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● *Original Contribution*

THE EFFECTS OF OXYGEN ON ULTRASOUND-INDUCED BLOOD–BRAIN BARRIER DISRUPTION IN MICE

Nathan McDannold, Yongzhi Zhang, and Natalia Vykhodtseva
Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

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Abstract—Numerous researchers are investigating the use of microbubble-enhanced ultrasound to disrupt the blood–brain barrier (BBB) and deliver drugs to the brain. This study investigated the impact of using oxygen as a carrier gas for anesthesia on microbubble activity and BBB disruption. Targets in mice were sonicated in combination with administration of Optison microbubbles (100 μL/kg) under isoflurane anesthesia with either oxygen or medical air. A 690-kHz focused ultrasound transducer applied 10-ms bursts at peak pressure amplitudes of 0.46–0.54 MPa ($n = 2$) or 0.34–0.36 MPa ($n = 5$). After sonication of two locations in one hemisphere, the carrier gas for the anesthesia was changed and the sonications were repeated in the contralateral hemisphere. The BBB disruption, measured *via* contrast-enhanced magnetic resonance imaging, was significantly greater ($p < 0.001$) with medical air than with oxygen. Harmonic emissions were also greater with air ($p < 0.001$), while the decay rate of the harmonic emissions was 1.5 times faster with oxygen. A good correlation (R^2, 0.46) was observed between the harmonic emissions strength and magnetic resonance imaging signal enhancement. At 0.46–0.54 MPa, both the occurrence and strength of wideband emissions were greater with medical air. However, at lower peak pressure amplitudes of 0.34–0.36 MPa, the strength and probability for wideband emissions were higher with oxygen. Little or no effects were observed in histology at 0.34–0.36 MPa. These findings show that use of oxygen as a carrier gas can result in a substantial diminution of BBB disruption. These results should be taken into account when comparing studies from different researchers and in translating this method to humans. (E-mail: njm@bwh.harvard.edu) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Ultrasound, Brain, Blood–brain barrier, Drug delivery, Oxygen, Anesthesia.**

INTRODUCTION

The combination of ultrasound and intravenously administered microbubble ultrasound contrast agents to disrupt the blood–brain barrier (BBB) is being investigated by numerous groups as a means to enable and target the delivery of drugs to the central nervous system (Burgess et al. 2015; Hynynen et al. 2001). As the BBB is a significant impediment to the use of most drugs in the brain (Abbott and Romero 1996; Pardridge 2010), this method holds great promise for the treatment of brain tumors and other central nervous system disorders.

Previously, our laboratory reported that the amount of a tracer extravasated into the brain after BBB disruption was significantly higher in animals anesthetized with intra-peritoneal injections of ketamine and xylazine compared to animals anesthetized with isoflurane and oxygen (McDannold et al. 2011). We posited that different vascular effects induced by these two protocols may have had an impact on the interactions among the ultrasound field, the microbubbles and the brain microvasculature. Around the same time, two studies reported that the circulation time for ultrasound contrast agents was substantially reduced when patients were breathing oxygen compared to medical air (Itani and Mattrey 2012; Mullin et al. 2011), which could also explain our results.

The purpose of this study was to test whether the use of oxygen as the carrier gas for isoflurane anesthesia was the reason for the reduced disruption observed in our earlier study. In experiments in mice, locations were sonicated in one hemisphere and then repeated in the contralateral hemisphere after switching between oxygen and medical air. We also recorded the acoustic emissions to determine whether they paralleled any differences resulting from the breathing of these different gases and to see if the amount of a tracer delivered to the brain was reflected by the magnitude of harmonic emissions, as has been observed previously (Arvanitis et al. 2012; Sun et al. 2015). Finally, we investigated whether

Address correspondence to: Nathan McDannold, 75 Francis Street, Boston, MA 02115, USA. E-mail: njm@bwh.harvard.edu

wideband emissions were correlated with vessel damage, as described before (McDannold et al. 2006). These emissions occur during inertial cavitation, the violent collapse of microbubbles that can induce damage (Lele 1987).

