Published in final edited form as:

Ultrasound Med Biol. 2018 August ; 44(8): 1810–1817. doi:10.1016/j.ultrasmedbio.2018.04.014.

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 zero end expiratory pressure and plus or minus 4 cm H₂O end expiratory pressures (PEEP or 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 derated 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.

Keywords

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 present a potential risk factor for diagnostic ultrasound (AIUM, 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 (Sartori and Tombesi, 2010; Volpicelli 2013; Lichtenstein 2014; Deitrich et al. 2017). The

use of portable ultrasound machines allows PDUS to be performed by the physician at the point of care for routine monitoring (Lumb et al. 2015; Irwin and Cook 2016; 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 have 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; Zachery et al 2006) and acoustical cavitation (Raeman et al. 1997; O'Brien et al 2000; O'Brien et al 2004). 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 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 physiological 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 has 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 cmH₂O (8–12 mmHg) (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 of 0.16–1.5 μ s for B Mode ultrasound, and the P_{urs} is low, 4.3–19.3 cm H₂O 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 CO₂ 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 the IPPV, which simulates normal respiration volume and rate, positive end expiratory pressure (PEEP) is often used at a low value of 4–5 cm H₂O 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 H₂O was not found to be beneficial in seriously ill patients receiving IPPV (Scott et al. 1972). NEEP was found to have no clinical application due 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 or chronic obstructive pulmonary disease leading to edema, which may be treated with positive airway pressure (Bhattacharya et al 2016).

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

Materials and 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 IP xylazine (XylaMed™ xylazine injection, MWI, Boise, ID, USA), 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 due to the pharmacological response of pulmonary capillaries.

A tracheostomy was performed and the trachea was intubated with a plastic tube (2.2 mm OD, 1.3 mm ID) 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 exposures 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 temperature of the rats. The rats were scanned by ultrasound for 5 min followed by euthanasia 5 min later.

The rats were able to breathe spontaneously through the tracheostomy tube. For normal intermittent positive pressure ventilation (IPPV), a rodent ventilator (TOPO Dual Mode ventilator, Kent Scientific, Torrington, CT, USA) was connected by a tubing TEE connector after initiating the ventilator function. The spontaneous breathing response in these anesthetized rats immediately synchronized to the ventilator without concomitant use of respiration paralysis. The settings were as recommended for rats in the operator's manual, which were designed to simulate normal breathing. Respiration rate was set to 75 breaths per minute, with 25% inspiration at 15 cm H₂O. For generation of 4 cm H₂O PEEP during IPPV, a bottle of water containing 4 cm of water was attached to the expiration port so that the expired gas bubbled up from the bottom of the bottle. For generation of -4 cm H₂O NEEP during IPPV, a 4 L vacuum bottle was attached to the same port. The vacuum bottle was a modified set up normally used for aspiration, using a vacuum pump (model 400-3910, Barnant Co. Barrington IL USA) with a valve to regulate the pressure in the bottle to achieve the desired differential (NEEP) below atmospheric pressure. The NEEP was monitored in cm H₂O by a low pressure gauge (± 5 PSI Traceable, Fisher Scientific Co. Houston TX USA).

Ultrasound

A Phillips HDI 5000 (Philips Healthcare, Andover MA USA) diagnostic ultrasound machine was used for B mode scanning in the same setup as described previously (Miller, 2012), except that a new Philips ENTOS CL15-7 Compact Linear Array probe was used. This probe gave slightly different Mechanical Index (MI) settings such that, at the maximum output setting, the on screen MI (MI_{OS}) was 1.1 for the new probe, compared to 0.9 for the older probe. The probe was set up in the water bath using an adjustable gantry to aim through an intercostal space at the right cranial or medial lobe of the rat lung. Scanning used 2 cm image depth, 1 cm focal depth, and 39 frames per second. The pleural surface was at a depth of about 5-6 mm, with the probe partially in contact with the skin. The pulses of ultrasound had a center frequency of 7.6 MHz with a pulse repetition frequency of 10 kHz. The MI_{OS} was set using the "output" toggle switch to 0.21 for aiming, and then quickly raised by toggling the switch to MI_{OS} = 0.37, 0.52, 0.7, 0.9 or 1.1 (maximum for this probe) for 5 min of scanning. For the IPPV-NEEP ventilation, a sham condition was tested to determine if the NEEP procedure would induce any detectable PCH, and the image was frozen (MI_{OS}=0) after aiming. For IPPV-PEEP, no PCH was seen for MI_{OS} = 0.52 or 0.7, and a separate MI_{OS}= 0 sham was not performed. The ultrasound pulse parameters were measured under free field conditions using a calibrated hydrophone with a 0.2 mm sensitive spot (model HMA-0200, Onda Corp., Sunnyvale, CA). The pulse pressure signals at a depth corresponding to the surface of the lung were digitized on an oscilloscope and transferred to a computer for determination of pulse characterization parameters. The water values were derated by 1.2 dB/cm/MHz (Miller et al, 2015a) to obtain in situ values. The derated peak rarefactional pressure amplitudes (PRPA) were used to calculate the in situ MI (MI_{IS}) as the PRPA divide by the square root of 7.6 MHz, and pulse waveforms were used to calculate the spatial peak pulse average intensity (I_{SPPA}). Exposure parameters for each MI_{OS} setting are

