Relative Blood Volume and Blood Hemodynamics Assessment By USPIO-Induced T1 Changes in MRI of Murine Colon Carcinoma

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Introduction

It is crucial to characterize the tumor vasculature and its response to blood hemodynamic modifiers, in order to assess and improve the effectiveness of current therapeutic treatments [1]. In this study, a method based on fast quantitative T_1 relaxation measurements was employed to assess relative blood volume in two types of murine colon carcinoma. The T_1 relaxation time was measured with the inversion recovery snapshot fast low angle shot (IR-FLASH) imaging sequence pre- and post- USPIO administration. Also, in order to assess the ability of this method to monitor hemodinamic changes, USPIO-induced T_1 changes were measured after administration of hydralazine - a central vasodilator which induces vasoconstriction in subcutaneous tumors by the steal effect mechanism [2]. Furthermore, in two separate groups of mice, the vascular characteristics of the two types of murine colon carcinoma were investigated by immunohistochemistry.

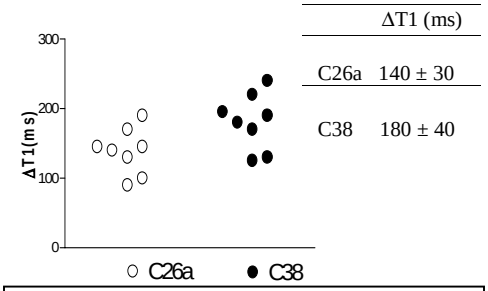

Figure 2. Column graph of the changes in T_1 relaxation times (ΔT1) following USPIO administration in C26a and C38 coloncarcinoma. In the legend, mean and standard deviation are reported. Changes in T1 relaxation times in C38 were significantly larger than in C26a (t-test, $p < 0.05$).

Materials and Methods

MRI experiments were performed on a SMIS 7T MR spectrometer using a 10-mm-diameter surface RF coil. IR FLASH imaging was performed on a slice through the center of subcutaneous C26a (n=8) and C38 (n=8) murine colon carcinoma before and after administration of an USPIO contrast agent (Sinerem, Guerbet, France). Imaging parameters were: TE= 2.7 ms,TR = 5 ms, matrix size of 64x64, FOV of 30 mm, slice thickness of 1.6 mm, inversion times TI = (52 + n*370) ms where n = 0,1,…15. For each tumor, one ROI which included the tumor core was considered. In 3 mice, i.p. injection of hydralazine was performed within 10 min after USPIO administration. Pixel-by-pixel T1 maps, pre- and post- USPIO, were generated from fitting the recovery curves. In two separate groups of mice (n = 6 for C38 and n = 5 for C26a), tumor vascularity was determined by immunohistochemistry, with a method described in [3]. In each tumor, the relative vascular area (RVA) was calculated.

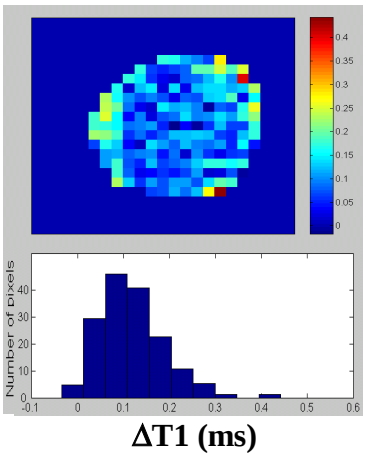

Figure 1. Decrease in T_1 relaxation time following USPIO administration. Pixel-by-pixel map (top) and histogram (bottom) of the ΔT_1 in a C26a murine colon carcinoma.

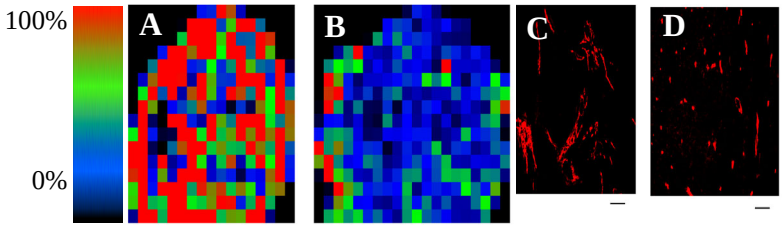

Figure 4. Map of RVA of a C38 (A) and C26a (B) tumor section. Each pixel represents a 0.23 x 0.23 mm ROI. Maps are scaled to 100% which corresponds to a value of RVA = 21%. In C and D a photomicrograph of a detail of the tumors in A and B, showing the typical vascular structure of C38 (C) and C26a (D) tumors. In C and D, Bar = 100 µm.

Results

USPIO administration resulted in a significant decrease in T_1 of all tumors. A relative blood volume map of the whole tumor is presented in Figure 1. After USPIO, the T_1 decrease in C38 tumors was significantly larger than in C26a tumors (N = 8, t-test, $p < 0.05$, Figure 2). The immunohistochemically determined RVA of C38 tumors was larger than the RVA of C26a tumors (0.059 ± 0.015 vs. 0.020 ± 0.011; $p = 0.0013$). This is illustrated in Figure 3, which shows an RVA map, as well as the vascular structure, of a typical C38 and C26a tumor. In the Table, T_1 relaxation times before and after USPIO and hydralazine administration in three murine colon carcinoma are shown.

Discussion and Conclusions

The decrease in the T_1 relaxation time following USPIO administration may be attributed to the exchange of water protons between the intra- and extravascular space and provides an index proportional to the tumor blood volume. One of the major advantages of fast quantitative T_1 measurements over quantitative T_2^*/T_2 is given by their higher temporal resolution (seconds in T_1 measurements versus minutes in T_2 measurements). The statistically significant difference between ΔT_1 in C26a and C38 coloncarcinoma indicates a difference in tumor vascular morphology, with the C38 tumor being characterized by an higher tumor blood volume. This is in agreement with the immunohistochemical data, which showed higher values of RVA in C38 tumors than in C26a tumors. With the present methodology, we can also assess changes in blood volume: after injection of USPIO, in fact, any change in blood volume is reflected in a T_1 change, that is, vasodilation or vasoconstriction would result in a decrease and increase of T_1, respectively. The increases in T_1 after hydralizine administration suggested a hydralizine-induced vasoconstriction in tumors, which is in line with the vasoconstriction effects measured in previuos studies [2]. The results of this study indicate that fast measurements of T_1 relaxation decays prior to and following USPIO administration offer a method to study the vascular morphology and physiology of tumors *in vivo*.

Tumor	T1 (sec) (Pre USPIO)	ΔT1 (%) (Post USPIO)	ΔT1 (%) (Post Hyd)
#1	2.15 ± 0.14	- 8.8 ± 3.5	+2.0 ± 2.0
#2	2.28 ± 0.08	- 8.4 ± 4.5	+3.1 ± 4.5
#3	2.18 ± 0.12	- 8.2 ± 3.8	+5.5 ± 3.2

Table 1. T_1 relaxation times before and after USPIO and hydralazine administration in three murine colon carcinoma.

References

[1] Kaanders JH et al., Lancet Oncol 2002;3:728-737. **[2]** Jirtle RL. Int J Hyperthermia 1988;4: 355-371. **[3]** Bussink J et al. Br J Cancer 1998;77: 57-64.