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● *Original Contribution*

PULMONARY CAPILLARY HEMORRHAGE INDUCED BY DIAGNOSTIC ULTRASOUND IN VENTILATED RATS

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Abstract—Pulmonary capillary hemorrhage (PCH) can be induced by diagnostic ultrasound—a potential safety issue. Anesthetized rats were intubated for intermittent positive-pressure ventilation (IPPV) with 0 end-expiratory pressure, +4 cm H_2O end-expiratory pressure (PEEP) and −4 cm H_2O end-expiratory pressure (NEEP). Rats were imaged at 7.6 MHz with a Philips HDI 5000 ultrasound machine. The output was low (mechanical index [MI] = 0.22) for aiming and then was raised for 5 min in 20 different exposure groups with n = 8. Peak rarefactional pressure amplitudes were measured in water and de-rated for chest attenuation. The PCH areas were measured on the lung surface. At 2.2 MPa, PCH was 9.3 ± 6.6 mm² for IPPV, 1.6 ± 3.2 mm² for PEEP ($p < 0.001$) and 26.8 ± 6.4 mm² for NEEP ($p < 0.001$). Thresholds were 1.3 MPa for IPPV, 2.1 MPa for PEEP and 1.0 MPa for NEEP. The small ventilator pressures subtracted or added to trans-capillary stress generated by diagnostic ultrasound pulses, virtually eliminating PCH for PEEP but enhancing PCH for NEEP. (E-mail: douglm@umich.edu)

Key Words: **Pulmonary diagnostic ultrasound, Mechanical Index, Comet-tail artifact, Mechanical ventilation, Diagnostic ultrasound safety.**

INTRODUCTION

Diagnostic ultrasound (DUS) imaging of post-natal mammalian lung can induce pulmonary capillary hemorrhage (PCH) across the scan plane (Miller 2012), a phenomenon discovered by Child et al. (1990) using pulsed ultrasound. Authoritative reviews indicate that DUS-PCH has been observed in different mammalian species and confirmed in different laboratories, and presents a potential risk factor for diagnostic ultrasound (American Institute of Ultrasound in Medicine 2000; Church et al. 2008). The lung was expected to receive mostly incidental exposure, such as during echocardiography, which appeared to minimize patient risk (Church et al. 2008). However, direct pulmonary diagnostic ultrasound (PDUS) examination is now performed in various clinical settings for diagnosis of pneumonia, pulmonary edema, embolism, pneumothorax, atelectasis, diffuse parenchymal disease, respiratory distress syndrome and lung cancer (Dietrich et al. 2017; Lichtenstein 2014; Sartori and Tombesi 2010; Volpicelli 2013). The use of portable ultrasound machines allows PDUS to be performed by the physician at the point of care for routine monitoring (Irwin and Cook 2016; Ahmad and Eisen 2015; Sekiguchi 2016). This rapidly expanding use of PDUS provides motivation for efforts to define the possible risks of PCH for patients and generate suitable safety guidance.

Recently, we used diagnostic ultrasound systems (early work utilized single-element laboratory systems) to develop a knowledge base for risk evaluation (Miller 2012). Interestingly the PDUS machines causing PCH also display its occurrence in the B-mode images as growing comet-tail artifacts (also known as B-lines) extending from the pleura toward the interior (Miller 2012). The artifact arises from reverberation under several different conditions, which the ultrasound machine displays as deeper echoes, and was first described by Thickman et al. (1983). The physical mechanism for PCH induced by pulsed ultrasound has not been clearly established (Miller 2016). Common mechanisms for ultrasound bio-effects were disproved, including heating (Hartman et al. 1992; Zachary et al. 2006) and acoustical cavitation (O'Brien et al. 2000, 2004; Raeman et al. 1997). Other proposed mechanisms appear to postulate unrealistic models for the effect (Miller 2016). DUS-PCH has a threshold that is well defined for a given set of conditions, but varies in different specific situations. The thresholds for PCH do not have a clear frequency

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dependence (Miller et al. 2015a), indicating that the frequency-independent ultrasonic radiation pressure on the lung surface (P_{URS}) is a potential mechanism for induction of PCH (Miller 2016). PCH induction depends on physical exposure parameters, such as pulse amplitude and duration, pulse repetition frequency and exposure duration (Church et al. 2008). However, PDUS-PCH also has a poorly defined but strong dependence on physiologic conditions. For example, the anesthesia methods are very important for PDUS-induced PCH in rats, which is enhanced by use of xylazine together with ketamine (Miller et al. 2015b). This enhancement phenomenon also occurs for dexmedetomidine, a common clinical sedative used in clinical imaging that causes little or no respiratory depression (Miller et al. 2016). These findings imply that many patient medical treatments or conditions could influence PDUS-PCH in unknown ways (*i.e.,* possibly increasing or decreasing the injury), greatly complicating the thorough characterization of risk.