listed in Table 1. In addition, the ultrasonic radiation surface pressure (P_{URS}) was calculated and listed in Table 1, as described in Miller (2016). This P_{URS} model assumes perfect reflection at the air-tissue interface at the lung surface, owing to the large differential in acoustical impedance. The reflection produces a steady state (i. e. without acoustical cyclic variation) radiation surface pressure P_{URS} at the tissue-air barrier given by

$$P_{URS} = \frac{2I_{sppa}}{c_{tis}}, \quad (1)$$

in which I_{sppa} is the incident ultrasonic intensity and c_{tis} is the speed of sound in the tissue (Nyborg, 1978; Duck, 1998; Wang and Lee, 1998).

Measured endpoints

A pulse oximeter probe (SurgiVet V3395 TPR, Smiths Medical Inc. St Paul, MN USA) was placed on a front paw before and after the scanning to measure heart rate and SpO_2 . Exposure related endpoints included the percentage of the bright-line image of the lung surface, which was involved with comet tail artifacts (CTAs) at the end of exposure. Upon euthanasia, the trachea was tied off, and the lungs were removed. The right lobes, which were the target of the imaging, were then examined and photographed using a stereomicroscope with digital camera (Spot Flex, Diagnostic Instruments Inc., Sterling Heights, MI USA). The photographs of the lungs were used to measure the approximate area of the region of PCH on the lung surface by manual outline of the region, using image analysis software (Spot v. 5.1, Diagnostic Instruments, Inc., Sterling Heights, MI USA).

Experimental plan and statistics

The study involved 20 groups of 8 rats each. These were segregated into spontaneous breathing (Spont) with sham, IPPV with sham, IPPV with 4 cm H_2O PEEP, and IPPV with -4 cm H_2O NEEP with sham. For each condition, 4-5 MI_{OS} values were used in different groups in an effort to determine the exposure response trends and the PCH threshold. The primary exposure parameter was the PRPA, because this is the regulatory parameter used in the MI, but other important parameters are also listed in Table 1. Because of the hit-or-miss nature of the PCH effect near the threshold, the thresholds can be estimated in several different ways. Here, thresholds were estimated by statistical determination of significance against shams ($p < 0.05$), which were the same as the occurrence thresholds using the Z test with Yates correction (i. e., occurrence in 5 of 6 rats was significant), as the mean of the lowest MI_{OS} with significant PCH area, and the next lower MI_{OS} setting. In addition, thresholds were estimated by linear regression of the mean PCH areas for groups with any PCH against PRPA; this method has the advantage that all PCH-positive observations are included, but can yield lower thresholds by including groups with statistically non-significant PCH relative to shams. Finally, the conditions were compared by 2 way analysis of variance in two tests: 1) spontaneous breathing and IPPV, and 2) IPPV, IPPV with PEEP and IPPV with NEEP.

Results

The rats were randomly selected for each condition, which gave groups with uniform mean weights, see Table 2. Results of the physiological monitoring with the pulse oximeter also are listed in Table 2. The heart rate increased significantly between the before (Pre) and after (Post) results for most conditions. The pulse oximeter oxygen saturation (SpO_2) values increased for the IPPV, IPPV sham and IPPV plus PEEP.

The measured endpoint results are presented in Table 3. The width of comet tail artifacts (CTAs) were measured as a percentage of the width of the bright line surface image, which closely tracked the length of PCH on the lungs. Figure 1 compares the percentage of CTAs for the maximal MI_{OS} of 1.1. IPPV decreased the CTA effect seen in the image, particularly for IPPV+PEEP, which greatly reduced PDUS-PCH (Figure 2). IPPV+NEEP restored the CTA effect to that seen with spontaneous breathing (Figure 3).

