High-resolution localization of fibrosis in a mouse model of viral chronic myocarditis using T2* weighted MRI

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Introduction: Myocarditis which is the major cause of heart failure and sudden death in young adults is most often induced by viruses, importantly by coxsackieviruses (CVB) belonging to the enteroviruses. The gold standard of the diagnosis relies on cardiac biopsies, an invasive procedure with limited sampling coverage on endomyocardium. Here we report a novel application of MR T2*WI on the murine model of coxsackievirus B3 (CVB3)-induced chronic myocarditis. Besides the potential value of characterizing the disease model in vivo, this new finding could be a novel technique for diagnosing chronic myocarditis in humans as well as some other fibrosis-related diseases.

Material and methods: Virus and animals: Four week-old mice from two mouse strains (SWR/J (H-2q), n=5, and A.BY/SnJ (H-2b), n=5) were infected with CVB3 for 8 weeks as described previously [1-2]. Non-infected animals (n=3 per strain) of both strains served as controls. MRI: Breath gated and ECG triggered multi-slice multiple spoiled gradient-echo short axis heart images were acquired on a Bruker Biospec 7T spectrometer, using a 870mT/m gradient system and a transmit/receive quadrature birdcage coil with inner diameter 3.5 cm. Typical MR parameters were: NSlices=7-11, matrix=256x170, FOV=3x2cm, SL.thick=0.5mm, TR=Heart period, FA=60-80°. Tacq=20min. Histology: 5-µm-thick tissue sections from paraffin-embedded hearts were cut and stained with Masson trichrome stain to assess myocardial injury, inflammation and fibrosis (blue areas).

Results: CVB3-infected mice from both strains show numerous hypointense regions within the myocardium (A) in T2* weighted images, while control animals (C) do not. All infected animals with large numbers of hypointense regions in MR show corresponding fibrosis patterns (D) in histology (ABY/SnJ). Animals with a mild chronic myocarditis and a weak fibrosis in histology (E, SWR/J mice) show moderate to very moderate dark spots (B) in T2* weighted images. Control animals (ABY/SnJ) show no fibrosis (F) and no abnormal hypointense regions in T2*WI images (C).

Discussion and conclusion: Using a T2* weighted FLASH sequence, numerous local foci of strong signal loss are observed in T2* weighted images of CVB3-infected mice with chronic myocarditis at moderate echo time values. Consistently, a close correlation of MRI findings with patterns of fibrosis was noted. This makes T2*WI a very sensitive tool to visualize noninvasively chronic myocardial damage and fibrosis in murine models. Nevertheless T2*WI use as a diagnostic tool must still be validated as image artifacts and vessels with black-blood render confident detection of dark spots in weakly infected animals challenging. The mechanism of the observed T2* contrast is not well understood yet. According to MR observations by Köhler et al (3), that the mesoscopic organization of muscle fibers in healthy myocardium is responsible for strong B0 inhomogeneities and T2* variations within the myocardium, we suggest that local pathological accumulations of connective tissue induces local susceptibility differences, responsible for strong local dephasing of magnetization, which in turn leads to dark spot formation in T2*WI. In conclusion T2*WI is a sensitive tool to detect myocardial lesions in murine virus-induced chronic myocarditis. T2*WI shows a negative contrast which correlates with fibrosis distribution within the myocardium. The contrast mechanism might be due to local static B0 field inhomogeneities induced by accumulated fibrotic tissue.

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