Captopril and S-nitrosocaptopril as potent radiosensitizers: Comparative MR study and underlying mechanisms.

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Purpose:

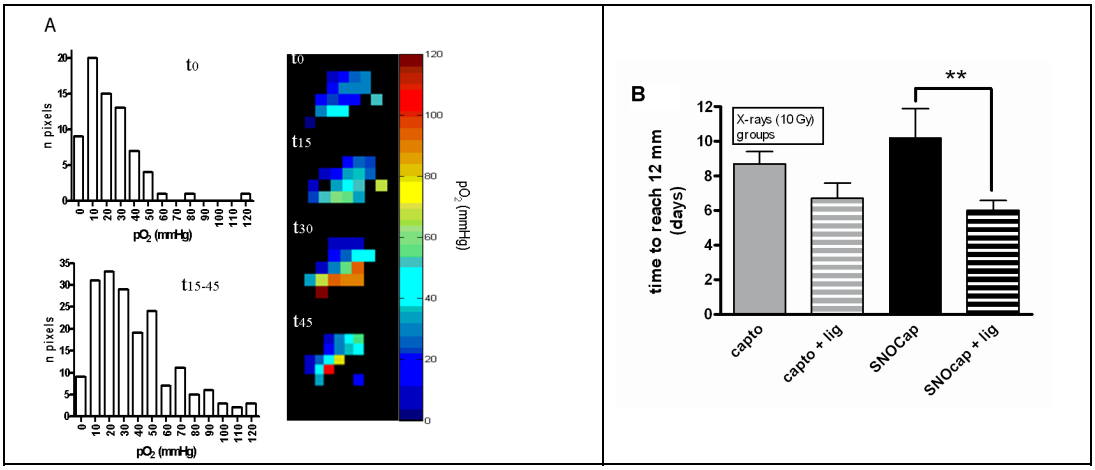
Hypoxia and blood flow heterogeneities are major obstacles for therapy of solid tumors. Many 'provascular' agents have been considered for transiently increasing tumor oxygenation or open the vascular bed in order to sensitize tumors to radiation or chemotherapy. In this context, NO-mediated treatments have been characterized with success as radiosensitizers[1]. In this study, S-nitrosocaptopril, a converting enzyme inhibitor with vasodilatory properties combined to a nitric oxide donor was studied for its effects on tumor hemodynamics using 19F-MRI and EPR oximetry, and compared with captopril.

Material:

TLT (transplantable tumor model) bearing mice were injected IP with either captopril (0.046 mmol/kg in saline), S-nitrosocaptopril (0.046 mmol/kg in ethanol/saline (1/9)), or vehicles. Local pO_2 was estimated using EPR (electron paramagnetic resonance) oximetry[2], and ^{19}F-MRI pO_2 maps were generated in order to probe the heterogeneity of response after intratumoral injection of HFB[3]. Changes in blood flow were probed by patent blue staining and the rate of oxygen consumption was measured using high frequency EPR[2]. Finally, the therapeutic relevance was evaluated by measuring regrowth delays after a single radiation dose of 10Gy of X-rays.

Results:

S-nitrosocaptopril significantly modified tumor pO_2 from 30 to 60 minutes post injection as showed by EPR oximetry, contrarily to captopril. The effect of S-nitrosocaptopril was confirmed by 19F-MRI mapping and the resulting histograms (Fig;A). Both treatments were able to significantly increase tumor blood flow to the same extent as shown by patent blue staining. A significant decrease in oxygen consumption by tumor cells (factor of 1.4) after S-nitrosocaptopril injection was observed using EPR, but not with captopril alone. Consequently, the administration of S-nitrosocaptopril contributed to the increase in efficacy of radiation therapy with 10Gy of X-rays, an effect that was not observed with captopril alone. In addition, the sensitization effect was abolished in clamped tumors, which demonstrates that the oxygen effect is involved in the radiosensitizing process (Fig.B).



Conclusions:

We identified a time window during which tumor oxygenation was improved, as a result of a combined effect on tumor blood flow and oxygen consumption rate, contrarily to captopril alone. Since both captopril and its S-nitrosylated derivative are able to increase tumor blood flow, this latter is not responsible for the superior effect of S- nitrosocaptopril on tumor oxygenation. Mechanistically, this pO_2 effect is shown to be the results of a profound change in tumor oxygen consumption by tumor cells, probably due to the NO-donor moiety of the compound. MR oximetry techniques (EPR and ^{19}F relaxometry) may therefore help in defining the time window for the irradiation after S-nitrosocaptopril administration.

References:

(1) Int J Cancer. 2004;109:768-73.
(2) NMR Biomed 2004;17:240-62.
(3) Magn Reson Med. 2009;61:634-8.