In Vivo Fluorine-19 MR angiography in a mouse model

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Introduction

Contemporary magnetic resonance angiography (MRA) is commonly performed using T_1-lowering gadolinium (Gd), time-of-flight (TOF) imaging, or phase contrast (PC) angiography. While Gd based MRA has been established as the gold standard for many applications, it may not easily be tolerated in patients with renal insufficiency. Unfortunately, the alternatives TOF and PC angiography are artifact-prone since the contrast is blood-flow dependent. Recently, highly sophisticated spin labeling techniques have been proposed [1,2]. However, spin labeling methods are also in-flow dependent, which may lead to additional image artifacts in regions of slow or turbulent flow such as stenoses and bifurcations. Therefore, an alternative flow-independent angiographic technique without Gd may be most valuable. To address this need, we propose MR imaging of a perfluorocarbon compound that, after intravenous injection, is only present in the lumen blood-pool. Perfluorocarbons such as perfluoro-15-crown-5-ether (CE) are excellent candidates for lumen imaging: they are chemically inert, have a long retention time when emulsified, are non-toxic and are in several phase 3 FDA trials [3], which also opens up the outlook for translation into the human setting. For these reasons, we have developed a ^{19}F MRI high-field MRA methodology using CE emulsions, have tested it *in vitro* and have, for the first time, explored its utility for ^{19}F angiography *in vivo*.

Materials and Methods

All experiments were performed on a Varian 9.4 T horizontal bore animal spectrometer in combination with a dedicated custom-built 18 mm diameter quadrature surface coil that is tunable to both ^{1}H and ^{19}F. The study was approved by the local animal ethics committee. Preparation of a 10% CE emulsion was carried out as previously described [4]. 0.5 ml of the emulsion were added to 1.4 ml human venous blood as well as to 1.4 ml saline (approximating arterial blood) to determine the T_1 and T_2 relaxation times of the CE with spatially unlocalized inversion recovery and spin echo sequences, respectively. Next, a dilution series (from 49 mM CE in the saline sample above in 5 steps to 198 µM) was created to determine the detection limit of the optimized sequence within 20 min of measurement time. ^{19}F images in this series were postprocessed with a 4-pixel disk filter and thresholding at 90% of the maximum signal intensity. In the *in vivo* part of the study, male balb/c mice (n=2, w≈29 g) were anesthetized and injected with 12 µl/g of the CE emulsion through the tail vein. The animals were positioned supine with the surface coil localized at the anterior abdomen. After acquisition of anatomic gradient echo (GRE) ^{1}H images (30x30x2 mm^2, 128x128, TE=2.9 ms, TR=50 ms, 8 slices, 16 averages), the coil was tuned to ^{19}F and GRE imaging at the same anatomical level was repeated (64x64, TE=2.7 ms, TR=40 ms, 512 averages, acquisition time = 21 min). In the aorta and in the heart chambers, the CNR was measured. The ^{19}F images were then postprocessed for better visualization with a 3-pixel Gaussian filter and a thresholding at 20% of the maximum signal.

