MOLECULAR MRI ALLOWS THE DETECTION OF ACTIVATED PLATELETS IN A NEW MOUSE MODEL OF CORONARY ARTERY THROMBOSIS

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Introduction:

The final event leading to myocardial infarction is adhesion and activation of platelets after rupture of an atherosclerotic plaque. Platelets then aggregate, culminating in thrombotic occlusion of the coronary artery. Imaging of imminent vessel occlusion may improve patient care. In this study we examined the feasibility of molecular MRI for the detection of coronary artery thrombosis in hearts from mice ex vivo.

Materials and Methods:

The left anterior descending coronary artery (LAD) was exposed by lateral thoracotomy and incubated with ferric chloride to induce non-occlusive thrombosis in intubated male C57Bl/6 mice. A single chain antibody targeting ligand-induced binding sites (LIBS) of activated glycoprotein IIb/IIIa or control antibody was conjugated to 1µm-sized microparticles of iron oxide (MPIOs), resulting in LIBS-MPIO or control-MPIO contrast agent, and injected intravenously. For MRI, hearts were fixed in 4% paraformaldehyde for at least 12 h, then perfused with 1.5 mM Gadolinium and placed in 100% FC84. All scans were perfomed with a 9.4 T MRI system (94/20 Bruker BioSpec, Bruker, Germany). A three dimensional high resolution gradient echo sequence (3D-FLASH) was adapted with the following parameters: T_R = 15.5 ms, T_E = 2.941 ms, 20° flip angle, field of view = 9.6mm × 7.7 mm × 7.7 mm, Matrix = 160 × 128 × 128, 64 averages and a total acquisition time of about 4.5 hours. The resolution of these images is 60 µm isotropic. The overall good image quality allowed for a robust identification of vessels, especially the LAD.

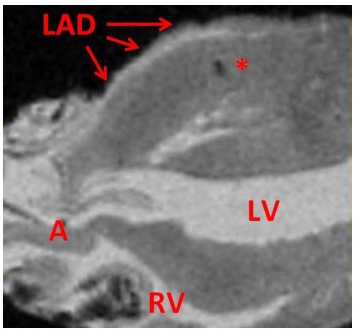

Figure 1: MRI revealed intact anatomy of fixed hearts (here with control MPIO) with left (LV) and right (RV) ventricular cavum, aortic valve (A) and left anterior descending artery (LAD) with hyperintense intraluminal contrast after perfusion with gadolinium. Sutures for fixation of the filter paper left intramyocardial defects (*).

Results:

Figure 1 shows an image of a heart with control-MPIO. Due to perfusion with Gadolinium the LAD appears as a hyperintense feature, which starts at the aortic valve and can be followed down to the apex. The region of interest is shown in Figure 2 again and directly compared to a heart with LIBS-MPIO, where the LAD can be identified as well, but comes along with significantly hypointense regions.

Discussion:

Severe hypointense regions along the LAD could only be detected in hearts from animals injected with LIBS-MPIO (in accordance with previous results in carotid artery thrombi and plaques in mice in vivo[1,2] and human plaques ex vivo[3]). Furthermore histological investigations confirmed both, the presence of a thrombus and the binding of MPIOs in the LAD region which was hypointense in MRI. This highly promising proof of principle suggests molecular MRI with LIBS-MPIOs allows the detection of coronary artery thrombosis in mice ex vivo. The translation to in vivo detection is the focus of our ongoing research. However, this is fairly challenging, given the desired resolution, an acceptable scan time and the movement of the heart.

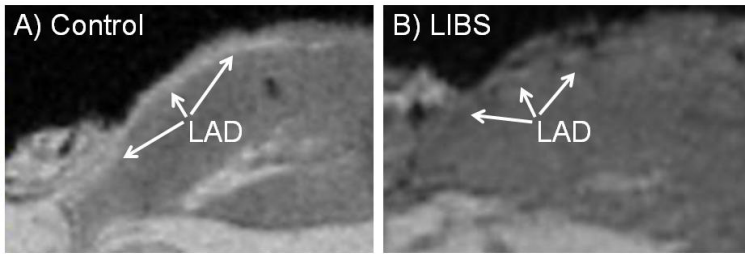

Figure 2: The proximal and medial part of the LAD after injection of control- (left) or LIBS-MPIOs (right) in hearts from different mice.

References:

(1) von zur Mühlen et al., Circulation. 2008 Jul 15;118(3):258-67.
(2) von Elverfeldt et al., Annual meeting of the ISMRM 2008 in Toronto, program # 477.
(3) Paul et al., Annual meeting of the ISMRM 2008 in Toronto, program # 3204.

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