Noninvasive Three-dimensional Mapping of endothelial dysfunction in Cardiac Ischemia by Dynamic Contrast Enhanced Magnetic Resonance Imaging Using Albumin-based Contrast Agent

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Target audience: Cardiovascular magnetic resonance researchers.

Purpose: Myocardial endothelial dysfunction after a myocardial infarction results in leakage of albumin from the intravascular space. This study aimed to develop a noninvasive method to quantify the dynamics of an albumin-based blood pool contrast agent for mapping the myocardial microvascular density and the rate of extravasation from myocardial blood vessels using in vivo dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).

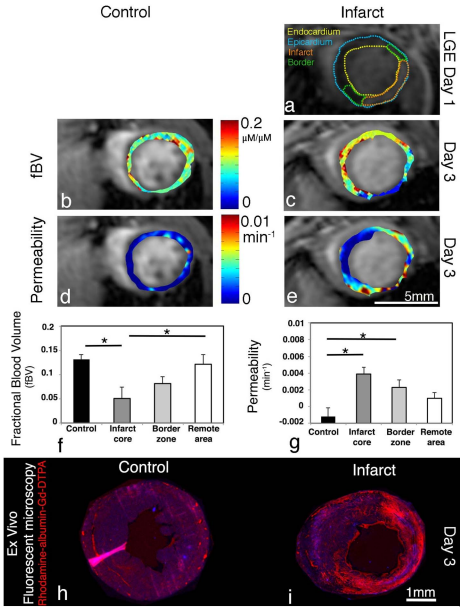

Fig. 1. (a) Late gadolinium-enhanced (LGE) images acquired 1 day after MI to define the regions of interest (ROIs) for analysis of DCE-MRI. Representative midventricular cardiac MR images in gray of the first postcontrast scan with in color parametric (b,c) fBV and (d,e) permeability maps of the myocardium. Values for fBV (f) and permeability (g) in different regions. (h,i) Ex vivo fluorescence microscopy of myocardium 30min after injection of albumin-based contrast agent.

Methods: C57BL/6 mice were imaged before (n=6) and 3 days (n=7) after a myocardial infarction (MI). Late gadolinium enhanced (LGE) MRI was performed one day after MI to verify similar infarct sizes using Gd-DTPA. LGE-MR images defined infarct core (hyper intense signal) and border zone (2mm area circumferentially away from the infarct core; Fig.1 a). Measurements were performed on a 9.4T Bruker using a 72-mm volume coil with a 4-channel phased-array coil (Bruker Biospin, Ettlingen Germany). Three-dimensional (3D) Intragate FLASH images of the entire heart with retrospective gating were acquired before and after intravenous injection of macromolecular albumin-Gd-DTPA (10mg/mouse in 200µl; Relaxivity r_1=130mM^{-1}s^{-1}; SyMO-Chem, Eindhoven, The Netherlands). After a series of precontrast 3D-FLASH images with increasing flip angle (2º, 5º, 8º, 11º, 13º) to determine the endogenous R_1, albumin-Gd-DTPA was injected through an indwelling tail vein catheter at a rate of 50µl/min. Consequently the dynamics of the contrast agent were imaged by 6 consecutive scans with flip angle = 13º (1,2). MRI parameters included: RFpulse of 1ms sinc pulse (10lobes, 20kHz); FOV 30x30x10mm; Matrix128x64x15 with zerofilling to 128x128x15; TE=1.784; TR=10; repetitions=22; and scantime=4min. For the navigator slice parameters included RFpulse=1.5ms; Gauss pulse (Bandwidth=1830kHz); slice thickness=3mm. Maps of fractional blood volume (fBV) and permeability surface area product (Permeability) were calculated in MATLAB (Mathworks, Natick, MA, USA) using a linear regression of the first 24min, after normalizing the concentration of contrast material in the selected ROIs (i.e., healthy (control) myocardium, remote myocardium, infarct core and border zone) by the concentration in the hepatic vein (2). Red fluorescent rhodamine covalently bound to the albumin-based contrast agent was used to validate the MR finding by ex vivo fluorescence microscopy.

Results: Three days post-MI fBV at the infarct core appeared significantly reduced compared to both healthy control mice and remote myocardium. In the border zone fBV values were reduced compared to healthy control tissue, but elevated compared to infarcted tissue (Fig. 1b,c,f). The permeability surface area product was significantly elevated in the infarct core and border zone compared to healthy control (Fig. 1d,e,g). Additionally these permeability findings were quantified and validated by ex vivo fluorescent microscopy. The myocardial percent area of red fluorescent rhodamine-albumin-Gd-DTPA was significantly elevated in the infarct core and border zone compared to healthy control and non-infarcted remote tissue (Fig.1h,i).

Discussion: The previously developed 3D cardiac R_1 mapping to monitor the accumulation of macromolecular contrast agents in a murine myocardial infarction (3) appeared robust enough to follow dynamics of albumin-Gd-DTPA with DCE-MRI and to measure 3D myocardial fBV and permeability. Measurements of reduced fBV in infarcted myocardium reflect the decreased (micro)vascular density in the infarct core. In healthy myocardial tissue, fBV values were comparable to previously published data (4).

Conclusion: This method enabled noninvasive 3D quantitative mapping of microvascular density and initial rate of extravasation of high-molecular-weight contrast materials in the distinct regions of infarcted myocardium with altered endothelial function and has the potential to longitudinally track endothelial dysfunction in models of myocardial healing.

References:

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