Radial Multi Gradient Echo DCE-MRI for 3D K^{trans} mapping with individual AIF measurement in mouse tumor models

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Purpose: Preclinical dynamic MRI on tumor models is typically performed with gradient- or spin-echo sequences and Cartesian k-space sampling which is not optimal for tumors experiencing respiratory motion (e.g. spontaneous tumors in transgenic mice). In these cases, radial k-space sampling, rather insensitive to motion, should be more appropriate. Quantitative methods to assess dynamically R_2*-corrected R_1 were previously described using a 2D (1) or 3D (2) radial multi gradient echo sequence. They were validated *in vitro* and *in vivo* in tumor bearing "freely breathing" anaesthetized mice. However, these techniques didn't allow measuring an individual arterial input function (AIF) and K^{trans} maps were calculated using separately measured mean AIF parameters. Simultaneous measurement of AIF and tumor DCE-MRI data remains a challenge, especially in mouse models. An approach with Cartesian k-space sampling for AIF assessment on the heart combined with 2D DCE-MRI on the tumor was described previously (3). The purpose of this work was to combine 2D and 3D radial acquisitions in an interleaved way to acquire simultaneously the AIF on the heart at high temporal resolution and 3D data on the tumor at a lower time resolution.

Materials and methods: The method was developed on a 4.7T small animal scanner (Biospec®, Bruker Biospin, Germany). A home-built quadrature birdcage coil was used (∅=40mm, length=70mm). 3D tumor acquisition was based on a previously described 3D radial multi gradient echo technique performed with a non selective excitation (3D RAD-MGE) (2). Parameters were TE_1=0.9ms, ΔTE=1.11ms, 10 echoes, bandwidth=100kHz, matrix=64^3, FOV=30^3mm^3, 64 readout points, 4096 projections, temporal resolution=2min, non selective excitation by a 50µs, 25 deg block pulse. Interleaved 2D acquisition on the heart was based on 2D RAD-MGE (1) (TE_1=1.9ms, ΔTE=1.11ms, 10 echoes, bandwidth=100kHz, matrix=64^2, FOV=30^2mm^2, slice thickness=2mm, 64 readouts points, 64 projections, temporal resolution=2.0s, selective excitation by a 1ms, 5 deg sinc3 pulse). 2D and 3D projections were alternated contributing either to the 2D heart image or to the 3D tumor data. Consequently, during acquisition of one 3D dataset for the tumor, 64 2D images of the heart were acquired. 300 dummy scans were applied prior to acquisition to achieve steady state. TR (defined as the delay between two 3D excitations) was 31ms. Prior to dynamic acquisition a pre-contrast 3D R_{10} map was acquired using the variable flip angle method (2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 50 and 70 deg). 3D data were processed using the SPGR signal equation corrected for R_2* effect as described before (2).

Pre-contrast and dynamic R_1 on the heart were both measured with interleaved 2D/3D excitations assuming that, in the presence of inflow effects, longitudinal steady state magnetization in the heart slice was mainly determined by the 3D non-selective excitations, and that the selective low angle readout pulse (5 deg) minimally disturbs the steady state. Consequently, pre-contrast 2D R_{10} in the heart was measured by varying the 3D non selective flip angle keeping the low angle readout pulse constant.

To provide proof of concept, male swiss nude mice (n=2) carrying a human colorectal tumor xenograft (TC302, Institut Curie, France) subcutaneously implanted at the abdominal level were imaged using this technique. For MRI examination, animals were anesthetized with isoflurane (AErrane®, Baxter France, France) and the body temperature was stabilized. For localization purposes a pre-contrast high resolution image was acquired with the same 3D FOV as in radial DCE-MRI covering the whole tumor (respiratory triggered multi-slice spin echo sequence: TR~1s, TE=10.7ms, matrix=128x128, slice thickness=0.47mm, 64 slices). The contrast agent (CA) Gd-DOTA (Dotarem®, Guerbet, France) was injected at a dose of 0.32mmol/kg (concentration 48mM, injection rate 600µL/min, injected volume 200µL). During DCE-MRI acquisition, 16 3D datasets (1024 2D datasets) were acquired continuously and simultaneously including one 3D pre-contrast image (64 2D pre contrast images).

