MR Cell tracking in reperfused myocardial infarction with microvascular obstruction and haemorrhage: Fluorine-19 MR could be a better solution

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PURPOSE

Iron oxide nano-particles have been intensively investigated for tracking stem cell transplantation and visualizing inflammatory cell infiltration in vivo in myocardial infarction (MI) animal models and possess the hope for clinical translation [1]. However, accumulating evidences indicate that microvascular obstruction (MVO) is a common phenomenon in acute MI after reperfusion therapy [2]. The magnetic susceptibility effects caused by the degraded hemoglobin products in MVO could interfere the detection of transplanted or recruited cells labeled with iron oxide nano-particles [3]. We hypothesized that 19F cardiac MR could detect cells labeled with perfluorocarbon (PFC) emulsions in MVO/hemorrhagic MI. This was demonstrated on blood monocytes recruited to MI.

METHODS

Six reperfused MI rats (120' occlusion) were injected i.v. with 900µl of a 30% v/v PFC emulsion 1 day post-MI. Labeling efficiency was examined by flow cytometer on blood samples after injection (fluorescence labeled PFC emulsion). All MR measurements were performed on a 7T small animal scanner. In vivo 1H/19F MR data were acquired using a 1H/19F birdcage coil and ex vivo 1H/19F MR data using a surface coil. Ex vivo imaging was performed on isolated hearts in buffer before deep freezing for later histology and immunohistochemistry studies. 1H-T1WI (FLASH) and 1H-T2WI (multiple Spin Echo) data were both acquired in vivo and ex vivo. In vivo 19F TSE imaging was performed using the following parameters: spatial resolution (SR) = 1.25×1.25×2mm, Turbo Factor (TF) = 40, number of averages (NA) = 256. Ex vivo 19F TSE data were acquired with SR = 0.5×0.5×1mm, TF = 40, NA = 256. 19F images were overlaid on corresponding 1H images to define the origin of 19F signal. In vivo and ex vivo 1H-T2WI were used to appreciate myocardial edema and T2 shortening by paramagnetic components in haemorrhagic MI core. H&E, anti-ED1 and pearl Prussian blue staining were applied to validate myocardial integrity, macrophages and iron contents in MI cores, respectively.

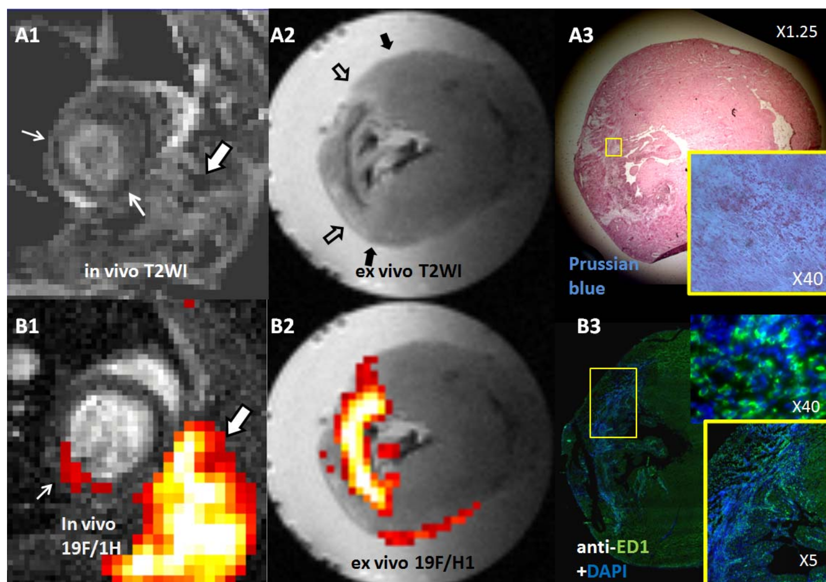

Figure 1: Monocyte/macrophage tracking in MI with MVO by 19F-CMR. Surrounded by slight hyper-intensity edematous myocardium, MVO shows hypo-intensity (**A1**) (between ➔) on in vivo T2WI. Ventricular blood appears hyper-intensity due to the slow flow. (⇨) indicates edema in operation wounds. Overlaid 19F (hot) /1H image (**B1**) detected 19F labeled monocytes/ macrophages recruited to MI (➔). (⇨) indicates inflammatory cells gathered in swollen operation wounds. Ex vivo T2WI (**A2**) revealed MVO in infarct core as a narrow dark zone (between ⇨) surrounded by hyper-intensity signal of myocardial edema (between ➔). 19F/1H overlay (**B2**) detected labeled blood monocytes /macrophages recruited to MI and Infiltrating MVO. Corresponding Prussian blue (**A3**) and anti-ED1(green) /DAPI(blue)(**B3**) staining validated the co-existence of excessive iron(light blue/brown) in the MVO region and recruited monocytes /macrophages.

RESULTS

Four of the six rats developed MVO as found by hypointensity zones in the infarct core on ex vivo T2WI (**A2**) and diffused fair blue/brown on Prussian blue staining (**A3**). In both in vivo (**B1**) and ex vivo (**B2**) 19H/1H MR, 19F signal was present in MI and MVO regions. Corresponding Prussian blue and anti-ED1 staining validated the co-existence of excessive iron (**A3**) and recruited monocytes/macrophages (**B3**) in MVO. In vivo T2WI (**A1**) either underestimated or failed to observe edema areas as estimated by ex vivo T2WI (**A2**) in these rats. 19F MR also depicted labeled cells in small infarcts without MVO in the other two rats. Flow cytometry revealed that blood CD11b/c+ cells (mainly monocytes/macrophages) were labeled by 19F.

DISCUSSION & CONCLUSION

We show for the first time in a rat model that 19F-MR can detect 19F labeled cells in MI with MVO. Cell tracking with iron oxide in MI with MVO could fail or be interfered using 1H-T2/T2*WI due to magnetic susceptibility effects caused by the degraded hemoglobin products in MVO. Thus, this study demonstrates that 19F cell labeling could be a better approach for MR cell tracking in MI with MVO and other scenarios with strong T2/T2* effect interference. It has been shown that these interferences also alter the 19F signal intensity [4, 5]. Thus, in order to achieve precise interpretation of the 19F signal in MI, further studies are needed to investigate the modulation of 19F signal by local magnetic susceptibility effects.

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