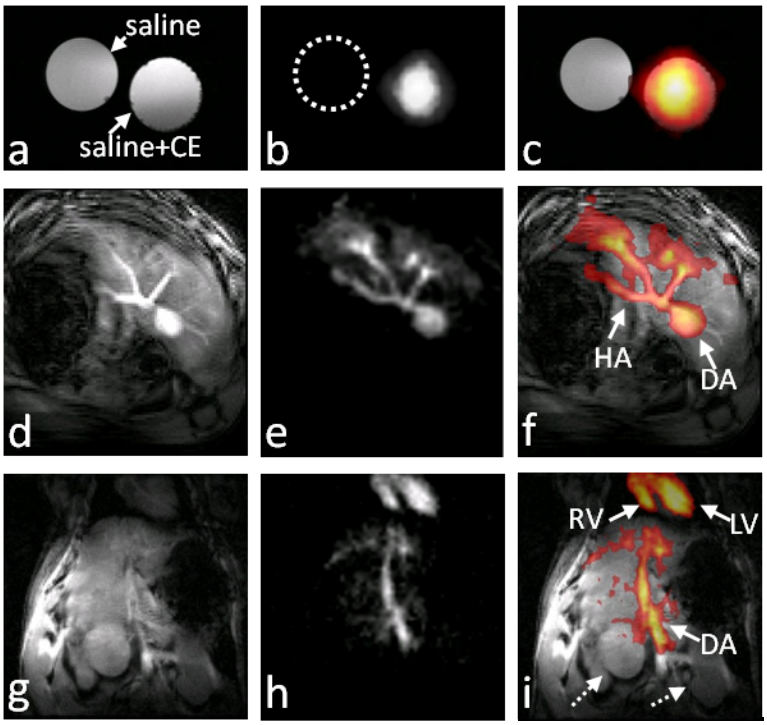

Figure 1. *Three series of 3 images, with ^{1}H reference images in the left column, ^{19}F images in the middle and the ^{19}F overlaid as hot iron on ^{1}H images in the right column.* ***a-c:*** *Demonstration of the detection limit of 390 µl in two Eppendorf tubes, with* ***b*** *showing the location of the tube without CE as a dashed circle.* ***d-f:*** *Axial slice at the level of the liver. In* ***e,*** *blood-vessels in the liver can exclusively be seen.* ***f:*** *HA=hepatic artery, DA=descending aorta.* ***g-i:*** *Coronal slice including the heart (LV=left ventricle, RV=right ventricle), the descending aorta (DA) and the kidneys (dashed arrows in* ***i****).*

Results and Discussion

In vitro, the ^{19}F T_1 relaxation time was very similar in saline and blood (1396±5 and 1351±8 ms), while the T_2 was drastically reduced by the presence of deoxyhemoglobin (440±25 to 25±2 ms). In the dilution series, the SNR was ranging from ~86 to ~1 and the CE detection limit within 20min of scanning time was 390 µM CE with an SNR of ~2 (Fig. 1a-c). This is well consistent with the predicted detection limit reported in the literature [4]. In the *in vivo* part of the study, the ^{19}F images clearly, selectively and exclusively visualized the blood-pool at different anatomical levels with high contrast (Fig. 1e,f,h,i). These ^{19}F images consistently co-registered with the corresponding anatomy on the proton images and do not only visualize the lumen of vascular structures but also the blood-pool in the left and the right ventricle. Considering a relatively long scanning time of 20 min, these findings are in agreement with the long expected intravascular retention time of ^{19}F CE in the blood-pool. The average CNR in the descending aorta and portal vein was ~15, while it was ~50 in the heart. In conclusion, intravenously administered ^{19}F is well-suited for a selective and exclusive visualization of the vasculature and the heart chambers *in vivo.* The high CNR and long intravascular containment makes ^{19}F MRI a promising alternative flow-independent angiographic MR technique. Since perfluoro-15-crown-5-ether is safe, a translation into the human setting may be possible. In addition, it has already successfully been demonstrated that CE ^{19}F can detect inflammation [4,5] *in vivo*. Therefore, it remains to be investigated whether the above-described methodology may be further exploited to simultaneously visualize ^{19}F plaque macrophage uptake in atherosclerosis.

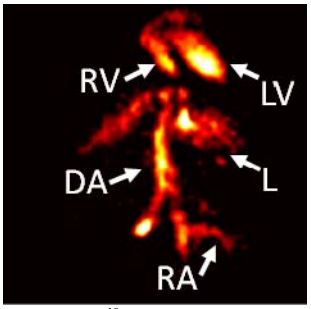

Figure 2. *^{19}F maximum-intensity projection (MIP) of several coronal slices, exclusively showing several anatomical structures: the right ventricle (RV), left ventricle (LV), descending aorta (DA), renal artery (RA) and liver (L).*

References

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