IMAGING OF ILLUMINATED TISSUE DURING THE PHOTODYNAMIC PROCESS BY PHOTOSENSITIZED BOLD MRI

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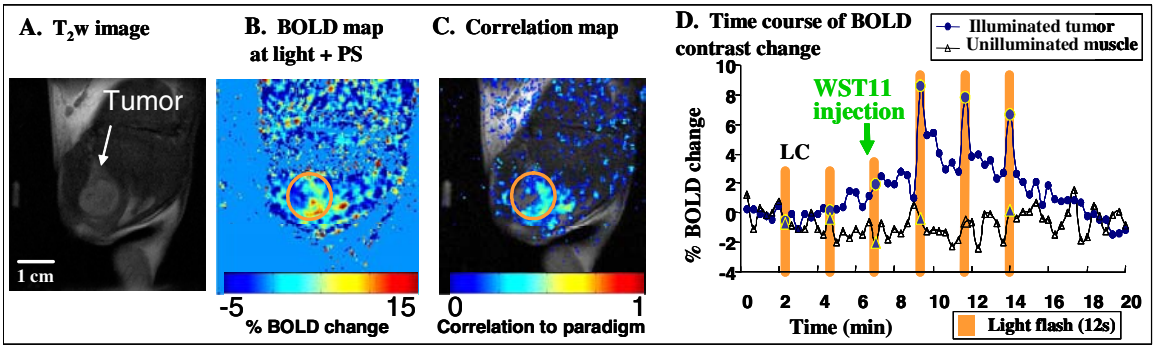
Introduction: The objective of this study was to test the light dependence of BOLD contrast changes during vascular targeting photodynamic therapy (VTP). VTP is an antivascular tumor treatment based on the in situ illumination of the i.v. injected photosensitizer (PS) (Pd-bacteriochlorophyll derivatives: WST09 or WST11). VTP induces photogeneration of Reactive Oxygen Species (ROS) in the blood which is coupled with photoconsumption of O_2 and local buildup of paramagnetic deoxyhemoglobin (DeoxyHb) that affects T_2* contrast. The consequent photodamage induces vascular stasis within minutes culminating in ischemic necrosis and tumor eradication (1, 2). We previously demonstrated that photogeneration of circulating DeoxyHb during VTP of tumors can be imaged online by BOLD contrast (as fMRI) (1, 3). Here, we hypothesized that temporally and spatially confined illumination shall coincidently change BOLD contrast and enable the mapping of the illuminated light zone.

Animals and tumor model: Fisher female rats were s.c. grafted to the flank with rat MADB106 carcinoma mammary cells, and tumors (~1 cm) were subjected to VTP. The rats were anesthetized [Ketamine 100 ml/kg /Diazepam 7.5mg/kg) and positioned supine/lateral above the tumor so as to minimize motion artifacts. **VTP protocol in the magnet:** The PS (WST11, 10mg/kg, Steba Biotech Israel) was i.v. injected via catheter. The tumor was immediately illuminated applying alternating cycles of 12s light and 142s dark generated by an inline laser-cut shutter (Ocean Optics, USA) electronically triggered by the "start" and "stop" commands of the scan. Illumination was conducted with a 1W diode laser (CeramOptec, Germany) emitting 100mW at 755 nm (illuminated area = 1 cm^2). **Online guidance of VTP by MRI:** DeoxyHb accumulation was monitored continuously by sequentially acquiring T_2*w images during the following experimental steps: (i) Pre-illumination (control) (ii) illumination (light control), (iii) PS i.v. injection to start VTP and (iv.) post illumination. Maps of % BOLD contrast change [(image/average of control - 1) x100] were extracted. MR images were acquired on a horizontal 4.7 T Bruker-Biospec spectrometer using a volume coil. Sequential coronal gradient echo sequence for BOLD images were acquired with : acquisition time 12s, TE/TR/α 10/100/30°, ns=1, in plane resolution 430 µm, slice thickness 1.5 mm, 128x128, FOV 5.5cm.

Results and Discussion: The T_2W anatomical image (Fig.1A) and the calculated BOLD contrast map (Fig 1B) are shown. The circle marks the illuminated area. In order to correlate between light and BOLD contrast during VTP, fractionated light:dark pulses (12:142s) were used as described above and consequent changes in BOLD contrast were analyzed. As can be seen, spikes in BOLD contrast intensity were observed, in temporal correlation with the incident light (4 rats, Fig.1D). Reversible BOLD contrast changes allowed mapping (Fig. 1C) of the corresponding illuminated region using the relevant illumination paradigm described above in the VTP protocol. No such changes were observed in the light control or in un-illuminated regions. The boundary of the illuminated region is somewhat larger than the light spot possibly due to tissue light scattering. The un-uniform distribution of the BOLD contrast in the illuminated zone may represent vascular heterogeneity and presence of necrotic regions in the tumor. The spike-like response of the BOLD contrast with 12s illumination pulses (Fig. 1D) indicates the reversible photochemical nature of this fMRI modality. It is anticipated that the short illumination protocol (12s x 4) used here does not induce significant vascular photodamage as blood flow continued after VTP protocol termination. This was confirmed by Gd-DTPA dynamic enhanced contrast imaging (not shown), whereas full treatment (10 min VTP) in the same model induced blood stasis (3). The gradual decline in the spike intensity with a $T_{1/2}$ of 53 ± 2s (n=2) may represent the clearance rate of WST11, corresponding with our previous report (4).

Conclusion: Here we show that BOLD-MRI is capable of mapping the illuminated tissue regions during VTP.



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