

The Structural Basis of Functional Improvement in Post-Infarct Rat Hearts with Stem Cell Treatment

Y. Chen^{1,2}, J. Zhong^{1,2}, W. C. Low³, J. Zhang⁴, and X. Yu^{1,2}

¹Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, United States, ²Case Center for Imaging Research, Case Western Reserve University, Cleveland, OH, United States, ³Department of Neurosurgery, University of Minnesota, ⁴Division of Cardiology, University of Minnesota

Myocardial infarction (MI) is one of the major causes of heart failure in the world. Due to the loss of viable myocardium and high myocardial wall stress after MI, the heart undergoes progressive remodeling that will eventually lead to heart failure. Recently, cellular transplantation using stem cells has been proposed as a treatment strategy for preserving the myocardium in infarct area and border zones, as well as for improving global and regional cardiac function. The therapeutic effect of various types of stem cells has been investigated and many studies reported improved myocardial function after the treatment. However, the mechanism for this improvement, particularly at ventricular structural level, is still poorly understood. In the present study, we combined in vivo functional assessment of ventricular function with ex vivo characterization of myocardial structure to investigate the long-term effects of stem cell therapy on the structural and functional remodeling in post-infarct rat hearts. The results show that the functional improvement with stem cell therapy is correlated to the structural alteration in myocardial fiber architecture.

Methods Twelve male Lewis rats were randomly allocated into three groups. (1) no surgery (**control**; n=5); (2) ligation of left anterior descending (LAD) coronary artery without any therapy (**untreated**; n=3); (3) LAD ligation with tail vein injection of human non-hematopoietic umbilical cord blood stem cells (UCBSCs; **therapy**; n=4). Displacement-encoding with stimulated-echo (DENSE) MRI was used to quantify the myocardial wall motion at high spatial resolution [1]. Multi-phase 2D DENSE images were acquired at base, mid-ventricle and apex for each rat. Cine FLASH images were also obtained at each imaging level to calculate LV volumes and ejection fraction (EF). After the in vivo measurement, heart was excised from the animal, arrested in diastole and fixed with 10% formalin. Diffusion-weighted images were acquired from the fixed hearts in a 9.4T vertical bore magnet with a 2 cm birdcage coil (6 gradient directions; b, 800 s/mm²). Seven to nine short-axis images were acquired to cover the whole LV. The myocardium in DENSE and DTI images was divided into three segments, i.e., infarct, border, and remote zones [2].

Results LV EF in UCBSC-treated rats was significantly improved as compared to untreated infarct rats and was similar to that of the control rats (Table 1). As shown in Fig. 1, both radial and circumferential strains in border zone were significantly decreased after MI. With the treatment, the radial strain in the border zone was significantly increased as compared to the untreated group. In addition, the torsion at peak systole was also increased by 43% in the therapy group than in the untreated group (Table 1).

Myofiber helix angle was quantified from DTMRI data (Fig. 2). Compared to the control hearts, the untreated myocardium exhibited decreased percentage of right-handed fibers (RHF), suggesting myocardial loss at the subendocardial region. As a result, the percentage of circumferential fibers (CFs) increased. However, stem cell treated hearts showed similar fiber distribution as the controls, suggesting preserved structural integrity.

Tab. 1: Animal characteristics and global cardiac function.

	Control	Untreated	Therapy
Weight (g)	649.6 ± 16.9	670.7 ± 61.3	661.5 ± 67.3
Diameter (mm)	9.2 ± 0.5	10.7 ± 0.3*	10.8 ± 1.1*
EF (%)	59.1 ± 4.9	39.7 ± 4.5*	52.8 ± 7.1 [#]
Torsion (degree/cm)	23.6 ± 2.6	14.3 ± 1.8*	21.2 ± 4.9

* represents significant difference compared with control group;
[#] represents significant difference compared with untreated group.

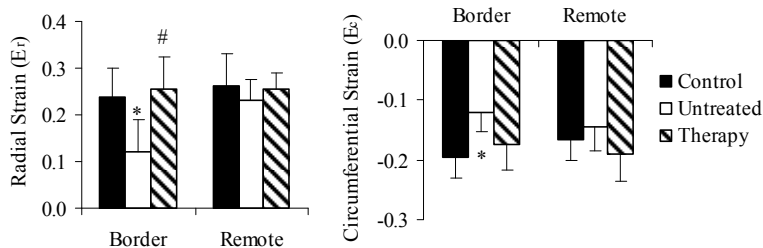


Fig. 1: Myocardial strain at apex (radial strain, left; circumferential strain, right). *P<0.05 control versus untreated; [#]P<0.05 untreated versus therapy.

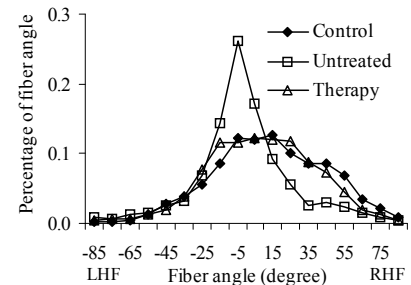


Fig. 2: Histogram of fiber helix angles in the infarct zone. RHF: right-handed fiber; LHF: left-handed fiber.

Discussion In this study, we investigated the long-term effect of stem cell therapy on myocardial function and structure in post-infarct rat heart. Our in vivo data demonstrated that the treatment with UCBSCs significantly improved the cardiac function in post-infarct myocardium. More importantly, stem cell treated hearts manifested preserved myocardial structure which provided structural basis for the improved cardiac function in post-infarct hearts with stem-cell therapy.

References

- [1] Zhong J and Yu X, ISMRM, 2009. [2] Wu EX, MRM, 2007, 58: 687-695.