Effect of Anesthesia on Tumor Vascular Permeability Measurements by DCE-MRI

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Introduction: It is customary to restrain animals with anesthesia in preclinical MRI studies to minimize motion artifacts due to the relative long image acquisition time. This is especially important when dynamic contrast-enhanced (DCE)-MRI is used to characterize tumor vasculature, following the pharmacokinetics of the injected contrast agent over an extended period. However, choice of anesthesia for animals in DCE-MRI is often only based on the consideration of safety, effectiveness, and conveniences despite the vasoactive nature of some anesthetics[1,2]. This report compared the DCE-MRI studies of tumor vasculature with a macromolecular contrast agent, albumin-(DTPA-Gd), performed on mice anesthetized by isoflurane alone, and a combination of ketamine/acepromazine induction and isoflurane maintenance.

Material and Methods: Female SCID mice bearing MCF-7 human breast tumor xenografts at the sizes of 100 – 200 mm^3 were used for this report. In preparation for DCE-MRI studies, mouse tail vein was cannulated with a 25G needle after the induction of anesthesia. Mice were divided into two groups. Anesthesia was induced by an intraperitoneal injection of a ketamine (25 mg/kg), acepromazine (2.5 mg/kg), and 0.9% sodium chloride solution (1:1:2 by volume), and maintained with 2% isoflurane delivered through a vaporizer by oxygen into a nosepiece at 70 ml/min in group 1. Anesthesia was induced by 4% isoflurane and maintained by 2% isoflurane delivered by oxygen through a vaporizer into a nosepiece at 70 ml/min in group 2. MR studies of the tumors were performed on a 9.4T Bruker Biospec spectrometer with a home built surface coil. Dynamic magnetic resonance contrast images of the tumor were acquired before and after the injection of albumin-(DTPA-Gd) at 0.1 mmol gadolinium/kg with a strong T1-weighted 3D saturation recovery gradient echo sequence (20 ms recovery delay, 1.5 ms echo time, 90° flip angle, and 27 ms repetition time, FOV 12x12x10mm, matrix 128x64x50, number of average 6, acquisition time about 6 minutes). Post contrast images were acquired 1 minute after the injection of albumin-(DTPA-Gd) and repeated every 7 minutes from 1 to 29 minutes. Mouse body temperature was maintained with a 37°C water pad placed under the coil during MRI studies.

Results and Discussions:

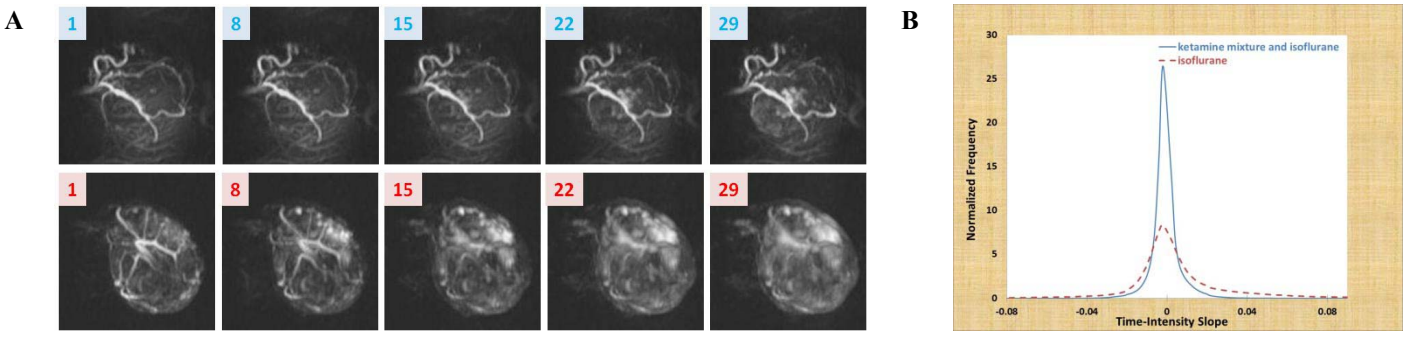

Figure A. Time series maximum intensity projection of 3D T1 weighted albumin-(DTPA-Gd) enhanced tumor images from mice received the ketamine mixture and isoflurane (top images), and isoflurane only (bottom images). Timing (minutes) after the injection of the contrast is shown on each image. **Figure B.** Normalized histogram of post contrast intensity-time slope of two representative mice received the ketamine mixture and isoflurane (blue), and isoflurane (red) only.

Figure A shows that contrast enhancement was mostly confined within the blood vessels and little change in the enhancement pattern was observed when anesthesia was induced with ketamine/acepromazine mixture and maintained with isoflurane over the entire DCE-MRI time period of 29 minutes. However, contrast enhancement had spread from the blood vessels into other regions of tumor tissues more readily in the mouse anesthetized with isoflurane alone. Permeability was further analyzed through a voxel-by-voxel linear fit of the post contrast intensity-time curves. Normalized histogram analysis showed magnitude difference in both positive and negative intensity-time slopes from each anesthesia groups, **Figure B.** A negative intensity-time slope corresponds to a loss of enhancement while a positive one corresponds to a gaining over the tracking period. As such, a high positive intensity-time slope corresponds to a fast wash out of the contrast from neighboring vasculature into tumor tissues and hence high microvascular permeability. The mouse received ketamine/acepromazine and isoflurane combination had more voxels (> 25%) at near zero intensity-time slope compared to the mouse received isoflurane only (< 10%), **Figure B**. Overall, mice received ketamine/acepromazine and isoflurane displayed both smaller negative and positive intensity-time slope that is consistent with a slower spreading of the contrast and lower vascular permeability. Our experimental observation of different permeability is consistent with the report that katamine is a vasoconstrictor[1] while isoflurane is a vasodilator[2].

Conclusions: Anesthesia changes tumor vascular permeability measured by DCE-MRI, implying that we need to pay special consideration to anesthesia methods when comparing preclinical DCE-MRI results.

References: 1. Ikeda, T. *et al.* Induction of anesthesia with ketamine reduces the magnitude of redistribution hypothermia. *Anesthesia and analgesia* 93, 934-938 (2001). 2 Schwinn, D. A., McIntyre, R. W. & Reves, J. G. Isoflurane-induced vasodilation: role of the alpha-adrenergic nervous system. *Anesthesia and analgesia* 71, 451-459 (1990).