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● *Original Contribution*

DEPENDENCE OF THRESHOLDS FOR PULMONARY CAPILLARY HEMORRHAGE ON DIAGNOSTIC ULTRASOUND FREQUENCY

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Abstract—Pulmonary ultrasound examination has become routine for diagnosis in many clinical and point-of-care medical settings. However, the phenomenon of pulmonary capillary hemorrhage (PCH) induction during diagnostic ultrasound imaging presents a poorly understood risk factor. PCH was observed in anesthetized rats exposed to 1.5-, 4.5- and 12.0-MHz diagnostic ultrasound to investigate the frequency dependence of PCH thresholds. PCH was detected in the ultrasound images as growing comet tail artifacts and was assessed using photographs of the surface of excised lungs. Previous photographs acquired after exposure to 7.6-MHz diagnostic ultrasound were included for analysis. In addition, at each frequency we measured dosimetric parameters, including peak rarefactional pressure amplitude and spatial peak, pulse average intensity attenuated by rat chest wall samples. Peak rarefactional pressure amplitude thresholds determined at each frequency, based on the proportion of PCH in groups of five rats, were 1.03 ± 0.02, 1.28 ± 0.14, 1.18 ± 0.12 and 1.36 ± 0.15 MPa at 1.5, 4.5, 7.6 and 12.0 MHz, respectively. Although the PCH lesions decreased in size with increasing ultrasonic frequency, owing to the smaller beam widths and scan lengths, the peak rarefactional pressure amplitude thresholds remained approximately constant. This dependence was different from that of the mechanical index, which indicates a need for a specific dosimetric parameter for safety guidance in pulmonary ultrasound. (E-mail: douglm@umich.edu) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Pulmonary ultrasound, Point-of-care ultrasound, Comet tail artifact, Bio-effects of ultrasound, Pulmonary hemorrhage, Mechanical index.**

INTRODUCTION

Pulsed ultrasound can induce pulmonary capillary hemorrhage (PCH) in mammals, a bio-effect that was discovered more than 20 y ago (Child et al. 1990). PCH was subsequently studied to determine its dependence on various pulsed-ultrasound parameters using laboratory exposure systems (American Institute of Ultrasound in Medicine [AIUM] 2000; Church et al. 2008). Only a few studies have used actual diagnostic ultrasound (DUS) machines. DUS was used for studies in monkeys (Tarantal and Canfield 1994) and rats (Holland et al. 1996), but the positive results were not clearly definitive. A study of human lungs indicated that echocardiography, which was thought to interact with the lung as incidental exposure, did not induce detectable PCH (Meltzer et al. 1998). Recently, DUS with a small linear array generated PCH in rats, which was detectable as growing comet tail artifacts in the images and was measured as hemorrhage areas on the lungs (Miller 2012). These DUS studies have had inconsistent methods and results, which are difficult to compare to define PCH thresholds and the dependence of the thresholds on DUS frequency. Nevertheless, these studies have clearly indicated that PCH can be induced by diagnostic ultrasound. This finding presents a potential risk of patient injury in pulmonary ultrasound examinations; however, despite a substantial research effort, the risk remains poorly understood.

Several authoritative reviews have been conducted to clarify the dosimetry of PCH, particularly with respect to the utility of the on-screen mechanical index (MI) for appraising PCH risk. Laboratory animal studies that used pulsed-ultrasound systems to determine thresholds for PCH were reviewed by the AIUM (2000). The thresholds at ultrasonic frequencies between 1 and 4 MHz were expressed in terms of the pulse peak rarefactional pressure amplitude (PRPA) derated for tissue attenuation. These results were plotted, and a least-squares fitted line approximated the functional form of the MI, with a

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Table 1. Diagnostic ultrasound scan settings for each probe used for imaging exposure*

System	Probe	Frequency (MHz)	Image depth (cm)	Focal depth (cm)	Lung depth (cm)	Frame rate (s^{-1})
GE Vingmed	FPA2.5	1.5	6	5	3.75	36.4
GE Vivid 7	7 L	4.5	3	1.3	1.0	32.1
Philips HDI	Cl15-7	7.6	2.0	1.0	0.6	39.0
GE Vivid 7	i13 L	12.0	1.5	0.65	0.6	50.8

