JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 3, NO. 1, 2018

PRECLINICAL RESEARCH

Diffusion Tensor Cardiac Magnetic Resonance Reveals Exosomes From Cardiosphere-Derived Cells Preserve Myocardial Fiber Architecture After Myocardial Infarction

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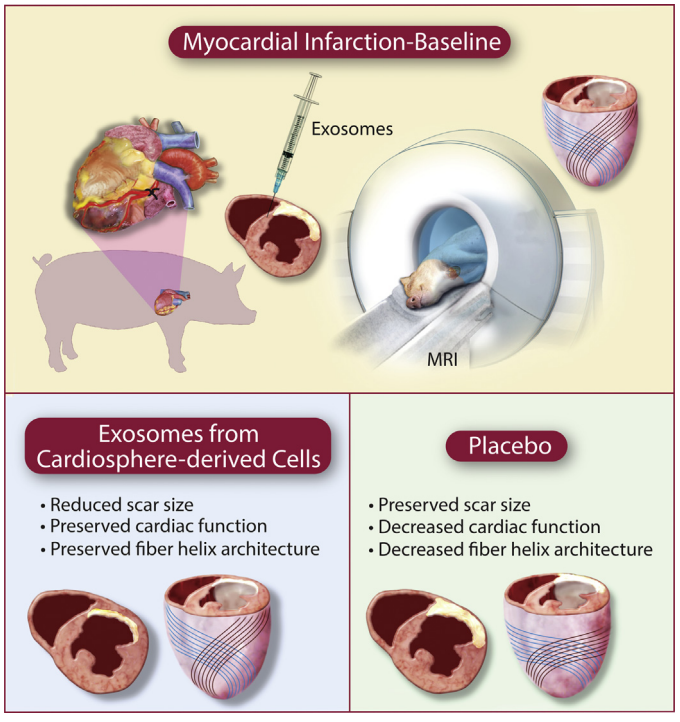
VISUAL ABSTRACT



Nguyen, C.T. et al. J Am Coll Cardiol Basic Trans Science. 2018;3(1):97-109.

HIGHLIGHTS

- **CDC_{EXO} are RNA-laden nanoparticles that reduce scarring, halt adverse remodeling, and preserve cardiac function in rodents and pigs after MI.**
- **The therapeutic effects of CDC_{EXO} on myocardial fiber architecture and how it relates to preserved cardiac function and reduced scarring remain unclear.**
- **After intramyocardial CDC_{EXO} treatment in MI pigs, DT-CMR elucidated myocardial fiber architecture was preserved indicated by the unchanged helix angle transmurality.**
- **Scar size measured by conventional CMR combined with helix angle transmurality measured by DT-CMR demonstrated significant improvement in the prediction of cardiac function.**
- **DT-CMR is a powerful technology for myocardial regenerative therapy evaluation revealing unique insight into the myocardium's microstructure.**

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ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2017.09.005

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 3, NO. 1, 2018
FEBRUARY 2018:97–109

ABBREVIATIONS AND ACRONYMS

CDC = cardiosphere-derived cell

DT-CMR = diffusion tensor-cardiac magnetic resonance

EDV = end-diastolic volume

ESV = end-systolic volume

EF = ejection fraction

CDC_{EXO} = exosomes secreted by CDC

HA = helix angle

HAT = helix angle transmurality

|HAT| = absolute helix angle transmurality

ICC = intra-class correlation

LGE = late gadolinium enhancement

LV = left ventricular

MI = myocardial infarction

MRI = magnetic resonance imaging

ROC = receiver operating characteristic

ROI = region of interest

SS = scar size

TD = transmural depth

TE = echo time

TR = repetition time

SUMMARY

The object of the study was to reveal the fiber microstructural response with diffusion tensor cardiac magnetic resonance after intramyocardial exosomes secreted by cardiosphere-derived cells (CDC_{EXO}) in chronic porcine myocardial infarction. Porcine with myocardial infarction underwent intramyocardial delivery of human CDC_{EXO} and placebo in a randomized placebo-controlled study. Four weeks after injection, viability improved in the CDC_{EXO} group, whereas myocardial fiber architecture and cardiac function were preserved. In the placebo group, fiber architecture and cardiac function declined. Myocardial regeneration by CDC_{EXO} is not tumor-like; instead, details of tissue architecture are faithfully preserved, which may foster physiological excitation and contraction. (J Am Coll Cardiol Basic Trans Science 2018;3:97–109)

Cardiosphere-derived cells (CDCs) have demonstrated regenerative and cardioprotective properties in various animal models (1-6) of myocardial infarction (MI), and in patients as well (7,8). Specifically, CDCs decrease scar size (SS), increase viable tissue, and halt adverse remodeling. Underlying mediation of the regenerative benefits of CDCs has been associated with the secretion of exosomes (9-11).

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These endogenous nano-scale lipid bilayer vesicles mediate cell-cell communication transferring microRNAs and other contents specific to the parent cell type (12). Exosomes secretion from CDCs (CDC_{EXO}) is necessary for the therapeutic benefits of CDCs, and CDC_{EXO} mimic the benefits of the parent CDCs (13-15). In a porcine model of convalescent MI, intramyocardial injections of CDC_{EXO} are beneficial by reducing SS, halting adverse ventricular remodeling, and preserving cardiac function (16), exhibiting a similar therapeutic benefit as intracoronary delivery of CDCs (17). However, the underlying mechanisms behind the regenerative properties of CDC_{EXO} remain to be revealed. One key feature of adverse ventricular remodeling during the healing phase following MI is the disruption of myocardial fiber architecture (18-20). It is currently unknown if CDC_{EXO} will affect myocardial fiber architecture post-MI. Preservation of correct fiber orientation following treatment with CDC_{EXO} could provide further insight into how cardiac function is maintained (or deteriorates) post-MI.

To characterize the impact of CDC_{EXO} on myocardial fiber architecture, a novel noninvasive technique is needed to monitor the therapy before and after delivery. One such technique is diffusion-tensor cardiac magnetic resonance (DT-CMR), which has demonstrated an ability to define myocardial microstructure before and after bone marrow-derived stem cell treatment in small animal MI models (21) and other potential cardiovascular therapies including left ventricular (LV) restoration (22), administration of *N*-acetylcysteine to treat cardiac hypertrophy (23), and human umbilical cord blood stem cell transplantation to treat MI (24). These preclinical studies demonstrated that a clear relationship exists between myocardial fiber architecture and cardiac function and that DT-CMR was sufficient to characterize such a relationship.

However, DT-CMR is not currently performed in a clinical setting because of major technical challenges centered on the inherent sensitivity of the technique to bulk motion. The previously mentioned DT-CMR-based therapy evaluation studies were in large part performed either in vitro or on small animal research magnetic resonance imaging (MRI) scanners capable of overcoming the deleterious effects of bulk motion. Recent technical advances have facilitated the acquisition in vivo of DT-CMR on clinical MRI scanners (25-29) in healthy human volunteers and large animals. Limited in vivo work has been performed preclinically in

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Manuscript received July 20, 2017; revised manuscript received September 11, 2017, accepted September 12, 2017.