and none-pharmacological therapies including established devices i.e. cardiac resynchronization therapy devices and implantable defibrillator / cardioverters [4-6].
The extracellular vesicles (EVs) are phospholipid-based endogenously produced particles (30-1000 nm in diameter), which contain cell-specific collections of proteins, glycoproteins, lipids, nucleic acids and other molecules [7]. Abundant cells including cardiomyocytes, blood cells, endothelial cells, immune cells, and even tumor cells are capable to secrete EVs of different size and compositions [8]. Depending on their origin EVs are graduated to follow subsets, i.e. the exosomes (30–100 nm in diameter), the microvesicles (50–1000 nm in diameter), ectosomes (100–350 nm in diameter), small-size MPs (<50 nm in diameter) known as membrane particles and apoptotic bodies (1-5 μm in diameter) [9].

There is large body evidence that the EVs could be used as therapeutic vehicles and as targets for the treatment of HF [10-]. Vicencio JM et al (2015) [10] presented the results clarifying the role of exosomes in deliver of endogenous protective signals to the myocardium by a pathway involving toll-like receptor-4 and classic cardioprotective heart shock proteins - HSPs (HSP27, HSP70). By now, exosomal microRNAs transportation has been found to deliver signals to mediate cardiac repair after acute myocardial infarction [11]. However, the exosomes quality and quantities are variable under different pathological conditions including myocardial infarction and HF. Overall these findings open serious perspectives for translation of remote ischemic preconditioning to clinical practice and provide new insights for the therapeutics to cardiac remodeling [12, 13]. Furthermore, EVs represent a proven, experienced transportation system that provides a safe haven for circulating small molecules with a built-in docking system [14]. Recently it has been found that EVs secreted by transplanted cells may exhibit their paracrine therapeutic effects on target cells in HF following myocardial infarction decreasing infarct size and improving cardiac function [15-18]. Moreover, EVs may be a cargo for drugs needed to be useful in attenuation of cardiac function. Al Kindi H et al (2014) [16] reported that use of new drug delivery system for milrinone using EVs in animal model of end-stage HF can prolong the effects of milrinone and improve global cardiac systolic function. Lu ZX et al (2014) [17] have evaluated the cardioprotective activity of placental growth factor (PGF) delivered through direct injection and a nanoparticle-based system model of acute myocardial infarction. Authors found that poly lactic-co-glycolic acid (PLGA)-based PGF-carrying nanoparticles may improve cardiac function in rats and exert the cardioprotective effect through regulating metalloproteinase-mediated myocardial tissue remodeling. The use of a EV system might allow localized and sustained cytokine release and consequently a prolonged biological effect with induction of tissue revascularization in HF. Indeed, Formiga FR et al (2010) [19] compared the effect of delivery of poly(lactic-co-glycolic acid) (PLGA) EVs loaded with VEGF(165) [vascular endothelial growth factor] with free-VEGF or control empty EVs in a rat model of ischemia-reperfusion. Investigators concluded that PLGA EVs were promising cytokine delivery system for treatment of myocardial ischemia and cardiac dysfunction. Overall, novel drug-delivery systems might be effective therapeutic tool in HF and other CV diseases.
Kervadec A et al (2016) [20] have reported that in this post-infarct HF animal model either human embryonic stem cell-derived cardiovascular progenitors or their secreted EVs enhance recovery of cardiac pump function and similarly affect cardiac gene expression patterns that could be related to this recovery. Authors concluded that paracrine effect in cell-based therapies is sufficient to functional recovery for post-infarction-related chronic HF, whereas exact mechanisms by which EVs improve cardiac function remain to be not fully determined.

By now, there are innovations regarding integrated application of our novel porous silicon EVs carrying adeno-associated virus nanoparticles, and the use of our ex vivo lung perfusion / ventilation system for the modulation of pro-inflammatory cytokines initiated by ischemic pulmonary conditions prior to organ transplant that often lead to complications [21]. Whether similar novel methods would be effective in HF patients are not fully clear, while these results are undoubtedly intriguing. Therefore, there is evidence regarding use of acetalated dextran MPs as a delivery tool for therapeutics to the heart after myocardial infarction [22]. Indeed, the EVs may release model proteins, myoglobin, and a sensitive growth factor, basic fibroblast growth factor, which are essential for attenuation of cardiac remodeling. Remarkably, transfer of drugs using EVs into target cells in vivo is promising, whereas large clinical investigations are required.

In conclusion, future perspectives regarding EVs’ utilization might relate to use of specific novel delivery drug systems released wide spectrum of biological active molecules that would be useful in cardiac remodeling attenuation.

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References


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