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## ● Original Contribution

# PULMONARY CAPILLARY HEMORRHAGE INDUCED BY DIFFERENT IMAGING MODES OF DIAGNOSTIC ULTRASOUND

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**Abstract**—The induction of pulmonary capillary hemorrhage (PCH) is a well-established non-thermal biological effect of pulsed ultrasound in animal models. Typically, research has been done using laboratory pulsed ultrasound systems with a fixed beam and, recently, by B-mode diagnostic ultrasound. In this study, a GE Vivid 7 Dimension ultrasound machine with 10 L linear array probe was used at 6.6 MHz to explore the relative PCH efficacy of B-mode imaging, M-mode (fixed beam), color angio mode Doppler imaging and pulsed Doppler mode (fixed beam). Anesthetized rats were scanned in a warmed water bath, and thresholds were determined by scanning at different power steps, 2 dB apart, in different groups of six rats. Exposures were performed for 5 min, except for a 15-s M-mode group. Peak rarefactional pressure amplitude thresholds were 1.5 MPa for B-mode and 1.1 MPa for angio Doppler mode. For the non-scanned modes, thresholds were 1.1 MPa for M-mode and 0.6 MPa for pulsed Doppler mode with its relatively high duty cycle ( $7.7 \times 10^{-3}$  vs.  $0.27 \times 10^{-3}$  for M-mode). Reducing the duration of M-mode to 15 s (from 300 s) did not significantly reduce PCH (area, volume or depth) for some power settings, but the threshold was increased to 1.4 MPa. Pulmonary sonographers should be aware of this unique adverse bio-effect of diagnostic ultrasound and should consider reduced on-screen mechanical index settings for potentially vulnerable patients. (E-mail: [dougim@umich.edu](mailto:dougim@umich.edu)) © 2017 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

**Key Words:** Pulmonary ultrasound, Comet tail artifact, Bio-effects of ultrasound, Ultrasound dosimetry, Diagnostic ultrasound safety.

## INTRODUCTION

The induction of pulmonary capillary hemorrhage (PCH) is a well-established non-thermal biological effect of pulsed ultrasound in animal models first reported in 1990 (Child et al. 1990). We have studied PCH induction by B-mode diagnostic ultrasound (Miller 2012). This phenomenon appears to be the only clearly demonstrable bio-effect of diagnostic ultrasound reported to occur in mammals (in the absence of ultrasound contrast agents). The safety issue presented by PCH initially was considered to be of low risk because only incidental lung exposure was expected (Church et al. 2008). However, in recent years, direct pulmonary examination by diagnostic ultrasound has become routine in point-of-care ultrasound and other settings.

Experimental use of pulmonary diagnostic ultrasound (PDUS) was explored as early as 1967 for detection of pleural effusion (Joyner et al. 1967) and pulmonary embolism (Miller et al. 1967). Probably the first routine use of PDUS was to rule out pneumothorax using modern PDUS (Lichtenstein and Menu 1995). PDUS has been found to be valuable in the diagnosis of pneumonia, pulmonary edema, embolism, atelectasis, diffuse parenchymal disease, respiratory distress syndrome and lung cancer (Sartori and Tombesi 2010). Chest sonography is accepted in children for diagnosis of neonatal respiratory distress syndrome (Copetti et al. 2008) and pneumonia (Liu et al. 2014; Pereda et al. 2015). The rapidly expanding use of portable ultrasound machines allows PDUS to be performed by the physician at the bedside, not unlike the ubiquitous stethoscope (Irwin and Cook 2016; Lumb and Karakitsos 2015; Sekiguchi 2016). Point-of-care PDUS has become routine in intensive care, emergency care and other medical settings (Ahmad and Eisen 2015; Dietrich et al. 2017; Lichtenstein 2014; Volpicelli 2013). There are now at least 10 different diagnostic signs for lung ultrasound

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(Lichtenstein 2015). PDUS can involve eight or more scan zones of the anterolateral and posterior chest (Gargani and Volpicelli 2014). Extensive scanning for quantitative analysis of PDUS comet tail artifacts (CTAs) aids in characterization of high-altitude pulmonary edema (Fagenholz et al. 2007), chest congestion in dialysis patients (Weitzel et al. 2015; Zoccali et al. 2013) and other conditions (Dietrich et al. 2016). The total usage of PDUS is impossible to determine because point-of-care ultrasound is performed in so many settings, often informally without billing records and often routinely on a daily basis to follow patient progress (Hall et al. 2016; Sferrazza Papa et al. 2017). Thus, the safety issue has become worrisome: It is possible that vulnerable patients are unknowingly injured by PDUS.