METHODS

Animals

All experiments were performed in accordance with procedures approved by the Harvard Medical School Institutional Animal Care and Use Committee. The animals were housed, fed and watered according to the Office of Laboratory Animal Welfare and the Association for Assessment and Accreditation of Laboratory Care regulations. The experiments were performed using male CD-1 mice (36–47 g). The animals were initially anesthetized with an intra-peritoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). The fur on the head was removed using clippers and depilatory cream, and a catheter was placed in the tail vein. The animal's head was fixed in a magnetic resonance imaging (MRI)-compatible stereotactic frame (constructed in-house), and the mouse then was placed on the focused ultrasound (FUS) device. Isoflurane was applied through a nosecone with either oxygen or medical air as the carrier gas. The isoflurane concentration was titrated based on the respiration rate and was typically 1%–2%.

At 1–2 h after the sonications, the animals were deeply anesthetized and euthanized, and the brains were fixed *via* transcardial perfusion (0.9% NaCl, 10 mL; 10% buffered formalin phosphate, 10 mL) and prepared for paraffin sectioning. Two 5-μm horizontal sections in the center of each brain were stained with hematoxylin and eosin and examined for tissue damage.

MRI-guided FUS

FUS exposures (10 ms bursts applied at 1 Hz for 120 s) were started immediately after the administration of the microbubble ultrasound contrast agent Optison (GE Healthcare, Little Chalfont, Buckinghamshire, UK; dose, 200 μL/kg; diluted 10× in phosphate-buffered saline) to disrupt the BBB under MRI guidance. The transcranial sonications were applied using a 690-kHz FUS transducer driven with a function generator (33220 A, Agilent, Santa Clara, CA, USA) and amplifier (240 L, E&I, Rochester, NY, USA). Electrical power output was measured using a power meter (E4419 B, Agilent) and dual-directional coupler (C5948-10, Werlatone, Patterson, NY, USA).

The transducer was mounted on a plastic plate which was attached to a manually operated, three-axis MRI-compatible positioning system. The mouse in the stereotactic frame was placed supine with the head within a 5 × 6-cm transmit/receive surface coil, and the system was placed in an animal 7 T (Biospec, Bruker, Billerica, MA, USA) MRI. Acoustic coupling was achieved by submersing the transducer and top of the mouse's head in degassed and deionized water. The acoustic power output for the spherically curved transducer (diameter/radius of curvature, 4/3 cm) was measured using a radiation force balance. Scans of the acoustic intensity were obtained with a 0.2-mm diameter needle hydrophone (HNC-0200, Onda, Sunnyvale, CA, USA). These calibrations were used to estimate the peak negative pressure amplitude at the focus in water (Hynynen 1990). The width and length of the 50% isopressure contours were 2.3 and 10.3 mm. The transducers, MRI coil and positioning system were assembled in-house.

Peak negative pressure amplitudes of 0.51–0.54 MPa were used in the first animal. This value was selected based on pilot studies with isoflurane and oxygen (data not shown). These exposures resulted in wideband emissions when medical air was used, so the pressure was reduced to 0.46–0.48 MPa in the second animal and to 0.34–0.36 MPa in the next five. We used two different exposure levels in each hemisphere. However, no meaningful differences in the BBB disruption or acoustic emissions were observed between these two levels, and in the analysis we divided the sonications into two groups: the eight locations sonicated at 0.46–0.54 MPa in the first two animals and the 20 locations sonicated at 0.34–0.36 MPa in the next five animals.

Before each experiment, we localized the focal point in the MRI coordinate space by visualizing heating in a silicone acoustic standoff pad using temperature-sensitive MRI. The mouse was then placed on the system and standard anatomic MRI was used to choose the targets. Two sonications were targeted in each hemisphere, one centered in the putamen and one in the thalamus. After the second sonication, we switched from medical air to oxygen (three animals) or vice versa (four animals). We waited for 2 min or longer between sonications to allow the bubbles to mostly clear from circulation. After the completion of the four sonications, axial T1-weighted rapid acquisition relaxation enhanced images (parameters: repetition time, 600 ms; echo time, 18 ms; echo train length, 4; field of view, 4 cm; matrix, 128 × 128; slice thickness, 1 mm; averages, 4) were acquired before and after intravenous injection of gadopentetic acid (Gd-DTPA; Magnevist, Bayer Schering Pharma, Leverkusen, Germany; dose, 0.25 mL/kg), an MRI contrast agent that normally does not cross the BBB.

Acoustic emissions recording

A planar (7 × 7 mm) air-backed passive cavitation detector with a center frequency of 1.48 MHz (bandwidth, ±30 kHz) was used to record the acoustic emissions during sonication. The detector was

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