After de-interlacing 2D and 3D data, images were reconstructed using a home-written (C++) standard regridding algorithm (4). Sliding window was performed for 3D data i.e. a new complete image was reconstructed each 1024 acquisitions, providing 61 3D images and a virtual temporal resolution of 30s. CA concentrations in voxels (tumor) or ROI (heart) were estimated from R_2* corrected $R_1(t)$ using relaxivity r_1=3.3s^{-1}mM^{-1} and Htc=0.47. AIF time constants were measured by fitting a biexponential decay to the concentration-time curve. K^{trans} values were assessed voxelwise using the Tofts-Kermode pharmacokinetic model (5) with either the individual AIF or, for comparison, with a same mean AIF determined in separate experiments (a_1=9.2kg.L^{-1}, a_2=4.2kg.L^{-1}, m_1=2.3min^{-1}, m_2=0.050min^{-1}) (3). Mean K^{trans} values and standard deviations were calculated over the whole tumor.

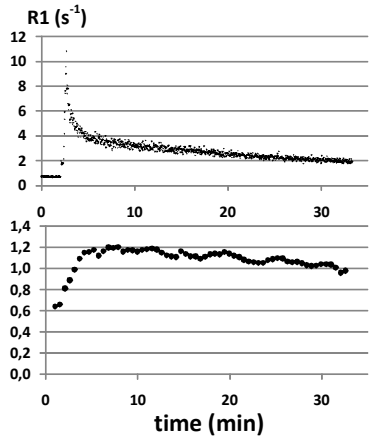

Fig 1: Simultaneously measured R_2*-corrected R_1 time courses for an AIF (top, time resolution: 2s) and in a tumor rim region (bottom, sliding window time resolution: 30s)

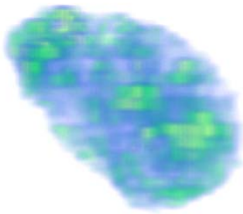

Fig 2: 3D K^{trans} map for an entire tumor (green colors: high K^{trans} values; blue colors: low K^{trans} values)

Results and discussion: R_1 time courses of an AIF and a tumor rim region are presented in figure 1. For the two mice, pre-contrast R_{10}^{heart} were (0.70±0.02)s^{-1} and (0.68±0.06)s^{-1} in good agreement with expected R_1 in blood. Peak ΔR_1^{heart} was about 10s^{-1} corresponding to [CA]=6.5mM. This value compares fairly well with a roughly estimated plasma concentration of 9mM assuming instant dissolution of the injected CA in the plasma volume. Fitted AIF values for the first mouse were a_1=8.1kg.L^{-1}, a_2=1.76kg.L^{-1}, m_1=5.1min^{-1} and m_2=0.030min^{-1} and for the second one 8.3kg.L^{-1}, 0.98kg.L^{-1}, 6.3min^{-1} and 0.013min^{-1}. These values were in accordance with the 2D Cartesian AIF measurements published before (3). A typical 3D K^{trans} map is depicted in figure 2. Mean K^{trans} values for the whole tumors were (0.021±0.020)min^{-1} and (0.019±0.018)min^{-1} with individual AIF, and (0.026±0.022)min^{-1} using the mean AIF for both mice. Mean v_e values were (0.16±0.12) and (0.14±0.12) with individual AIF, and were (0.27±0.18) and (0.31±0.21) with mean AIF. K^{trans} and v_e values were in the same order as in previous experiments. High standard deviations reflect tumor heterogeneity. For comparison, in a more homogeneous local tumor ROI, mean K^{trans} were (0.012±0.005)min^{-1} with individual AIF and (0.015±0.005)min^{-1} with mean AIF (25% variation), and in another ROI corresponding K^{trans} values were respectively (0.063±0.027)min^{-1} and (0.070±0.029)min^{-1} (10% variation). The non-constant AIF dependent variation of K^{trans} values in the tumor confirms the interest of individual AIF measurement.

Conclusion: In this study, we presented proof of concept for a new radial DCE-MRI technique allowing simultaneous measurements of an individual AIF in the mouse heart and $R_1(t)$ in the tumor yielding 3D K^{trans} and v_e maps. $R_1(t)$ are R_2* corrected which should optimize the use of high relaxivity CA at high magnetic field. Furthermore, as the technique doesn't require respiratory triggering, it should be most useful for characterization of microvasculature in motion animated orthotopic tumors spontaneously growing in clinically relevant transgenic mouse models.

References: (1) Vautier J. *et al* in Proc ISMRM 2008 3831; (2) Vautier J. *et al* in Proc ISMRM 2009 311; (3) Heilmann M. *et al* MAGMA (2007); 20:193-203; (4) Jackson J.I. *et al* IEEE Trans Med Imaging 1991, 10:473-8; (5) Tofts P.S.*et al* MRM 1991 17:357-367

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