Comparison of Thresholds for Pulmonary Capillary Hemorrhage Induced by Pulsed-wave and B-mode Ultrasound.

Douglas L. Miller*a, Chunyan Doua, Krishnan Raghavendranb

aDepartment of Radiology, University of Michigan, Ann Arbor MI 48109 USA
bDepartment of Surgery, University of Michigan, Ann Arbor MI 48109 USA

Abstract

Pulsed ultrasound was found to induce pulmonary capillary hemorrhage (PCH) in mice about 25 years ago but remains a poorly understood risk factor for pulmonary diagnostic ultrasound. In early research using laboratory fixed beam ultrasound, thresholds for PCH had frequency variation from 1-4 MHz similar to the Mechanical Index. In recent research, thresholds for B mode diagnostic ultrasound from 1.5-12 MHz had little dependence on frequency. To compare the diagnostic ultrasound method to laboratory pulsed exposure, thresholds for fixed beam ultrasound were determined using comparable methods at 1.5 and 7.5 MHz. PCH thresholds were lower for simple fixed-beam pulse modes than for B mode and in approximate agreement with early research. However, for comparable timing parameters, PCH thresholds had little dependence on ultrasonic frequency. These findings suggest that the MI may not be directly useful as a dosimetric parameter for safety guidance in pulmonary ultrasound.

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1. Introduction

Pulsed ultrasound was reported to induce pulmonary capillary hemorrhage (PCH) in mice 25 years ago (Child et al. 1990). Subsequently, PCH has been studied by several different research groups and confirmed to occur with diagnostic ultrasound (AIUM, 2000; Church et al. 2008; Miller 2012). This phenomenon is not only of basic scientific interest; it also appears to be the only clearly demonstrable bioeffect of diagnostic ultrasound reported to
occur in mammals (in the absence of ultrasound contrast agents). Direct pulmonary examination by diagnostic ultrasound has become routine for diagnosis of patient conditions such as pulmonary edema and effusion. The PCH bioeffect could present a risk of injury and progression in these patients; however, the risk of PCH induction remains poorly understood. Further research is needed to define the risk and to support safety guidance for sonographers.

Nomenclature

Mechanical Index (MI) An on-screen dosimetric parameter for diagnostic ultrasound, proportional to an estimated in situ peak rarefractional pressure amplitude divided by the square root of the ultrasonic frequency.

2. Methods

Initial research explored the frequency dependence of PCH thresholds for diagnostic ultrasound (DUS) from 1.5 to 12 MHz (Miller, 2012; Miller et al. 2015a). The results of that research appeared to contrast with earlier findings for laboratory ultrasound (LUS) using in fixed beams of pulsed focused ultrasound. DUS thresholds for PCH had little variation with ultrasonic frequency, while LUS results from 1-4 MHz appeared to be similar to the Mechanical Index of 0.63 (AIUM, 2000). A follow-up study (Miller et al. 2015b) was undertaken to re-examine PCH with LUS at 1.5 and 7.5 MHz using methods comparable to those of our DUS research.

Female rats were anesthetized with ketamine and xylazine with all animal procedures approved by the University of Michigan Committee on Use and Care of Animals. The fur was shaved over the right thorax for ultrasound transmission, and the rat was mounted in a 38°C bath. Ultrasound exposure was 5 min in duration. Measured Peak rarefactional pressure amplitudes (PRPAs) values included attenuation by rat chest-wall samples. The PCH was measured on the lung surface. The proportion of 5 rats positive for PCH at each PRPA level was evaluated for significance of occurrence with the Z-test relative to 0/5 in shams. Thresholds were identified as the mean of the lowest PRPA with significant positive results and the next lower PRPA.

2.1 DUS methods

B mode scanning was performed with diagnostic ultrasound probes on three different ultrasound machines: a 1.5 MHz phased array (FPA2.5,GE Vingmed System V), 4.4 MHz and 12 MHz linear arrays (7L and I13L, GE Vivid 7 Dimension) and a 7.6 MHz linear array (CL15-7, Philips HDI 5000). The 1.5 MHz probe had poor image quality in the rats, and was aimed with the aid of an 8 MHz image (FPA10, GE Vingmed System V) operated at -20 dB, while the other images were of sufficient quality for aiming and exposure. Exposure parameters are listed in Table 1.

