Temporal Evolution of Three-Dimensional Myocardial Dysfunction during Post-Infarct Left Ventricular Remodeling in Mice

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Introduction:

The mouse animal model is increasingly being used to investigate both the genetics and pharmacologic therapy of left ventricular (LV) remodeling after myocardial infarction (MI). Local changes in myocardial contractile function (strain) can be quantified using MR tagging in the plane of the scan [1]. However, the motion and strain patterns during remodeling are complex and three-dimensional (3D). In order to quantify the 3D changes in myocardial strain after MI, we studied five mice, using a comprehensive model-based 3D MRI tagging analysis, at baseline and 1 day, 7 days and 28 days after reproducible induction of a large antero-lateral MI.

Methods:

Five C57BL/6 mice were used in this study, which was approved by the Institutional Animal Care and Use Committee. MI was surgically induced by 60 min occlusion of the left anterior descending coronary artery followed by reperfusion as described previously [1]. This protocol has been shown to reproducibly infarct the apex and antero-lateral midventricle. For MR scanning, the mice were anesthetized with isoflurane (1% in oxygen). MRI was performed on a 4.7T Varian scanner using a custom-made birdcage RF coil. The imaging protocol included: 1) localizer scanning; 2) short axis imaging with black-blood myocardial tagging (8 slices); 3) long axis imaging with black-blood myocardial tagging (4 slices). All tagged images used a FLASH imaging sequence (1 mm slice thickness, 25.6 mm FOV, 192x96 image matrix, 20º flip angle, TE 4.8 ms) with a 6 lobe SPAMM pulse sequence (4.8 ms duration) applied after the ECG trigger (180º tag flip angle, 0.7 mm tag separation). Twelve frames were acquired per slice. The short axis images had two sets of tagged images acquired per slice (horizontally and vertically oriented tags) with the higher-resolution readout direction always perpendicular to the tag orientation. Long axis images had one set of tagged images with the tag orientation perpendicular to the left ventricular long axis. Three dimensional displacements of the tags were tracked in all images and a 3D finite element model of the LV was used to reconstruct the 3D deformation and strain, as described previously [2].

Results:

The mean global mass and volume results are shown in Table 1. As expected, mass, EDV and ESV increased during remodeling while EF decreased.

Table 1. LV mass and volume, mean±SEM (n=5) at four time points. p<0.05 vs baseline.*

	Mass(mg)	EDV(µl)	ESV(µl)	SV(µl)	EF(%)
baseline	95±3	45±3	18±1	27±2	59±2
1 day	103±4	45±2	28±2*	17±1*	38±3*
7 days	102±3*	61±4*	40±4*	21±2*	34±3*
28 days	118±6*	72±4*	48±6*	24±4	34±5*

The 3D principal strain associated with maximal contraction (a composite measure of 3D contractile function) is shown in Figure 1 (left). The 3D principal strain in the apex showed marked reduction at day 1 ($p<0.05$) with little change thereafter. Similarly, the lateral and anterior wall in the mid-LV showed marked reduction at day 1 ($p<0.05$) with little subsequent change. The mid-ventricular septum maintained function at all time points, whereas the mid-posterior wall (adjacent to the infarct) demonstrated intermediate function. The basal septum exhibited augmented function, increasing from baseline to day 7 ($p<0.05$) and persisting to day 28. In the non-infarcted basal lateral and anterior walls, shortening was decreased at day 1 ($p<0.05$), with subsequent recovery of function. These results were similar in the strains measured with respect to the longitudinal and circumferential directions.

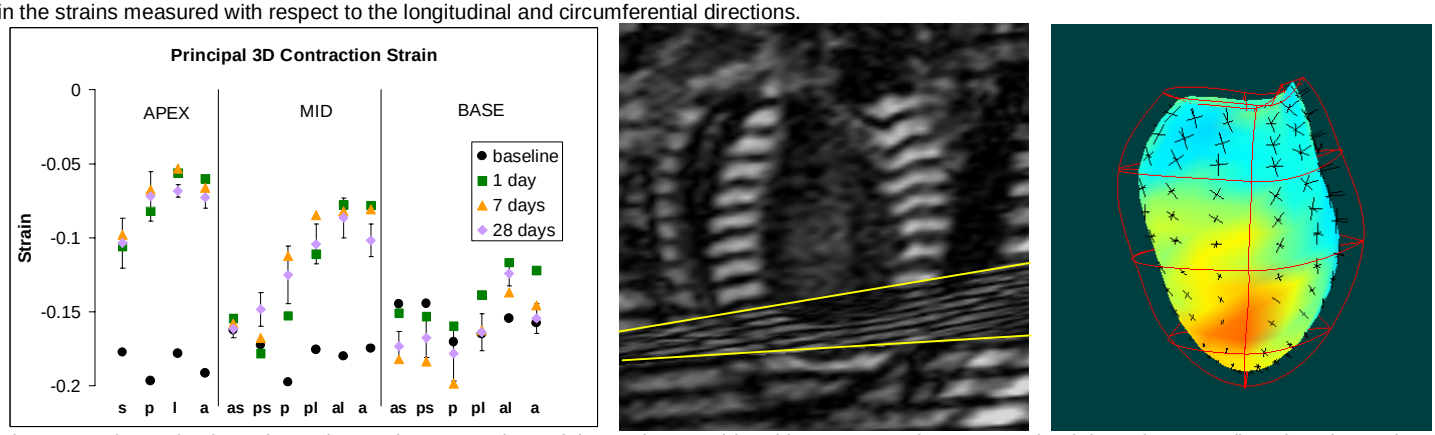

Figure 1. Left: Maximal 3D shortening strain at 16 regions of the LV (apex, mid and base; a=anterior, p=posterior, l=lateral, s=septal), at four time points (mean of n=5, bars denote SEM at 28 days). Middle: Tagged long axis image at ES with short axis slice (yellow outline) shown in 3D (28 day infarct). Right: 3D finite element model at ES (28 day infarct), crosses denote principal strains, surface colour denotes maximal shortening (blue –0.2, red 0.0).

Discussion:

This study demonstrates the feasibility of performing comprehensive 3D analyses of myocardial deformation patterns in mice to study post-infarction LV remodeling. The 3D quantification of regional strain patterns after MI extend 2D findings previously described in mice including dysfunction within noninfarcted regions [1] that subsequently resolves. In addition, this study detected augmented function at days 7 and 28 in the basal septum. These results will be useful in determining the effect of genetic manipulation and/or pharmacologic therapy on post-MI remodeling.

References:

[1] Epstein FH et al. Magnetic Resonance in Medicine 48:399-403 (2002).
[2] Young AA et al. IEEE Trans Medical Imaging 14:413-421 (1995).