Hyperpolarised MRI of cardiac inflammation and repair

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Abstract

Background Myocardial infarction remains a major killer despite optimised reperfusion systems, highlighting a need for novel therapeutic approaches administered in the days after the event. Inflammation in healing myocardium is one such therapeutic target, though clinical exploration has been hampered by the absence of imaging biomarkers. We hypothesised that metabolic reprogramming in activated macrophages within healing myocardium could be detected by use of hyperpolarised [1-^{13}C]pyruvate MRI.

Methods Experimental myocardial infarction was induced in rodents before hyperpolarised [1-^{13}C]pyruvate MRI at days 3 or 7, using a 7T MRI scanner and a custom-designed ^{13}C imaging sequence. In-vitro [1-^{13}C]pyruvate spectroscopic experiments were performed with macrophage-like cell suspensions and an 11·7T magnet. The resulting [1-^{13}C]lactate signals from these cell and rodent models were compared with immune cell number (by flow cytometry), phenotype (ELISA), and cytokine gene expression (real-time PCR).

Findings Myocardial infarction caused intense [1-^{13}C]lactate signal in healing myocardial segments at both day 3 (maximum inflammatory macrophage phase) and day 7 (reparative phase), compared with sham operated controls. Macrophage depletion normalised the lactate signal at both day 3 and day 7. Mechanistically, polarisation of macrophage suspensions using lipopolysaccharide almost doubled hyperpolarised lactate label flux in vitro; blockade of glycolysis with 2-deoxyglucose normalised lactate flux and markedly inhibited production of key proinflammatory cytokines without cytotoxicity. Systemic 2-deoxyglucose after rodent myocardial infarction normalised hyperpolarised [1-^{13}C]lactate signal in healing myocardial segments and also improved myocardial inflammatory cytokine levels and remodelling.

Interpretation We show that high hyperpolarised [1-^{13}C]lactate signal in the days after myocardial infarction is caused by macrophage-driven inflammation, and reflects not just the number of inflammatory cells infiltrating the myocardium but also the inflammatory phenotype of those cells. Hyperpolarised MRI therefore provides a novel method for the detection of myocardial inflammation with high translational potential as both a biomarker and novel potential pharmacological target.

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Contributors

AL and DT conceptualised the study. JM was responsible for MRI sequence development, software, and data analysis. AL, JM, and CC carried out investigations. RC, DT, and SN were responsible for resources. AL drafted the abstract. OR, RC, SN, and DT reviewed and edited the abstract. OR, SN, and DT supervised the study.

Declaration of interests

DT's laboratory has received equipment support from GE Healthcare. We declare no other competing interests.