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# Exosomes and cardioprotection – A critical analysis

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ABSTRACT

Exosomes are nano-sized vesicles released by numerous cell types that appear to have diverse beneficial effects on the injured heart. Studies using exosomes from stem cells or from the blood have indicated that they are able to protect the heart both in models of acute ischaemia and reperfusion, and during chronic ischaemia. In addition to decreasing initial infarct size, they are able to stimulate angiogenesis, reduce fibrosis and remodelling, alter immune cell function and improve long-term cardiac contractile function. However, since the technology and techniques used for the study of exosomes is relatively immature and continually evolving, there remain many important caveats to the interpretation of studies. This review presents a critical analysis of the field of exosomes and cardioprotection. We analyse the effects of exosomes from all types of stem cells investigated to date, summarize the major effects observed and their potential mechanism, and offer our perspective on the major outstanding issues.

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## 1. Introduction

The involvement of larger extracellular vesicles (EVs) such as microparticles or microvesicles (MVs) in thrombosis has been understood for many years (Boulanger et al., 2017). MVs are also understood to be a potential source of biomarkers of pathology (Jansen et al., 2017; Sluijter et al., 2017). More recently, interest has turned to their smaller cousins, namely exosomes, as it has become apparent that they have the ability to transmit signals including protein and miRNA between cells (Valadi et al., 2007). It therefore seems likely that exosomes are involved in normal physiological, and potentially also pathological processes (Lawson et al., 2016). Since blood contains enormous numbers of exosomes released by platelets, endothelium, and other cell types, it is clearly of interest to investigate their role in the cardiovascular system, and to determine their contribution to cardiovascular diseases (Sluijter et al., 2017; Lawson et al., 2016).

Cardiovascular disease is the major cause of death not only in developed countries but world-wide (Hausenloy and Yellon, 2013). A major cause of cardiovascular disease is damage to the vasculature resulting in gradual build-up of atherosclerotic plaques that can partially occlude the vessel. If this occurs in the heart, it can result in the distal myocardium becoming ischaemic under situations of increased cardiac demand. In some circumstances, the plaque can rupture, exposing the intravascular wall to the coaggulative components of the blood which rapidly cause thrombotic occlusion of the artery, followed by ischaemia, with the development of an acute myocardial infarction. If the clot is not quickly removed by thrombolysis or percutaneous coronary intervention, or is not bypassed surgically (CABG), then the ischaemic myocardium will die. Thus, it is crucial to reperfuse the vessel as quickly as possible. However, it has been known for many years that reperfusion causes a degree of additional injury, referred to as “reperfusion injury” (Hausenloy and Yellon, 2013; Bell et al., 2016; Hausenloy et al., 2017; Lecour et al., 2014). As the final infarct size in patients with acute myocardial infarction (AMI) predicts long-term clinical outcome (Lonborg et al., 2013), it is envisaged that the identification of means of minimizing this injury will reduce patient mortality and morbidity.

To this end, many interventions have been investigated with the aim of reducing reperfusion injury. However, despite their success in animal studies, few have shown efficacy in patients (Bell et al., 2016; Hausenloy et al., 2017; Lecour et al., 2014; Kloner et al., 2017). One of the most potent methods of protecting the heart in experimental models is to subject it to several brief (3–5 min) periods of ischaemia prior to a longer period of injurious ischaemia and reperfusion, a procedure called ischaemic preconditioning (IPC) (Hausenloy and Yellon, 2013; Hausenloy et al., 2017; Lecour et al., 2014). Although the efficacy of IPC has been demonstrated

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in humans, it is clearly impractical to apply prior to myocardial infarction in the majority of cases that occur spontaneously (Yellon et al., 1993). There is therefore great interest in the potential for remote IPC (RIPC), in which the preconditioning stimulus can be easily applied to a limb remote from the heart, up to the time that the myocardium is reperfused (Hausenloy and Yellon, 2013; Bell et al., 2016; Davidson et al., 2013; Sharma et al., 2015). RIPC is highly effective and reproducible in animal studies (Bromage et al., 2017), and numerous phase I clinical trials have suggested efficacy at preventing myocardial injury in the setting of an AMI (Heusch and Rassaf, 2016), yet it remains to be validated in a larger clinical trial (Hausenloy et al., 2015).

One alternative approach to protecting the heart against the initial insult of IR injury, is to attempt to restore the lost myocardium, or at least improve its function. Unfortunately, since mammalian cardiomyocytes are terminally differentiated there is extremely limited scope for the spontaneous recovery of myocardium by cardiomyocyte proliferation. However, a great deal of effort has been expended in attempting to regenerate myocardium by injecting different types of stem cells (Madonna et al., 2016). Unfortunately this approach has also been largely unsuccessful in creating new myocardium, despite some encouraging effects being observed with respect to the preservation of existing myocardium, and improvements in cardiac contractile function (Madonna et al., 2016). Since these benefits were clearly not mediated by an increase in cardiomyocyte number, attention has recently turned to factors that may be released from the remaining stem cells, and that may mediate this paracrine effect. In particular, exosomes have been proposed as an important potential paracrine factor (Fig. 1) (Davidson et al., 2017a; Yellon and Davidson, 2014).

