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Detection of early inflammation in myocarditis by molecular magnetic resonance imaging of activated platelets

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Introduction: A noninvasive imaging strategy for diagnosis and localization of early myocarditis would be of great clinical interest. However, resolution of current imaging techniques is limited. Platelets play an important role in inflammatory processes but the role in myocarditis is unknown. Therefore, the aim of this project was to examine the role of platelets in myocarditis and establish a sensitive non-invasive molecular MRI in-vivo imaging strategy for diagnosis of myocarditis with a contrast agent against activated platelets in mice.

Methods: Myocarditis was induced by subcutaneous injection of an emulsion of porcine cardiac myosin and complete freud's adjuvant (CFA) in Balb/c mice. Inflammatory activity was targeted with a contrast agent against activated platelets consisting of microparticles of iron oxide (MPIO) conjugated to a single chain antibody directed against ligand-induced binding sites (LIBS) on activated glycoprotein IIb/IIIa (=LIBS-MPIO). In comparison, we applied an unspecific control antibody linked to microparticles of iron oxide (control-MPIO) and injected LIBS-MPIO to mice subjected to incomplete freud's adjuvant (iCFA). All imaging results were correlated to immunohistochemistry findings.

Results: Histological evaluation showed significantly higher binding of LIBS-MPIOs to platelet enriched, CD41-positive inflamed myocardium two days after induction of myocarditis in comparison to later time points (7d, 14d, 21d) ($p<0.05$) and control-MPIO ($p<0.05$) injection. In iCFA injected mice no significant LIBS-MPIO binding was found ($p<0.05$). In 3D in-vivo MRI we could specifically detect focal signal effects in LIBS-MPIO injected mice 2 days after induction of myocarditis, whereas in control-MPIO injected mice no signal effect was visible. Quantification of the myocardial MRI signal confirmed a signal decrease after LIBS-MPIO injection and significant fewer signals in comparison to control-MPIO injection ($p<0.05$).
As a perspective, we also found CD41 positive areas in histology of human myocarditis specimens.

Conclusions: Platelets are involved in the inflammation of myocarditis. Molecular MRI with LIBS-MPIO can image them at an early time point. This noninvasive imaging strategy is of clinical interest for both diagnostic and prognostic purposes, and highlights the potential of molecular MRI for characterization of cardiovascular pathologies such as myocardial inflammation.