

# Utilization of Novel Delivery Drug Systems Based on Release of Extracellular Vesicles in Heart Failure

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## Abstract

Heart failure (HF) remains to be a serious public and health problem, which associate with higher morbidity, mortality and disability. Although there are high-quality developed clinical recommendations regarding prevention and treatment of HF, patients with HF have 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 mini review 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

Heart failure (HF) continues to have a sufficient impact on morbidity, mortality and disability in developed countries [1,2]. Although improving the management of HF remains a priority for health care services, the outcome of HF patients remains poor despite modern pharmacological and non-pharmacological therapies including established devices, i.e., cardiac resynchronization therapy devices and implantable defibrillator/cardioverters [3-6]. Meanwhile, it has suggested that functionality and repair ability of target cells in heart and vessels could be regulated specifically by direct cell-to-cell cooperation using appropriate extracellular microvesicles expressed on their surfaces complimentary receptors and antigens [7]. The target cells could recognize the vesicles with cargo of drugs and thereby target transfer of the drug into cells might occur. In this context, the methods to deliver the drugs into cells involved in the pathogenesis of HF based on extracellular vesicle transfer might appear to be promised. The aim of the mini review: to determine the role of specific novel delivery drug systems released wide spectrum of biological active molecules based on EVs' releasing in HF.

## Definition of Extracellular Vesicles

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 [8]. Abundant cells including cardiomyocytes, blood cells, endothelial cells, immune cells, and even tumor cells are capable to secrete EVs of different size and compositions [9]. 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) [10].

The majority (more than 90%) of EVs in healthy controls are of platelet origin, whereas less than 10% originate from granulocytes and less than 5% from endothelial cells, red blood cells and monocytes [11-13]. Since all types of particles contain surface proteins derived from their cell of origin (including antigen-presenting cells), while there are additional biomarkers confirming origin of the EVs. Recently EVs are considered a cargo for various molecules. Indeed, EVs carry proteins, RNA, micro-RNA, and DNA fragments from their cells of origin to

other parts of the body via blood and other body fluids. Within last decade it has become to know that EVs would act as information transfer for target cells [12]. Growing evidence supports the idea that regarding association between immune pattern of EVs originated from different cells (endothelial cells, mononuclears, dendritic cells, platelets) and nature evolution of various diseases including CV diseases, cancer, sepsis, eclampsia, autoimmune and metabolic states, etc. [13,14].

## Nanoparticles as Promising Drug Delivery Systems

Despite many drugs suffer from serious problems concerning insolubility, instability in biological environments; poor uptake into cells and tissues [15], EVs can be designed as drug delivery systems [7,10]. By now, exogenously constructed nanoparticles prepared on modified albumin structure, dendrons, polymers, peptides, nucleic acids, lipids, and human EVs are used to bind drugs and deliver it to the cells [16]. Therefore, there are carbon-based drug delivery systems, and systems prepared on gold nanoparticles [17]. It has suggested that EVs prepared from modified albumin or lipid-polymers might have several advantages compared with other EVs. The particular advantages of albumin used in drug delivery systems include ready availability, ease of chemical modification, good biocompatibility, and low immunogenicity. Lipid-polymeric nanoparticles have been explored to produce EVs due to their features and applications, i.e., as high drug entrapment, physical-chemical stability and controlled release properties [18].

There is large body evidence that the human EVs could be used as therapeutic vehicles and as targets for the treatment of HF [19-22]. Vicencio JM et al. [19] 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

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Received April 29, 2016; Accepted June 06, 2016; Published June 15, 2016

Citation: Berezin AE (2016) Utilization of Novel Delivery Drug Systems Based on Release of Extracellular Vesicles in Heart Failure. Cell Dev Biol 5: 173. doi:10.4172/2168-9296.1000173

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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 [20]. 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 [21,22]. Furthermore, EVs represent a proven, experienced transportation system that provides a safe haven for circulating small molecules with a built-in docking system [23]. Sufficient number of hopes and speculations are existed around the use of nanosize drug delivery systems prepared on human EVs or exogenously constructed nanoparticles. However, the regulatory approvals that have been received for several albumin-based therapeutic agents suggest that this approach will continue to be successfully explored.

### The Results of Animal Studies Regarding Use of EV Delivery Systems

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 [24-27]. Moreover, EVs may be a cargo for drugs needed to be useful in attenuation of cardiac function. Al Kindi et al. [25] 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 et al. [26] 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 the EV system might allow localized and sustained cytokine release and consequently a prolonged biological effect with induction of tissue revascularization in HF [27]. Indeed, Formiga et al. [28] 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 et al. [29] 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 [30]. Whether similar novel methods would be effective in HF patients are nor 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 [31]. 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 [32].

### Clinical Perspectives and Future Directions

The one of serious obstacle to implement of nano drug delivery systems is the lack of tissue or cell specificity that is suitable exogenous EVs. This is a leading problem associated with a risk of unexpected side effects or toxicity after their clinical application. Unfortunately, there are no FDA approvals or clinical trials in process to resolve situation around toxicity of drug delivery systems. Despite the many advantages of the drug delivery systems used in the failing human heart, there are not the regulatory approvals for evaluation of clinical efficacy of several drug delivery systems based on nanosized particles except lipid-polymeric nanoparticles and albumin-based EVs. However, a lot of clinical investigations are required to explain the advantages of different drug delivery systems.

### 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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