Exosomes, like all EVs, are enclosed by a lipid bilayer membrane, and contain components originating from their cell of origin. Exosomes are some of the smallest EVs, typically only 50–150 nm in diameter (Fig. 2). This renders them difficult to visualize using standard light imaging techniques, since they are smaller than the wavelength of light. Most isolation procedures are able to achieve a relative concentration of exosomes, but these preparations usually also contain a certain number of MVs and other EVs, due to their overlapping size distributions (Fig. 2). In particular, exosomes' similar size and/or density to different lipoprotein particles makes them extremely challenging to isolate at high purity from blood. To avoid interference from bovine exosomes, cultured cells may be grown in nominally exosome-free medium, although even here the risk of contamination by lipoprotein particles remains (Shelke et al., 2014). Alternatively, in some studies, cells are cultured for several days in serum-free medium, although this also runs the risk of artefactually altering the cells. Consequently, using current techniques, it is challenging to ascribe particular functional effects specifically to exosomes. For this reason, some studies refer to "exosomal" preparations more conservatively as "small EVs" (sEVs). Given this uncertainty, it is crucial to consider the method of EV isolation used in each individual study, since this determines to a large extent the type of EVs in the preparation. This issue, and the effect of different isolation methods has been extensively reviewed (Sluijter et al., 2017), and is also discussed in other articles in this series.

Despite the above caveats, important clues have been obtained to suggest that EVs do play a role in cardiovascular health and disease (Lawson et al., 2016). Recent reviews have given an excellent description of the role of EVs more broadly in cardiovascular and metabolic disease (Boulanger et al., 2017; Lawson et al., 2016; Sluijter et al., 2014). The aim of the present review is to critically review the literature investigating exosomes, their ability to protect the heart and restore its function after IR injury.

## 2. Mesenchymal stem cell-derived exosomes

Mesenchymal stem cells (MSCs) have generated extensive interest due to their multi-lineage differentiation potential and their ability to be expanded *in vitro* (Madonna et al., 2016; Zomer et al., 2015a). A further advantageous characteristic is that MSCs can be obtained from different tissues, whether foetal, young or adult, although it appears that those derived from younger source tissues are the more potent (Madonna et al., 2016). Interestingly, MSCs also appear to have immunosuppressive properties (De Miguel et al., 2012), raising the possibility that EVs originating from MSCs might be able to confer multiple benefits, not just on the heart directly but via effects on cells of the immune system.

Lai et al. were the first to show that exosomes from MSCs are cardioprotective acutely (Lai et al., 2010a). They used HPLC to purify exosomes released by MSCs in culture and injected them into the tail veins of mice undergoing 30 min myocardial ischaemia via ligation of the coronary artery (Lai et al., 2010a). In injected mice, infarct size was significantly reduced 24 h later (Lai et al., 2010a),

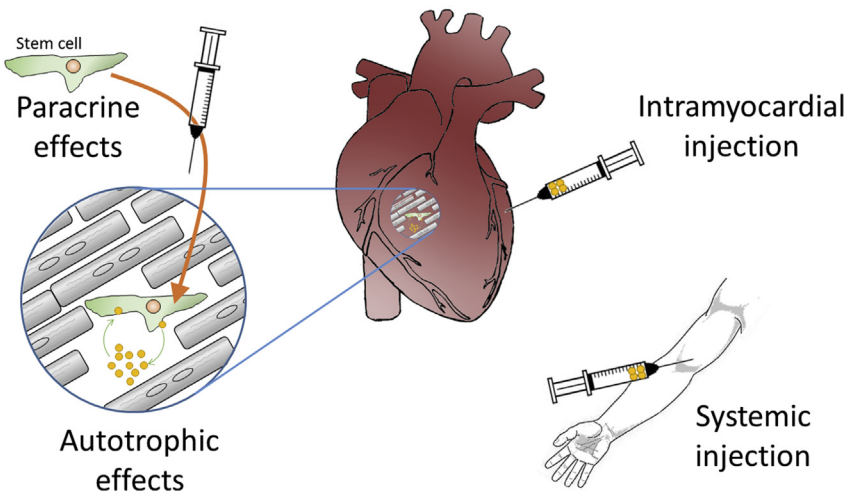


**Fig. 1.** Exosomes can potentially exert effects on the heart via multiple different pathways. 1) Exosomes produced from intramyocardially injected stem cells can exert paracrine effects. 2) Resident cardiac stem cells may cause autotrophic stimulation of themselves or other cell types in the heart. 3) Exosomes injected intramyocardially can affect different cell types directly. 4) Exosomes administered systemically interact with cells of the cardiovascular system, including endothelium, blood cells and the heart.

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