Simultaneous Blood Volume and Vessel Size Imaging Technique for Localized Therapy Response Detection

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Introduction

MR imaging of the tumor microvasculature is a field of intense research. In the last few years, a broad range of MR techniques were devised to provide feedback about surrogate therapy response markers such as the tumor blood volume, perfusion, vessel permeability, oxygenation and vessel size [1-5]. These methods aim at the early detection of vascularization changes in response to therapy to guide patient management based on the individual response pattern. For this, it is essential to evaluate to what extent MR imaging techniques are capable of delineating the process of micro-vascular changes during therapy from other pathologic changes. In this work, we present an approach to accurate response analysis, including efficient data acquisition, precise relaxometry, dedicated statistical analysis that accounts for the tumor heterogeneity, and a comprehensive multi-parametric depiction of changes in blood volume and vessel size. Devised for the usage of (super-)paramagnetic blood pool agents and applied to the quasi-equilibrium distribution of the contrast agent after the first-bolus passage, it allows for the visualization of vascularization maps with high spatial resolution for local therapy response evaluation.

Methods

Imaging was done on a clinical 3T whole body system (Philips Achieva, The Netherlands) in nude mice with a human breast fibrosarcoma (HT1080) implanted in the thigh. To assess the sensitivity of the proposed technique to physiologic changes in response to therapy, the animals underwent repetitive imaging examinations (Day 0,4,7) during anti-vascular treatment with a multiple receptor tyrosine kinase inhibitor (Pfizer, SU11248, Day 0 and 3, 40mg/kg b.w.). Imaging included ADC, $\Delta R2$ and $\Delta R2^*$ quantification. ADC protocol: 2 slices à 2mm, $\Delta x = 0.7$mm, TR = 2s, b = 300, 600, 1000 mm^2s^{-1}, FOV = 50 x 50 mm. For the simultaneous acquisition of R2 and R2*-weighted data, a multi-spin echo (SE), multi-gradient echo (GE) sequence with FID sampling was used before and after intravenous injection of 80µmol/kg of a long-circulating iron-oxid blood pool agent (SH U 555 C, Bayer Schering Pharma). Protocol: 4 slices à 1mm, $\Delta x = 0.4$mm, FOV 50 x 50 mm^2, $\Delta TE_{GE} = 3.1$ ms, $\Delta TE_{SE} = 57$ms, TR = 1.2 s, 2 SEs, 15 GEs, 5 FID echoes. $\Delta R2$ and $\Delta R2^*$ were quantified by fitting adjunctive mono-exponential functions to the ratio of the multi-GE-multi-SE-trains acquired pre and post injection [6]. The vascular volume fraction (VVF) map was estimated $VVF = \Delta R2^* / \Delta R2^*_m \cdot VVF_m$. VVF_m is the fractional blood volume in muscle with 1.89% [7], and the $\Delta R2^*_m$ value was obtained from a ROI drawn in a muscle region. The ADC maps were co-registered to the high-resolution $\Delta R2(^*)$ maps for pixel-wise estimation of the mean vessel size (VS) according to the equation given in [4]. Potentially invalid values (VVF > 30%, VS > 200µm, or $\Delta R2(^*) \leq 0$) were masked out from the statistical analysis of regions of interest (ROI) in the tumor.

Results

Since $\Delta R2$ and $\Delta R2^*$ are estimated from the ratio of the multi-echo data acquired pre and post injection, B0 and B1 inhomogeneities as well as the influence of T1 changes can be expected to be of minor influence in the analysis [6]. The usage of validity masks prior to statistical analysis prevents distortion of the treatment results by invalid data. Fig. 1 depicts the results of a control and a treated animal. In response to treatment, the mean VS slightly increases, whereas it decreases in the control animal. However, these changes, as well as the observed changes of the VVF, which is an estimate for the relative blood volume, are not significant. Further, the ROI statistics do not differ significantly between the two animals, in spite of the obviously different evolution of tumor size and ADC value over time. But, more importantly, the VVF and VS maps indicate differences in how vascularization distributes over the tumor: in the control group, high vessel density is observed mainly in the rim of the tumor, whereas a centric increase in blood volume is detected in the treated group (D4), although the therapy success is not reflected by the tumor size at that time.

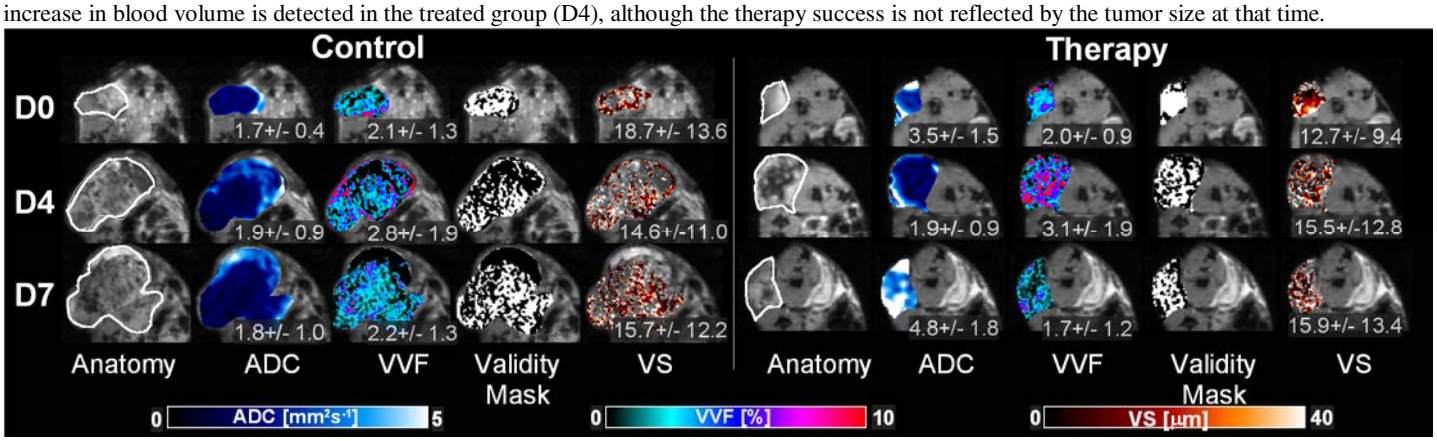

Figure 1. *Control animal (left), animal under anti-vascular therapy (right). The VVF and the mean VS were estimated from the same data, i.e. ΔR2 and ΔR2*maps obtained with a multi-spin-echo, multi-gradient-echo sequence. The values indicate the mean value +/- standard deviation in the region of interest. Statistical analysis was done after exclusion of invalid data (Validity Mask). See text for further details.*

Discussion/Conclusion

As indicated by the example, physiologic changes in response to treatment might be only poorly described by statistical ROI analysis. Instead, they manifest in how vascularization changes distribute over the tumor region, motivating the generation of vascularization maps with high spatial resolution in all three dimensions. This constrains the usage of dynamic first-pass techniques for blood volume measurements, especially in preclinical studies that require sub-millimeter sampling. We presented a new technique for time-efficient and accurate relaxometry that allows for comprehensive multi-parametric and localized insight into vascularization changes in therapy follow-up studies using blood-pool agents.

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