NONINVASIVE MONITORING OF TUMOR OXYGENATION RESPONSE TO ANTI-HYPOXIA DRUG USING NEAR-INFRARED SPECTROSCOPY

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Tumor hypoxia is a characteristic feature of solid tumors, which will lead to enhanced tumor metastasis and resistance to radiation therapy. Many strategies have been proposed to increase the overall functional oxygenation and radiosensitivity of hypoxic tumors, by delivering more oxygen to the hypoxic tumor or reducing the oxygen consumption within the tumor by using anti-hypoxia agents. Preliminary data indicated that FDA approved drug papaverine could effectively reduce the mitochondrial oxygen consumption rate of human lung tumor cells (A549) *in vitro* and thus can reduce hypoxia-induced radiation resistance. However, the real-time tumor oxygenation response to papaverine *in vivo* remains to be characterized, and the optimal temporal window for delivery of radiation after anti-hypoxia therapy requires to be determined. Optical spectroscopy, particularly frequency-domain near-infrared spectroscopy (FD-NIRS), provides a new noninvasive approach for continuously monitoring tumor hypoxia *in vivo*.

In this study, we have developed a side-firing fiber optic surface sensor and an FD-NIRS instrument with four laser wavelengths for quantifying tumor oxygenation in response to papaverine in human tumor xenograft models. Nude mice bearing subcutaneous A549 xenografts on the flank were used for tumor hypoxia study. Heathy nude mice without tumors were assigned as a control. The side-firing surface sensor was attached to the skin above the tumor or the muscle tissue on the flank of the animals. All animals were administrated with a constant flow of compressed air mixed with isoflurane throughout the experiments. 30-minute baseline measurement prior to injection, followed by 120-minute continuous measurement after injection were conducted for each animal. Intravenous tail injection of papaverine at 2 mg/kg or the same volume of 0.9% saline solution was applied to the animals. Typical results are presented in Fig. 1. The baseline measurement became stable with a small fluctuation of ±2% in ~15 minutes when the animals became fully anesthetized and breathed regularly. The slightly increase in tissue oxygenation (SO2) prior to injection was mainly due to injection preparing procedures like tail heating and injecting attempts. Significant increase in SO2 was observed for A549 tumors in response to papaverine (from ~48% to~57%). SO2 reached the highest reading within 20 minutes after papaverine injection and remained at the highest for 30 minutes. In comparison, the difference in SO2 between the post papaverine injection and the baseline readings for muscle tissue was small. Similarly, the change in SO2 after saline injection for tumor-bearing mice was not obvious.

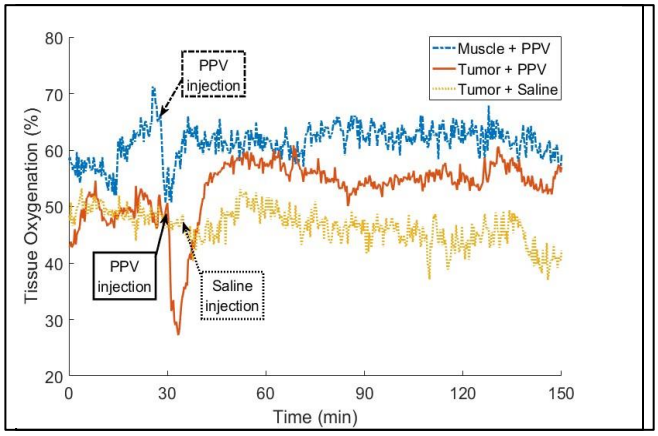

Figure 1 – Typical tissue oxygenation change of A549 tumor and normal muscle tissue in response to papaverine (PPV) and saline

An immediate drop right after papaverine injection was also recorded, which was likely due to the acute pain caused by the drug injection. In conclusion, according to our study, the FD-NIRS instrument with a side-firing fiber optic sensor can noninvasively and continuously quantify tumor oxygenation during anti-hypoxia treatment, and thus provide an effective feedback on the effectiveness of the drug and the optimal temporal window for delivery of irradiation.