SUPPLEMENTAL MATERIAL

SUPPLMENTAL METHODS

Exosome Isolation and Preparation

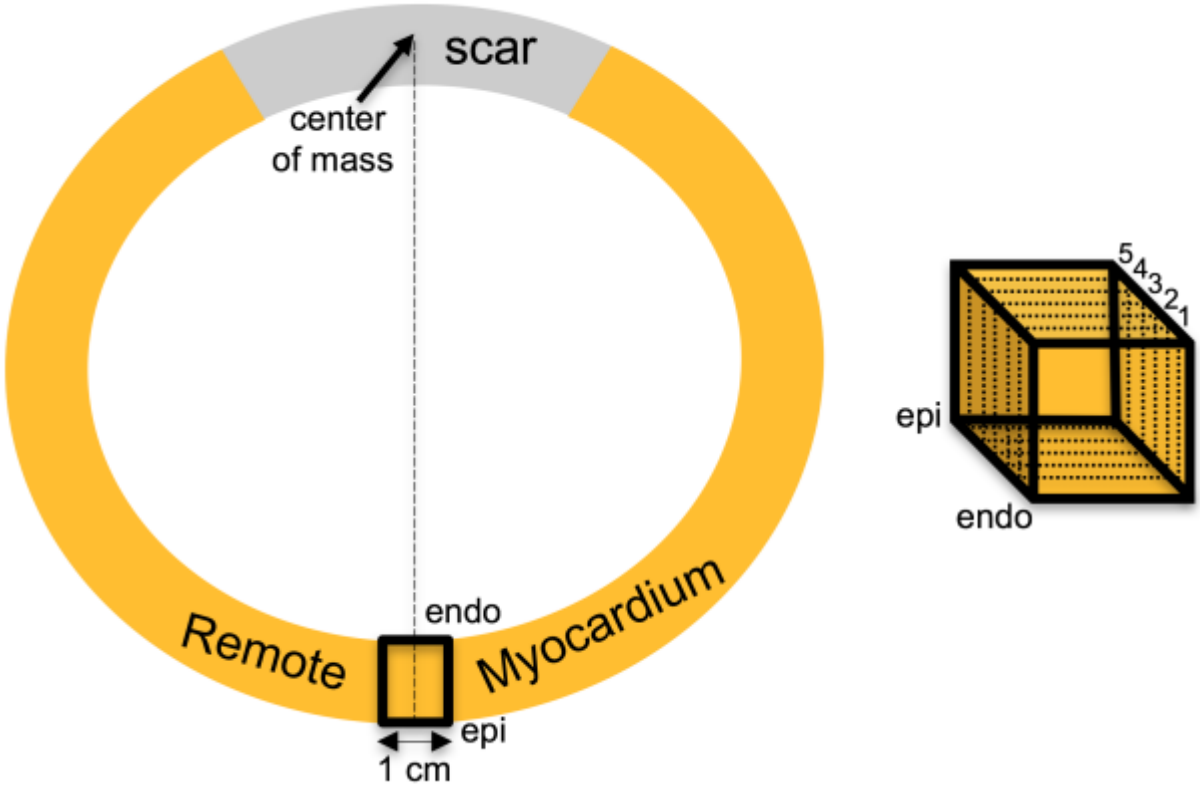
The biopsies were placed in collagenase and then cultured on 20 mg/ml fibronectin (BD biosciences) coated dishes. After 2-3 weeks of culturing, cells were harvested using 0.25% trypsin (GIBCO) and cultured in suspension on 20 mg/ml poly d-lysine (BD Biosciences) to form self-aggregating cardiospheres. CDCs were obtained by seeding cardiospheres onto fibronectin-coated dishes and passaged. The remaining CDC medium was subjected to two successive centrifugation steps (2000g for 20 min and 10000g for 30 min) to isolate the CDC_{EXO}[1]. The resulting supernatant was precipitated by polyethylene glycol (ExoQuick^{TC}) followed by overnight incubation at 4°C. The conditioned media was passed through a 0.2μm filter yielding various extracellular vesicles including the desired CDC_{EXO}, larger ectosomes, and apoptosomes. Final serial centrifugation at 2000g and 10000g pelleted the CDC_{EXO} and removed media and larger particles.