Ultrasound-induced PCH has received significant interest because of the apparent safety issue (American Institute of Ultrasound in Medicine [AIUM] 2000; Church et al. 2008). Typically, research has been performed using laboratory pulsed ultrasound systems or, recently, the B-mode of DUS. In our recent study, the laboratory pulsed ultrasound had somewhat lower thresholds than B-mode ultrasound (Miller et al. 2015a), which might be expected because it is focused at one position, whereas B-mode delivers a much lower number of pulses to a specific point when the beam scans the lung surface. Thresholds have been sought for different conditions and parameters, but the number of parameters, *in situ* values of exposure and possible patient conditions complicate this process. For example, the PCH threshold has little dependence on ultrasound frequency (Miller et al. 2015b), which makes use of the on-screen mechanical index ( $MI_{OS}$ ) problematical for simple safety adjustments. The thresholds also depend on biological conditions such as age (Dalecki et al. 1997; O'Brien et al. 2003a), specific anesthetics (Miller et al. 2015c) and even common patient sedatives (Miller et al. 2016a). More definitive information on the etiology of PCH would be valuable to clarify the extensive database presently available and to assist in mitigating risks. M-Mode is commonly used for pulmonary examina-

tions, with the ultrasound seashore sign indicating normal lung function (Ahmad and Eisen 2015). Other modes can also interact with the lung during transthoracic examination, such as pulsed Doppler and color Doppler imaging in echocardiography for pulmonary hypertension (Bossone et al. 2015; Vargas and Lopez-Candales 2016). The purpose of the present study was to detail PCH occurrence and thresholds in a rat model of PDUS for B-mode, M-mode, pulsed Doppler and color angio mode Doppler imaging.

## METHODS

### Ultrasound

A clinical GE Vivid 7 Dimension (GE Vingmed Ultrasound AS, Horten, Norway) diagnostic ultrasound machine was used in this study. The 10 L linear array probe was used throughout. The image application was set up with 3-cm depth and single focus at 1.3-cm image depth. The  $-6$ -dB width of the beam was 1.2 mm. The machine was operated in four standard modes: B-mode, M-mode, pulsed Doppler mode and color Doppler angio mode, as listed in Table 1 (together with PCH thresholds, see Results). The frequency was set to 7.5 MHz for B- and M-mode, 6.6 MHz for pulsed Doppler and 6.4 MHz for angio mode. The probe was held with a gimbal mount in a heated water bath filled with vacuum-degassed water. The ultrasound pulse parameters were measured at the position of the maximum peak rarefactional pressure amplitude (1.3 cm depth on the probe axis) using a calibrated hydrophone with a 0.2-mm sensitive spot (Model HMA-0200, Onda, Sunnyvale, CA, USA) and are listed in Table 1. The digitized pulse pressure waveform, measured in water, was derated by an attenuation factor of 1.2 dB/cm-MHz (Miller et al. 2015b) and was  $-4$  dB for the approximate chest wall thickness of 0.5 cm and ultrasound frequency of 6.6 MHz. This provided the approximate *in situ* values at the lung surface of the peak rarefactional pressure amplitude (PRPA), peak compressional pressure amplitude and peak mean pressure amplitude (PMPA). The pulse duration was calculated as 1.25 times the interval between

Table 1. Pulsing parameters used for the four exposure modes with corresponding PCH thresholds, all with an observed frequency of 6.6 MHz\*

Mode	Pulse (ns)	PRP ( $\mu$ s)	fps (Hz)	PRPA (MPa)	$r^2$	PMPA (MPa)	$I_{SPPA}$ (W/cm <sup>2</sup> )	$MI_{IS}$ (MPa/MHz <sup>1/2</sup> )
B-Mode	268	96	60	1.5	0.69	2.2	87	0.58
M-Mode 15 s	269	1000	—	1.4	0.45	2.1	85	0.54
M-Mode 5 min	269	1000	—	1.1	0.51	1.6	50	0.44
Angio Doppler	319	335	17.5	1.1	0.76	1.3	42	0.41
Pulsed Doppler	1130	147	—	0.6	0.35	0.7	12	0.24

Pulse = pulse duration observed at  $-6$ -dB power setting; PRP = pulse repetition period; fps = frames per second; PRPA = peak rarefactional pressure amplitude *in situ*; PMPA = pulse mean pressure amplitude *in situ*;  $I_{SPPA}$  = spatial peak pulse average intensity *in situ*;  $MI_{IS}$  = mechanical index *in situ* calculated as *in situ* PRPA (MPa)  $\times$  (6.6 MHz)<sup>-1/2</sup>.

\* The Doppler mode sample volumes were 0.4 mm for angio mode and 1 mm for pulsed Doppler. Thresholds are given for the PRPA, PMPA,  $I_{SPPA}$  and *in situ* MI based on linear regression of pulmonary capillary hemorrhage area versus PRPA, as illustrated in Figures 3 and 5.

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