The hypothesis that PCH is caused by P_{URS} implies that the blood–air–barrier trans-capillary pressure is the key parameter for modulation of the capillary rupture effect giving PDUS-PCH. The pulmonary capillary pressure is nominally 11–16 cm H_2O (8–12 mm Hg) (Levitzky 2013). Large variation in pulmonary blood flow can occur from sleep to vigorous exercise, which normally is accommodated expeditiously without undue capillary stress by recruitment and distension of alveolar capillaries. However, the accommodation of very rapid pressure change is uncertain, and pulmonary capillaries under pre-existing stress may be vulnerable to relatively small stress impulses. The P_{URS} impulse from diagnostic ultrasound pulses is quite brief, typically in the range 0.16–1.5 μs for B-mode ultrasound, and the P_{URS} is low, 4.3–19.3 cm H_2O, for the tissue–air interface (Miller 2016).

One common clinical treatment is mechanical ventilation of the lungs to assist lung function and support in respiratory dysfunction (West 2013). Modern intermittent positive-pressure ventilation (IPPV) is used to achieve oxygenation and gas exchange maintaining near-normal CO_2 levels. Long-term mechanical ventilation can lead to ventilator-induced lung injury ascribed to differing mechanisms, including alveolar stretching, the cyclic effect of IPPV and surfactant dysfunction among others. Weaning from mechanical ventilation as soon as possible is preferred with the institution of spontaneous breathing trials (Ghadiali and Huang 2011; Slutsky and Ranieri 2013). In addition to IPPV, which simulates normal respiration volume and rate, positive end-expiratory pressure (PEEP) is often used at a low value of 4–5 cm H_2O to maintain oxygenation and prevent alveolar collapse. Higher PEEP can be used to recruit alveoli and minimize pulmonary edema (Wiesen et al. 2013). By maintaining positive pressure, PEEP tends to compress the capillaries, reduce trans-capillary pressure and reduce capillary perfusion (Nieman et al. 1988). Conversely, negative end-expiratory pressure (NEEP) can be applied during IPPV, and is expected to increase trans-capillary pressure. As the clinical use of IPPV developed, NEEP was thought to be helpful to assist cardiac output and was an available feature on ventilators (Nunn 1987). However, the use of NEEP was uncertain. For example, NEEP of 5–7 cm H_2O was not found to be beneficial in seriously ill patients receiving IPPV (Scott et al. 1972). NEEP was found to have no clinical application because of a lack of proven benefit and potential adverse effects such as airway atelectasis (Nunn 1987). Negative pulmonary pressures can occur for patient conditions such as sleep apnea and chronic obstructive pulmonary disease leading to edema, which may be treated with positive airway pressure (Bhattacharya et al. 2016).

The present study was undertaken to assess the influence of IPPV on PDUS-PCH. We hypothesized that PEEP should reduce the PCH effect through its opposition to P_{URS} at the lung surface. Conversely, we hypothesized that NEEP should increase the PCH because of the increased trans-capillary pressure, which would predispose the blood–air barrier to injury by even relatively low impulsive stress.

METHODS

Animal preparation

All *in vivo* animal procedures were conducted with the approval and guidance of the Institutional Animal Care and Use Committee (IACUC) of the University of Michigan. Female rats (Sprague Dawley, Charles River, Wilmington, MA, USA) were used for this study, as described previously (Miller 2012). Anesthesia was accomplished with intraperitoneal injection of 91 mg/kg ketamine (Zetamine ketamine hydrochloride injection, MWI, Boise, ID, USA) plus 9 mg/kg intraperitoneal xylazine (XylaMed xylazine injection, MWI), which is the recommended anesthetic for rats. The omission of xylazine from the anesthetic reduces the magnitude of PDUS-PCH relative to use of the combination (Miller et al. 2015b), possibly because of the pharmacologic response of pulmonary capillaries.

A tracheostomy was performed and the trachea was intubated with a plastic tube (2.2-mm o.d., 1.3-mm i.d.) with Luer lock fitting. The right thorax of all rats was shaved and depilated for ultrasound transmission, and the rats were mounted on a holding board in dorsal recumbent position. The board was mounted vertically in a 38 °C degassed water bath for ultrasound exposure of the right lung with the tracheal tube stabilized on the mounting stand. This water bath method provides reproducible ultrasound coupling and exposure and maintains the body