Transient decrease in tumor pO_2 by ^{13}C-pyruvate injection

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Abstract

MRI using hyperpolarized ^{13}C-labeled pyruvate is a promising tool to biochemically profile tumors and monitor their response to therapy [1,2]. In this technique hyperpolarized [1-^{13}C]pyruvate is injected into tumor-bearing animals and monitors its metabolism. However, influences of exogenously injected pyruvate on tumor physiology are not well understood. In this study we elucidate that the pyruvate injection affects tumor oxygen status by using electron paramagnetic resonance imaging (EPRI) with triarylmethyl radical as a tracer [3].

Squamous cell carcinoma (SCC) cells (5×10^5 cells) were implanted s.c. into a right hind leg of female C3H Hen MTV mice. Partial pressure of oxygen (pO_2) in the SCC tumors was measured by EPRI after 9 days from the tumor implantation. EPRI measurements were performed with a 300 MHz pulsed EPRI system, and MRI anatomical images were acquired with a 7 T scanner controlled with ParaVision 3.0.2 (Bruker Bio-Spin MRI GmbH).

Figure 1A shows anatomy and pO_2 maps of a SCC tumor bearing mouse measured before and 30 min after 1.15 mmol/kg body weight of [1-^{13}C]pyruvate injection. A significant decrease in the tumor pO_2 level was observed 30 min after the [1-^{13}C]pyruvate injection. The median pO_2 in the tumor significantly decreased and the hypoxic fraction significantly increased 30 min after the pyruvate injection compared with that before the injection. The decrease in the tumor pO_2 is transient, and the pO_2 level recovered to the pre-injection level 5 h after the [1-^{13}C]pyruvate injection (Figure 1B). Immunohistochemical analysis using hypoxic marker pimonidazole independently verified that the SCC tumor transiently became more hypoxic by pyruvate injection. This transient decrease of pO_2 in the SCC tumor influenced the growth suppression by X-irradiation. The tumor growth was suppressed for 6–7 days by the 12 Gy X-irradiation. However, the suppression of the tumor growth was reduced to 3–4 days when pyruvate was injected to mice 30 min before X-irradiation. When the hyperpolarized [1-^{13}C]pyruvate technique is applied clinically, it is important to take account the transient decrease in tumor pO_2 by the pyruvate injection, because tumor oxygen status is an important factor in determining outcomes of therapies.

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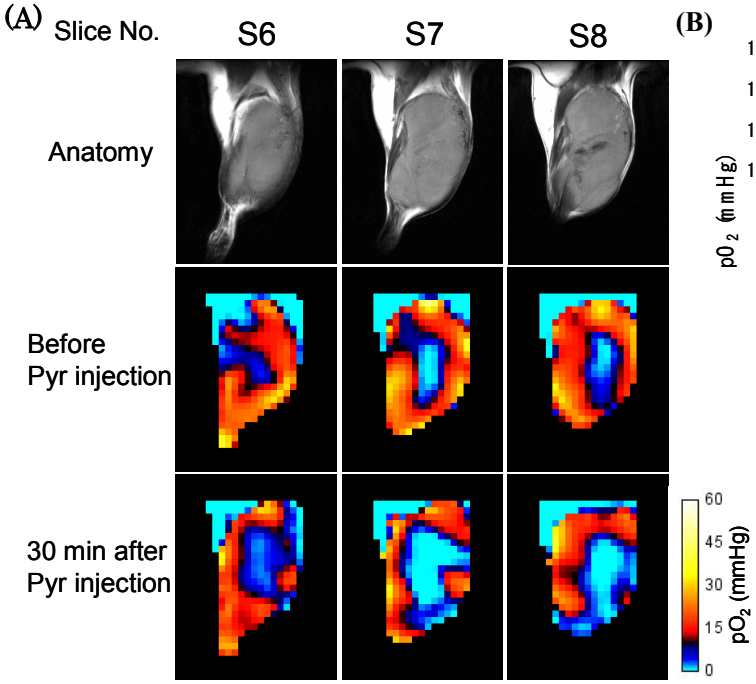

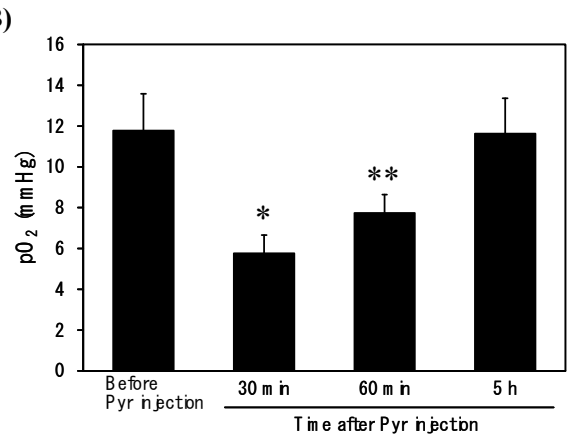

Figure 1 (A) Anatomy and pO_2 maps before and 30 min after the [1-^{13}C]pyruvate injection. (B) Changes in median pO_2 in tumor region by the [1-^{13}C]pyruvate injection. * $p<0.01$, ** $p<0.05$ compared with before pyruvate injection.