In vivo fluorine-19 MRI at 3 Tesla to visualize myocardial infarction inflammation in a porcine model

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Introduction

Myocardial infarction (MI) results in permanent left ventricle (LV) scarring that causes diminished pumping efficiency and undesirable myocardial remodeling, which may eventually lead to heart failure. Towards the repair or regeneration of myocardial contractility, there is increasing interest in reparative biological materials, such as cells and proteins, which are introduced into the infarct zone early after MI. Although direct LV injection (DLVI) of these biological materials into the LV wall presents a promising location for the delivery of biological materials, the utility of DLVI has been hampered by the lack of methods for accurate spatial targeting of affected tissue. Gd-enhanced MRI can show myocardial lesions, but displays non-specific contrast enhancement from a wide range of pathologies. Given that inflammation is a key early response to the ischemic insult, images of its spatial location represents a promising means to identify recently infarcted regions. With this information, one can potentially deliver therapeutic biological materials to the infarct boundary by DLVI with precision. In this study, we demonstrate the feasibility of using intravenously infused perfluorocarbon (PFC) emulsion and ^{19}F MRI detection to visualize myocardial macrophage burden in a porcine model of MI. PFC emulsion is taken up by macrophages *in vivo* which accumulate at sites of inflammation. The study was performed using a 3 Tesla clinical scanner and clinically relevant scan times.

Materials and methods

Animal model of MI: MI was induced in adult wild-type swine (35-45 kg) by positioning a coronary fluoroscopy-guiding catheter into the left main coronary artery ostium via right femoral artery. The balloon catheter was advanced into the circumflex artery and inflated for 30 minutes. Twelve hours after deflation, 0.5 liter PFC emulsion (VS-1000, Celsense, Inc., PA) was slowly administered over ~30 minutes via a peripheral vein.

***In vivo* ^{19}F MRI:** Two days after PFC injection, animals underwent ^{19}F/^{1}H MRI using a 3 T Siemens Tim Trio scanner. A custom-built ^{19}F/^{1}H surface coil (Stark Contrast, Inc., Germany) was placed on the torso for transmit and receive. The ^{19}F images of the heart were acquired using a conventional FLASH sequence in a total of 3.2 minutes scan time; the imaging parameters were TR/TE=500/6 ms, number of averages 12, FA=90°, slice thickness 4 mm, NS=20, FOV=34×34 cm^2, and matrix size 64×32. For anatomical reference, co-registered ^{1}H TrueFISP images were collected with parameters TR/TE=164/1.2 ms, NA=1, FA=55°, slice thickness 4 mm, slice spacing 5 mm, NS=20, FOV=24.4×34 cm^2, and matrix size 256×184.

***Ex vivo* ^{19}F MRI:** After the *in vivo* experiment, the animal was sacrificed and the heart was fixed for high-resolution *ex vivo* MRI. The fixed heart was placed in a Bruker 7 T horizontal bore scanner with a 72 mm bird-cage coil that could be tuned to either ^{19}F or ^{1}H. For ^{19}F imaging, a MSME sequence was used with parameters TR/TE=2000/10 ms, NA=16, slice thickness 2 mm, number of slices 49, FOV=8×8 cm^2, matrix size 256×128, and resolution 0.31×0.62 mm^2. Co-registered anatomical ^{1}H images were acquired using MSME with the same parameters as for ^{19}F, except NA=1. The ^{19}F/^{1}H data were rendered using Amira (VSG, MA) software.

Results

Fig. 1 shows representative ^{19}F/^{1}H MRI images of the swine heart. The ^{19}F signal (hot-iron scale) is visible in the apical-lateral region of the heart at the putative site of MI. Previously, it has been shown that ^{19}F emulsion droplets co-localize with the macrophages/monocytes (1-2). The *in vivo* SNR of ^{19}F images was ~18 at 3 Tesla with 3.2 minutes of scan time. High resolution *ex vivo* ^{19}F/^{1}H images acquired at 7 Tesla confirmed the macrophage infiltration mainly to the later wall of the LV (Fig. 1b). No obvious ^{19}F signal was observed in the remote zone.

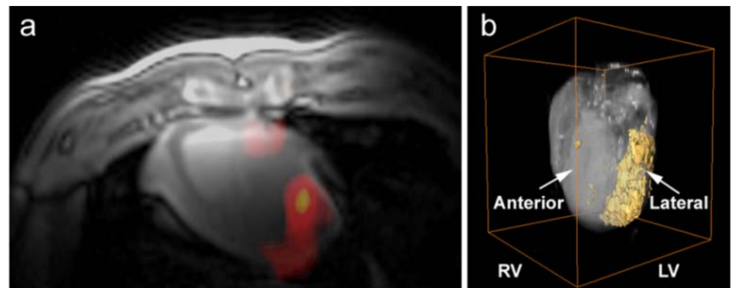

Fig 1. MRI images of myocardial inflammation in MI porcine model using PFC emulsion. (**a**) A composite *in vivo* ^{19}F/^{1}H scan shows the inflammation regions. The ^{19}F signal is shown in hot-iron scale. The ^{19}F image SNR was ~18. Panel (**b**) shows a 3D rendering of an *ex vivo* MRI scan at 7 T of the same heart after being fixed, where the ^{19}F is in pseudo-color and the ^{1}H is in grayscale.

Conclusions

In this study, we evaluated *in vivo* ^{19}F MRI methods in a clinical setting to localize inflammation loci induced by myocardial infarction. These methods were effective in displaying the infarcted region regions. Our results indicate that ^{19}F imaging on a clinical scanner is feasible to visualize recent MI. The use of the PFC agents have the advantage that the uptake is predominantly by macrophages, which is only present in recent infarcts, thus providing a well-defined signal of known biological origin that can be quantified against a null background. Image data of this nature will enable precise delivery of biological therapeutics by DLVI.

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References

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