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● *Review Article*

# MECHANISMS FOR INDUCTION OF PULMONARY CAPILLARY HEMORRHAGE BY DIAGNOSTIC ULTRASOUND: REVIEW AND CONSIDERATION OF ACOUSTICAL RADIATION SURFACE PRESSURE

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**Abstract—Diagnostic ultrasound can induce pulmonary capillary hemorrhage (PCH) in rats and other mammals. This phenomenon represents the only clearly demonstrated biological effect of (non-contrast enhanced) diagnostic ultrasound and thus presents a uniquely important safety issue. However, the physical mechanism responsible for PCH remains uncertain more than 25 y after its discovery. Experimental research has indicated that neither heating nor acoustic cavitation, the predominant mechanisms for bioeffects of ultrasound, is responsible for PCH. Furthermore, proposed theoretical mechanisms based on gas-body activation, on alveolar resonance and on impulsive generation of liquid droplets all appear unlikely to be responsible for PCH, owing to unrealistic model assumptions. Here, a simple model based on the acoustical radiation surface pressure (ARSP) at a tissue–air interface is hypothesized as the mechanism for PCH. The ARSP model seems to explain some features of PCH, including the approximate frequency independence of PCH thresholds and the dependence of thresholds on biological factors. However, ARSP evaluated for experimental threshold conditions appear to be too weak to fully account for stress failure of pulmonary capillaries, gauging by known stresses for injurious physiologic conditions. Furthermore, consideration of bulk properties of lung tissue suggests substantial transmission of ultrasound through the pleura, with reduced ARSP and potential involvement of additional mechanisms within the pulmonary interior. Although these recent findings advance our knowledge, only a full understanding of PCH mechanisms will allow development of science-based safety assurance for pulmonary ultrasound. (E-mail: douglm@umich.edu) © 2016 World Federation for Ultrasound in Medicine & Biology.**

*Key Words:* **Non-ionizing radiation biology, Pulmonary ultrasound, Point-of-care ultrasound, Mechanical index, Lung injury mechanisms.**

## INTRODUCTION

The induction of pulmonary capillary hemorrhage (PCH) by pulsed ultrasound was discovered by Child et al. (1990). A substantial literature has accumulated over more than 25 y of research on this bioeffect in various laboratory animals using pulsed ultrasound from research systems (Church and O'Brien 2007) and from actual diagnostic ultrasound scanners (Miller, 2012). PCH should be expected clinically under favorable physical and biological conditions (Church et al. 2008). An example of the ultrasound images and PCH produced by 12 MHz diagnostic ultrasound is shown in Figure 1 (Miller et al. 2015a). An interesting aspect of PCH is that induction of PCH caused by the ultrasound scanning is displayed by the ultrasound image as comet tail artifacts (CTAs), see Figure 1. These artifacts, also called B lines, are clinically indicative for diagnosis of pulmonary edema and other conditions (Ahmad and Eisen 2015; Lichtenstein et al. 2009). A threshold exposure response can be defined for PCH as a function of pulse pressure amplitude or intensity for a given set of exposure parameters. The studies of the threshold and magnitude of PCH have included consideration of physical parameters, such as ultrasonic frequency and pulse timing. Several mechanisms, including heating and cavitation, have been explored to explain the phenomenon, but the exact etiology remains elusive. This notable gap in our understanding of potential risks of diagnostic ultrasound represents a question of some importance, because, over this same period, the use of trans-thoracic diagnostic ultrasound for pulmonary examination has grown to be an indispensable tool in the

