Lipid-shelled microbubbles for ultrasound-triggered release of Xenon for neuroprotection

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Introduction

Ischemia-reperfusion-induced neurological injury is a primary cause of stroke disability. Xenon (Xe), a bioactive gas, has potential as an effective and nontoxic neuroprotectant for the treatment of ischemic stroke [1]. When Xe is delivered by inhalation, high concentrations (50–70% v/v) are necessary to obtain a therapeutic effect, but limit the fraction of inspired oxygen. The goal of this work was to develop Xe-loaded lipid-shelled microbubbles for site-specific release of Xe upon pulsed ultrasound exposure in the neurovasculature. By encapsulating Xe into micron-sized lipid-shelled microbubbles, the therapeutic gas can be shuttled through the vasculature until delivery is triggered by ultrasound exposure.

Methods

Xenon-loaded microbubbles (Xe-MBs) were synthesized by high-shear mixing of 1 ml lipid dispersion (9:1 molar ratio of DSPC and 18:0 PEG2000 PE) in a vial that contained 1 ml Xe, or a combination of Xe and octofluoropropane (OFP) (90/10% v/v), in the headspace. The size distribution and acoustic attenuation spectrum of XeMB were measured using a Coulter counter and broadband attenuation spectroscopy (over 2 – 25 MHz), respectively [2]. Gas chromatography–mass spectrometry was employed to measure Xe dose.[3, 4].

Results

Co-encapsulation of OFP increased the total volume, attenuation coefficient, and stability of microbubbles, shown in Figures 1 and 2. Triggered release of the Xenon gas payload was demonstrated with 6-MHz duplex Doppler and 220-kHz pulsed ultrasound. The total Xe dose in Xe-MB and Xe-OFP-MB were 111.8 ± 16.1 and 127.0 ± 29.1 μl per mg of lipid, respectively, shown in Table 1.
Table 1. Xenon concentration measured using gas chromatography/mass spectrometry. Four vials were tested for Xe-MB and Xe-OFP-MB, and 3 vials for Xe-saturated and Xe-OFP-saturated solution.

<table>
<thead>
<tr>
<th>Agent</th>
<th>[Xe] (ml/ml of solution)*</th>
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<tbody>
<tr>
<td>Xe-MB</td>
<td>111.8 ± 16.1</td>
</tr>
<tr>
<td>Xe-OFP-MB</td>
<td>127.0 ± 29.1</td>
</tr>
<tr>
<td>Xe-saturated solution</td>
<td>34.1 ± 2.7 (with sonication)</td>
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<td>57.6 ± 4.2 (8 hr equilibration)</td>
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<tr>
<td>Xe-OFP-saturated solution</td>
<td>39.1 ± 2.1 (with sonication)</td>
</tr>
<tr>
<td></td>
<td>51.0 ± 3.3 (8 hr equilibration)</td>
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</tbody>
</table>

* The Xenon dose per ml of solution is equivalent to the Xe dose per mg of lipid.

Conclusions

These results motivate the continued investigation of lipid-shelled microbubbles for ultrasound-triggered Xe delivery. Intravenous administration of microbubbles carrying a neuroprotective gas in combination with ultrasound exposure has potential as a novel noninvasive strategy for local therapeutic delivery to modulate the effects of cerebral ischemia.

References


