Quantification of proton exchange by histological verification of fractional blood volume determined by an intravascular T1 contrast agent at prostate tissue and prostate tumor

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Introduction

Blood volume is increasingly used as a parameter to characterize tumors. Typically, tumor vascularity and blood volume increase with malignancy. Blood pool contrast agents enable technically more easy and accurate quantification of blood volume than low molecular extravasating contrast agents. By using such an intravascular T1 contrast agent the fractional blood volume can be determined by subtraction of the precontrast images form the post contrast images. The proton exchange between blood and surrounding tissue might modify the signal from the intravascular contrast agent. Therefore, a verification study was performed to quantify blood volume in the same animals by MRI and histology. Blood volume was determined in an experimental prostate tumor model and normal prostate tissue in rats. The differences were used to determine the proton exchange between blood and tissue.

Material and Methods

The study was performed in 15 Copenhagen rats weighing 281 ± 39 g at the time of the MRI examinations. 0.1 ml of a suspension containing 1×10^6 cells of the G-Dunning tumor was inoculated into the ventral lobe of the prostate. Tumors of the G subline are characterized by slow growth, sensitivity to androgen, and little metastatic spread. The doubling rate of G-tumors is 4.0 ± 0.2 days in uncastrated rats [1].

Imaging was performed on a 1.5-T whole-body MR scanner (Magnetom Sonata, Siemens, Erlangen, Germany) using a high-resolution four-channel wrist array coil (MRI Devices Europe GmbH, Würzburg, Germany). The dynamic measurements was performed using an IR turboFLASH sequence with a slice thickness of 2 mm, an image sampling frequency of 1.6 images per second, and a total duration of 3 min. The further sequence parameters were: inversion time (TI) 320 ms, TE 2.51 ms, TR 6.10 ms, FOV 80 × 80 mm^2, matrix 128^2, α= 15°, and V 2.0 x 0.61 x 0.61 mm^3. Eighty seconds after the start of image acquisition, the contrast medium VSOP-C 184 with a hydrodynamic diameter of 7.0±0.15 nm (Ferropharm) was administered as a bolus of 0.03 mMol ferrum per kg. Directly after the dynamic measurement 7 ml blood were extracted from the caudal vena cava. After heparinization the contrast agent concentration was quantified by measuring the T1 relaxation rate with a relaxometer (Minispec mq40, Bruker). The contrast agent concentration measured by relaxometer served to calibrate the MR signal change using an experimentally determined signal-to-concentration function. The calibration factor was applied to the fractional blood volume map generated by substracting the precontrast images form the postcontrast images.

For histologic work-up, the prostate tissue was embedded in paraffin after zinc fixation and cut into 3 µm thick slices. The cuts were made following the slice orientation of the axial T2-weighted MR images. The histologic slices were deparaffinized and stained with hematoxylin & eosin (H&E). Vessel endothelium was stained with a glycohistochemical technique (Griffonia Bandeiraea simplicifolia Lektin (BSL I)). The fractional vessel volume was determined separately in tumor (ventral lobe) and prostate tissue (dorsal lobe) by semiautomatic segmentation of the vessel walls using a morphometry software (Lucia M, Nikon). Twenty lens coverages with 400-fold magnification were evaluated (0.37 mm^2). Histologic and MRI blood volume were correlated. The water exchange was determined according to the methods of Larsson et al. [2] by using the histologic data as an independent verification of the MRI measurements.

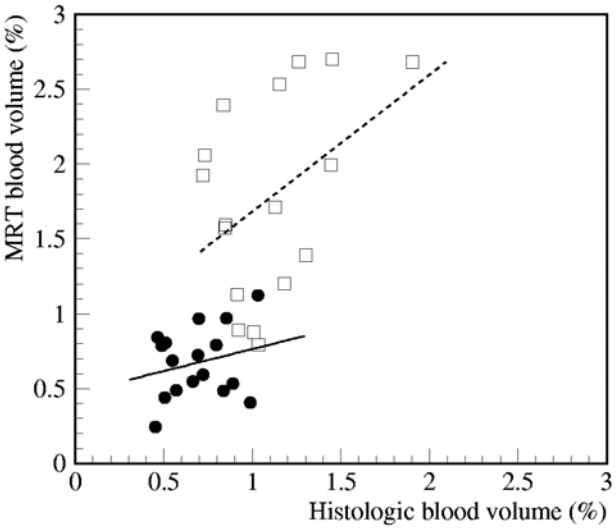

Fig.1: Correlation plot of fractional blood volumes measured by MRI and histology. The open squares represent the prostate tumor values and the filled circles the prostate tissue values. Both groups were fitted separately by using the linear regression.

Results

The correlation between histology and MRI in blood volume was not significant in both groups, tumor and prostate tissue. The mean fractional blood volume in prostate tissue was 0.69 % as determined by MRI and 0.68 % as determined by histology. The mean fractional prostate tumor blood volume was 1.71 % and 1.02 %, respectively. As a result, a much larger proton exchange was much larger in the prostate tumor blood as compared with the normal prostate tissue, 0.13 versus 14.5 s. Additionally, tumor vessels were found to have a significantly smaller mean cross section than normal prostate vessels, 35.38 µm versus 204.8 µm.

Conclusions

Whereas histology and MRI yield nearly identical blood volume values for normal prostate tissue, the tumor blood volume differs significantly. The tumor blood volume is overestimated by MRI. Proton exchange depends on the vessel diameter and decreases as the vessel diameter increases. Therefore, large differences in vessel diameter have an impact on the blood volume ratio between tumor and tissue. Simulations have to be performed to explain if the differences in proton exchange can be caused by differences in vessel cross section.

References

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