DT-CMR Reconstruction

Diffusion tensor MRI reconstruction was calculated using a weighted least squares fit [2] and eigenvalue decomposition yielded eigenvectors to calculate fiber orientation for each voxel. HA was calculated using the same geometric definition as Streeter, et al [3], with the local tangent vector, *t*, being orthogonal to the radial vector, *r*, defined by the center of mass of the LV blood pool to the voxel of interest and the long axis, *u* (Figure 1). HAT was calculated by automatically segmenting the LV into five transmural concentric rings. Then, the slope was extracted from the linear regression of

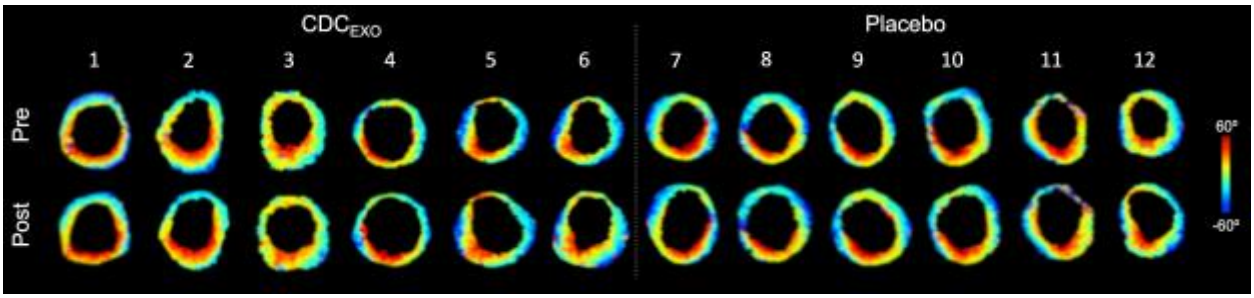
the HA against transmural depth along 120 radial chords. As HAT tends towards zero, the myocardial architecture reflects a less helical characteristic with overall less inclination of the myocardial fiber orientation relative to the short axis plane. Normal HAT is typically negative with endocardium, mid-myocardium, and epicardium having $\alpha > 0$, $\alpha \approx 0$, and $\alpha < 0$, respectively.

SUPPLEMENTAL FIGURES AND FIGURE LEGENDS



Supplemental Figure 1 – Schematic of histological sectioning. In the mid short axis section, the remote myocardium exactly opposite of the center of mass of the scar was further sectioned transmurally with a 1-cm width. The transmurally sectioned remote myocardium was sliced from endocardium to epicardium into 10-um cuts. Five

equidistant transmural cuts were selected and prepared for conventional H&E staining and optical imaging.



Supplementary Figure 2 – Representative HA maps from all subjects at both pre and post therapy time points. The HA maps are rotated so that the center of scar for each subject is at the 12 o'clock position.

SUPPLEMENTAL REFERENCES

1. Tseliou E, Fouad J, Reich H, Slipczuk L, de Couto G, Aminzadeh M, Middleton R, Valle J, Weixin L, Marbán E. Fibroblasts Rendered Antifibrotic, Antiapoptotic, and Angiogenic by Priming With Cardiosphere-Derived Extracellular Membrane Vesicles. *Journal of the American College of Cardiology* [Internet]. 2015;66:599–611. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0735109715027291

2. Chung S, Lu Y, Henry RG. Comparison of bootstrap approaches for estimation of uncertainties of DTI parameters. *NeuroImage*. 2006;33:531–541.

3. Streeter DD, Spotnitz HM, Patel DP, Ross J, Sonnenblick EH. Fiber orientation in the canine left ventricle during diastole and systole. *Circulation Research*. 1969;24:339–347.

SUPPLEMENTARY TABLE 1.

Reproducibility of Myocardial Fiber Architecture and Cardiac Function

		All Subjects (Pre-MI)
|HAT|	Time 1 [°/%TD]	1.01 [0.06]
	Time 2 [°/%TD]	1.03 [0.08]
	Δ [%]	2 [5]
LVEF	Time 1 [%]	54 [2]
	Time 2 [%]	56 [3]
	Δ [%]	3 [4]
LVEDV	Time 1 [ml]	57 [5]
	Time 2 [ml]	55 [4]
	Δ [%]	3 [8]
LVESV	Time 1 [ml]	25 [3]
	Time 2 [ml]	24 [4]
	Δ [%]	6 [9]
SV	Time 1 [ml]	31 [3]
	Time 2 [ml]	32 [2]
	Δ [%]	3 [4]

Median [Interquartile Range], *Time 1 vs Time 2 (1 week apart), $p<0.05$, TD: transmural depth, |HAT|: absolute helix angle transmurality, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic volume, SV: stroke volume, Δ: normalized change
(Time 1 – Time 2)/(Time 1)