* The frequencies listed were the center frequency of the pulses as measured with a hydrophone, which were obtained with on-screen settings of 1.5 MHz (FPA2.5), 4.0 MHz (7 L) and 14 MHz (i13 L). The settings for the previously employed 7.6-MHz system (Miller 2012), which did not show the frequency on screen, are also listed for comparison.

threshold constant of 0.63 and a frequency exponent of 0.54. For reference, the guideline upper limit for diagnostic ultrasound is MI = 1.9 with the 0.5 frequency exponent (Food and Drug Administration 2008). At that time, cavitation was thought to be involved (Holland et al. 1996), and thus, the MI seemed to be a good dosimetric guide for PCH.

These early results were obtained mostly in mice, but ultrasound-induced PCH also has been observed at about the same derated PRPAs in mice, rats, rabbits, pigs and monkeys. Another authoritative review organized by the AIUM found no consistently defined risk for diagnostic ultrasound (Church et al. 2008). Ultrasound scanning of patient's lungs at that time was considered to arise mostly from incidental exposure during echocardiography, which would have lower PRPAs than direct exposure. In addition, the study by Meltzer et al. (1998) of human lungs with potential incidental exposure found no evidence of PCH for 3.5-MHz DUS up to 2.4 MPa (MI = 1.3). However, direct pulmonary ultrasound examination now has become routine as an aid in patient evaluation and for diagnosis of such conditions as pulmonary edema and effusion, pulmonary embolism, atelectasis, diffuse parenchymal disease, adult and newborn respiratory distress syndrome and lung cancer (Sartori and Tombesi 2010). This method is well suited to point-of-care settings (Koenig et al. 2011) owing to the small footprint and portability of modern DUS machines. Modern DUS machines also have the on-screen readout of the MI, a dosimetric parameter that is specifically related to ultrasonic cavitation and might be useful as a safety guide for pulmonary sonography.

Several studies have examined the cavitation hypothesis and found that cavitation is probably not the mechanism underlying PCH (O'Brien et al. 2000, 2004; Raeman et al. 1997). This finding complicated the use of the MI as a safety parameter for PCH. Studies in rats and mice have investigated the influence of specific parameters of pulsed ultrasound on PCH. A meta-analysis of 14 studies found that widely varying thresholds had been reported that depended on pulse duration, pulse repetition frequency and exposure duration, in addition to PRPA and frequency (Church and O'Brien 2007). In that review, a dosimetric parameter specifically relevant to PCH was derived that included pulse duration, pulse repetition frequency and exposure duration. However, this review depended on data from laboratory pulsed-ultrasound systems with a single fixed beam, rather than from DUS machines.

In the recent DUS study from our laboratory (Miller 2012), a 7.6-MHz linear array was used to induce PCH in rats scanned for 5 min above a threshold of about MI = 0.44 (on-screen readout) for PCH occurrence. This result provided new information at a relatively high diagnostic frequency. However, differences in methods, particularly the use of DUS scanners, make comparisons with previous research using fixed-beam laboratory pulsed-ultrasound systems difficult. The objective of this present research was to extend the use of diagnostic ultrasound methods (Miller 2012) to explore the dependence of thresholds for PCH on DUS frequency, which may help to clarify the risk of PCH for different pulmonary ultrasound examinations. Results at 7.6 MHz were augmented with comparable data from scanning at 1.5, 4.5 and 12.0

Table 2. General pulse parameters and attenuation determined by hydrophone measurements using the lowest power settings, which approximated linear propagation conditions*

System	Probe	Frequency (MHz)	Pulse interval (μs)	Pulse duration (ns)	−6-dB thickness (mm)	Attenuation coefficient (dB/cm/MHz)
GE Vingmed	FPA2.5	1.5	420	1510	4.30	1.1
GE Vivid 7	7 L	4.5	162	390	3.75	1.1
Philips HDI	Cl15-7	7.6	100	250	1.05	1.3
GE Vivid 7	i13 L	12.0	84	160	0.75	1.2

* The −6-dB thickness of the beam perpendicular to the scan plane was determined as the width at half the maximum pressure amplitude. The approximate attenuation coefficients were calculated from the spatial peak, pulse average intensity values for a 5-mm tissue thickness.