<table>
<thead>
<tr>
<th>Frequency (MHz)</th>
<th>Pulse Duration (µs)</th>
<th>Pulse Interval (ms)</th>
<th>Frame Rate (Hz)</th>
<th>6 dB Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>1.51</td>
<td>0.42</td>
<td>36.4</td>
<td>4.30</td>
</tr>
<tr>
<td>4.4</td>
<td>0.39</td>
<td>0.162</td>
<td>32.1</td>
<td>3.75</td>
</tr>
<tr>
<td>7.6</td>
<td>0.25</td>
<td>0.100</td>
<td>39</td>
<td>1.05</td>
</tr>
<tr>
<td>12.0</td>
<td>0.16</td>
<td>0.084</td>
<td>50.8</td>
<td>0.75</td>
</tr>
</tbody>
</table>

2.2 LUS methods

The laboratory exposure system consisted of damped 1.5 or 7.5 MHz transducers, which were 1.9 cm in diameter and focused at 3.75 cm. A function generator produced a continuous pulse train of specific pulse durations (number of whole cycles) and pulse intervals. This pulse train was modulated for some groups by a repetitive Gaussian signal (1.9 ms long at half maximum repeated each 25 ms) to simulate a scanned beam exposure at a single spot. A power amplifier drove the transducers. The fixed beams were aimed with the aid of an 8 MHz image (S10, GE Vivid 7 Dimension) operated at -20 dB. Thresholds were determined for five conditions, see Table 2.
Table 2. Exposure parameters for the LUS exposures.

<table>
<thead>
<tr>
<th>Frequency (MHz)</th>
<th>Pulse Duration (μs)</th>
<th>Pulse Interval (ms)</th>
<th>Frame Rate (Hz)</th>
<th>6 dB Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>10.3</td>
<td>25</td>
<td>no modulation</td>
<td>3.8</td>
</tr>
<tr>
<td>7.5</td>
<td>10.3</td>
<td>25</td>
<td>no modulation</td>
<td>0.8</td>
</tr>
<tr>
<td>1.5</td>
<td>1.7</td>
<td>0.5</td>
<td>40</td>
<td>3.8</td>
</tr>
<tr>
<td>7.5</td>
<td>1.5</td>
<td>0.5</td>
<td>40</td>
<td>0.8</td>
</tr>
<tr>
<td>7.5</td>
<td>0.3</td>
<td>0.1</td>
<td>40</td>
<td>0.8</td>
</tr>
</tbody>
</table>

3. Results

The results for the areas of PCH measured on the lungs are shown in Fig. 1.

The areas were much larger for the DUS exposures, because of the much larger areas scanned, relative to the single spots of exposure for the fixed beam LUS. All thresholds were within a narrow range, well within the diagnostic range, below MI=1.9. Thresholds for the fixed-pulse LUS exposures were less than those for the modulated pulse modes and the DUS exposures, as shown in Fig. 2. The AIUM line from 1-4 MHz follows a trend equal to the MI with a value of 0.63, which has been extended to the axis by the dotted line.
4. Discussion and Conclusions

The LUS results can be compared to earlier fixed-beam pulsed ultrasound results, such as those from Child et al. (1990), Zachary et al. (2001) and O’Brien et al. (2003). Child et al. (1990) found a threshold in mice for 10 μs pulses at 1.2 MHz of 0.7 MPa, which was the same as our 1.5 MHz result for 10 μs pulses. For 3.7 MHz, the threshold of 1.0 MPa was somewhat higher (than our 7.5 MHz result), and possibly indicative a dependence of the thresholds on ultrasonic frequency. However, the differences were small, and may be attributable to the different species or to uncertainties in threshold determinations, which include uncertainties in dosimetry (typically ± 10-15% for the PRPA). Overall, our results and those of Child et al. (1990) 25 years ago might be considered to be in rough agreement.

The threshold results from Zachary et al. (2001) and O’Brien et al. (2003) were substantially higher than our results or those of Child et al. (1990). A key difference in the exposure parameters might be the 10 s exposure duration, compared to 3 min for Child et al. (1990) and 5 min for our study. An interesting finding was that mice had somewhat higher thresholds than rats (Zachary et al. 2001). The thresholds at 2.8 MHz and 5.6 MHz were not significantly different for mice or for rats, indicating little dependence on frequency. The influence of pulse duration on thresholds was examined by O’Brien et al. (2003), and a clear trend of decreased thresholds for increased pulse duration was found, which was also evident in this present study.

The results of this research indicated a minimal dependence of PCH thresholds on ultrasonic frequency, which was different than the frequency dependence of the MI. The curve-fitting of the early research results (AIUM, 2000) clearly does not fit the present results, see Fig. 2. For DUS, the comparable value of PRPA divided by the square root of frequency was 0.84 MPa/MHz⁰.⁵ at 1.5 MHz but only 0.39 MPa/MHz⁰.⁵ at 12.0 MHz. For LUS, PCH thresholds had little or no dependence on ultrasonic frequency for similar timing parameters. These results suggest that the thresholds do not depend on ultrasonic frequency per se, but may vary for different frequencies of diagnostic ultrasound due to imaging-related changes in pulse-timing parameters. These findings suggest that the MI may not be directly useful as a dosimetric parameter for safety guidance in pulmonary ultrasound.

Acknowledgements

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References