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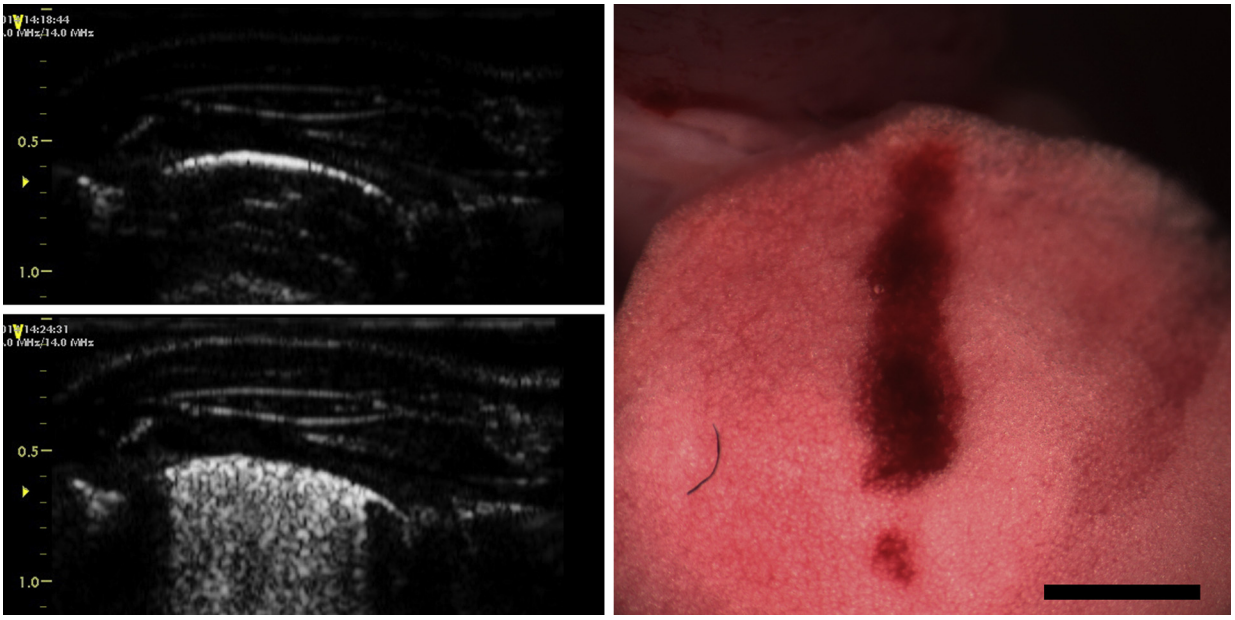


Fig. 1. Diagnostic ultrasound images at 12.0 MHz before (left, top) and after (left, bottom) scanning with the resulting PCH shown on the right (scale bar: 2 mm). The ultrasound images show a portion of the rat thorax with the bright lung surface images displayed at about 5 mm from the skin surface. At the end of scanning, CTAs extended across nearly the entire lung surface image, which corresponded to the PCH seen on the lung surface. Reproduced from Miller et al. (2015a). CTA = comet tail artifacts; PCH = pulmonary capillary hemorrhage.

point-of-care settings of emergency and intensive care (Lichtenstein 2014; Volpicelli 2013), as well as in traditional radiology studies. PCH appears to be the only well documented bioeffect of diagnostic ultrasound with a direct relevance to clinical pulmonary examination. Only a full understanding of PCH mechanisms will allow development of appropriate safety guidance for sonographers.

The present safety system for diagnostic ultrasound includes the detailed measurement by the manufacturer of temporal and spatial parameters of the ultrasound field generated by an ultrasound probe, including a derating attenuation factor of 0.3 dB (cm MHz)$^{-1}$ to approximate *in situ* tissue conditions. Two dosimetric indices are displayed on screen to aid the operator in recognizing changes in acoustical output as different settings and modes are utilized. The thermal index (TI) presents a reasonable worst case estimate of temperature elevation for long duration imaging with fixed position. The mechanical index (MI) provides a gauge of the potential worst case inception of cavitation activity by the ultrasound and indicates the derated pulse peak rarefactional pressure amplitude (PRPA) divided by the square root of ultrasonic frequency. The primary regulated safety limitation is that the MI must be less than 1.9 MPa MHz$^{-½}$, based on the highest MI value estimated for ultrasound probes in use before May 28, 1976 (Nyborg 2000). The TI is also generally limited to about 6 for normal approval under the 510 k process of the US Food and Drug Administration. PCH does not seem to fit this safety system, because this clearly injurious biological effect has been shown to be directly induced by diagnostic ultrasound in mammals below the regulatory limit of MI = 1.9.

Here, the experimental characterization of PCH induction by clinical diagnostic ultrasound equipment and by pulse-wave simulation of diagnostic ultrasound exposure are outlined. Five physical mechanisms, which have been proposed as hypothetical explanations for PCH, are critically reviewed. Furthermore, the mechanism of acoustical radiation surface pressure (ARSP) at a tissue–air interface is proposed as a potential explanation of PCH induced by pulsed ultrasound. The ARSP hypothesis is evaluated relative to the experimental evidence and to more complex bulk-tissue transmission parameters reported for lung. The ARSP hypothesis provides valuable insights into the phenomenon but does not appear to fully explain the PCH bioeffect.

*Experimental background*

No new animal studies were performed for this research, and no human studies were reviewed. Animal studies performed for cited papers were approved by the appropriate institutional animal care and use committee or followed ethical research guidelines of their institutions at the time of publication. The selection of papers