Electric Pulses Induced Changes in Tumor Blood Flow: Dynamic Contrast-Enhanced MRI Study

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Abstract: Dynamic contrast-enhanced MRI was used to identify and characterize reduction of blood flow in tumors treated with electric pulses. Specifically, tissue permeability surface area product PS and fractional blood volume BV were calculated on a pixel-by-pixel basis using MR data collected after administration of contrast agents: Gd-DTPA, gadomer-17 and polysylsine-Gd-DTPA. PS and BV values of untreated tumors were compared to those of treated tumors. On average, the values dropped, depending on the contrast agent used.

INTRODUCTION

Reduction in tumor blood flow can lead to an increase in hypoxia and extra-cellular acidification. Additionally, if blood flow is chronically impaired, a cascade of tumor cell death will occur due to lack of nutrients and accumulation of catabolite products [1]. Clinical use of agents or therapies that would affect only tumor vascular function (blood flow) is limited by systemic toxicity although, experimental studies have demonstrated that blood flow effects can improve therapeutic outcome. Recently, it has been shown that application of short intense direct electric current pulses induces changes in tumor blood flow [2]. To measure this change, an 86RbCl extraction technique was developed [3]. Briefly, 86RbCl tissue radioactivity was used to calculate relative blood flow as a proportion of cardiac output. The procedure is rather complicated therefore it would be desirable to replace it by a noninvasive one.

In this study, the potential for gadolinium-enhanced MR imaging in evaluating changes in tumor perfusion by calculating permeability surface area product PS and fractional blood volume BV on a pixel-by-pixel basis is presented. Because reported studies have demonstrated that prototypic macromolecular contrast agents specifically enhance tumor blood pool in contrast to Gd-DTPA, that readily diffuses across endothelium of normal and neoplastic microvessels, macromolecular agents gadomer-17 and polysylsine-Gd-DTPA were used to quantify the reduction. PS and BV values of untreated tumors were compared to those of treated tumors.

MATERIALS AND METHODS

In experiment, 30 A/J mice of both sexes, purchased from Rudjer Bošković Institute, Croatia, were used. Fibrosarcoma SA-1 (The Jackson Laboratory, Bar Harbor, ME) syngeneic to A/J mice was used as a tumor model. A mixture of Domitor® (Pfizer GmbH, Germany) 1.0 mg/kg body weight and Ketamin 10%® (Veyx-Pharma GmbH, Germany) 75.0 mg/kg body weight (bw) administrated i.p. was used for anesthesia. Electric pulses were delivered by two flat parallel electrodes 8 mm apart. Electrodes were placed percutaneously at the opposite margins of the tumor. Square wave high voltage direct current pulses (1040 V, pulse width 100 µs and repetition freq. 1 Hz) were applied. In total, 8 electric pulses were applied; each set oriented perpendicularly to the first set, with a time interval of 1 s. Treatment was performed 10 min prior to imaging without anesthesia and was well tolerated.

MRI was performed on a 2.35 T Bruker Biospec system. First, pre-contrast image was acquired: TR = 600 ms, TE = 18 ms, matrix 256 × 256, slice thickness 2 mm, field of view 7 cm and acquisition time 5 min. Then, contrast agent was administered, and a central data subset of the k-domain with dimensions 32 × 256 k-space data points was acquired repetitively for 100 min. Each such subset was acquired in 38 s, then completed with the data from the pre-contrast acquisition and reconstructed with 2D inverse Fourier transformation.

Clinically available Gd-DTPA (Magnevist®, Schering AG, Berlin, Germany) was used as a low-molecular-weight contrast agent, administered in a dose of 0.1 mmol Gd/kg bw. Gadomer-17 (Schering AG, Berlin, Germany) was used as an intermediate molecular size contrast agent (30 kDa) with complete renal elimination and plasma half-life in rats of 37.5 min. Gadomer-17 was administered in a dose of 0.025 mmol/kg bw. Polysylsine-Gd-DTPA (Schering AG, Berlin, Germany) was used as a representative macromolecular contrast agent (= 50 kDa) with plasma half-life in rats of 94 min. Polysylsine-Gd-DTPA was also administered in a dose of 0.025 mmol/kg bw. All three contrast agents were administered in a bolus via 23-gauge i.v. cannula (Vygon 247 Venoflux infusion set, France) inserted into a tail vein.

Using the method described in [4], BV and PS were calculated.

RESULTS AND DISCUSSION

Qualitative MRI data on Figure 1 show that untreated tumors enhanced heterogeneously with contrast agents.
used. Highly vascular rim enhanced more than partly vascular, partly necrotic tumor core. Prompt and marked enhancement of the highly vascularized tumor rim was achieved with polylysine-Gd-DTPA and somewhat less pronounced with gadomer-17 (Fig. 1). The enhancement increased gradually with both macromolecular agents, reflecting diffusion from blood into the interstitial space. Tumors treated with electric pulses showed no enhancement of the tumor within the first hour after the treatment, due to reduced blood flow (Fig. 1). Afterwards, enhancement started to increase since the reduction is reversible.

![Image 1](untreated-electric-pulses.png)

**Figure 1:** MR images of untreated (left) and treated tumors (right), enhanced with a) Gd-DTPA, b) gadomer-17 and c) polylysine-Gd-DTPA. Images are arranged in clusters. Each cluster contains 4 images presenting pre-contrast, 1 min, 20 min and 60 min post-contrast intensity.

Fig. 2 shows the time course of gadomer-17 and polylysine-Gd-DTPA accumulation in the untreated tumors and tumors treated with electric pulses. After the treatment, blood flow was reduced and with it also contrast agent accumulation.

![Image 2](representative-intensity-curves.png)

**Figure 2:** Representative intensity curves of gadomer-17 and polylysine-Gd-DTPA enhancement of tumors.

Fig. 3 shows BV and PS calculated values for untreated and treated tumors. In untreated tumors, high mean BV and PS values obtained with Gd-DTPA indicate rapid transendothelial equilibration. Approximately equal mean BV and PS values that were obtained with gadomer-17 and polylysine-Gd-DTPA, but lower compared to Gd-DTPA, indicate slow diffusion of both agents from blood into the interstitial space due to larger molecular size. Large molecular size aggravates passages through vascular endothelial compared to small Gd-DTPA, even though intercellular gaps are present due to malformation. Within the first hour after the treatment with electric pulses, on average BV and PS values dropped for more than 90 %, compared to those of untreated tumors. The reduction with electric pulses was maximal for several hours, thereafter slowly increasing.

![Image 3](BV-PS-values.png)

**Figure 3:** BV and PS values (1 untreated 2 treated tumors).

**CONCLUSIONS**

Dynamic contrast-enhanced MRI showed qualitatively that electric pulses cause the reduction of tumor blood flow, and quantitatively by means of BV and PS calculations. Dynamic contrast enhanced MRI showed also that this reduction is reversible. This approach could therefore be used for monitoring the time window and the extent of the tumor blood flow reduction.

**REFERENCES**