The primary measure was the PCH area (see Table 3). PCH was observed in 2 or more rats for all the groups, except none was seen for IPPV+PEEP at MI_{OS} of 0.7 and 0.52, or shams. The proportions of positive findings for each group are listed in Table 3, and the statistical significance relative to shams for the PCH area data are noted by an asterisk. Thresholds can be defined by the significance criterion as the mean of the lowest scan PRPA with significant PCH and the next lower PRPA, which are listed in Table 3. The significance threshold was 1.3 MPa for spontaneous breathing and IPPV, similar to the previous result without intubation of 1.2 MPa (Miller et al. 2015a). IPPV + PEEP increased the threshold to 2.05 MPa, while IPPV + NEEP reduced it to 0.96 MPa. Thus the threshold shift from PEEP to NEEP was equivalent to a full 6 dB change (three MI_{OS} exposure steps, Table 1). Thresholds can also be defined by the zero crossing of a linear regression on all means with non-zero PCH, see Figure 4. By this method, the thresholds were lower, 0.9–1.1 MPa, except for IPPV+PEEP with 1.8 MPa. The conditions can also be compared by analysis of variance. For ANOVA comparing spontaneous breathing and IPPV, the IPPV significantly reduced the PCH ($p<0.05$). For ANOVA comparing end expiratory pressures, the PCH was significantly reduced by PEEP ($P<0.02$) and increased for NEEP ($P<0.001$), relative to IPPV.

Discussion and Conclusion

The influence of positive pressure ventilation on pulmonary capillary hemorrhage (PCH) induced by diagnostic ultrasound induced was evaluated. IPPV reduced the magnitude of PCH relative to spontaneous breathing, but the threshold for PCH was the same (Table 3). The modest reduction in PCH magnitude likely was due to the application of the 15 cm H_2O intermittent positive pressure for 25% of the time (a typical setting to assure lung inflation) for the IPPV condition. When PEEP was applied with IPPV, the magnitude was further reduced and the threshold was increased. Conversely, when NEEP was applied with IPPV, the magnitude of PCH was increased and the threshold reduced relative to IPPV. Although the increase in PCH magnitude might have been expected, due to the possible enhancement of bleeding from the capillary hemorrhages by the negative pressure, the large change in threshold suggests a quantitative alteration (independent of bleeding) of the operative mechanism initiating PCH. The 4 cm H_2O variation in pressure is quite small (e. g.

atmospheric pressures is $\sim 1,000$ cm H₂O). However, the changes in internal air pressure acting on the lung surface capillaries by application of 4 cm H₂O PEEP and -4 cm H₂O NEEP are comparable in magnitude to the expected ultrasonic radiation surface pressure (P_{URS}) on the surface of the lung (Table 1) for the threshold changes (Table 3). These results support the hypothesis that positive airway pressure mitigates the ultrasonic application of stress responsible for PCH, consistent with the ultrasonic radiation surface pressure hypothesis.

Another factor, which could be affected by modulation of lung air pressure during ventilation, is ultrasound transmission into the lung. As noted by Miller (2016) increased transmission into the lung would reduce the ultrasonic radiation surface pressure resulting from reflection. In a study of the effect of lung inflation, O'Brien et al. (2002) showed that inflating the lungs during pulsed ultrasound essentially eliminated PCH, while deflation led to maximal PCH. Inflation was created during a pause in IPPV by injecting 3 ml (partial inflation) or 6 ml of air into the tracheal tube using a syringe, and deflation was allowed by opening the tracheal tube to the atmosphere (i. e. not to application of negative pressure). This test was not the same approach as IPPV with PEEP or NEEP used here, nor were the air pressures well known. However, the result of reduced PCH, due to increased pulmonary air pressure by added air volume, is in general agreement with our findings. O'Brien et al. attributed the changes in PCH to changes in transmission of ultrasound into the lung without a specific reference to physical mechanisms for PCH. The inflation reduced transmission into the lung, due to the higher volume fraction of gas, and the deflation increased transmission into the lung.

The potential inflation or deflation due to PEEP or NEEP in this study may be estimated by consideration of lung compliance. The total (lung and chest) compliance is given by $1.56 W^{1.04}$, in which W is the weight in kg, and the result is in ml/cmH₂O (Stahl, 1967). For our 0.24 kg rats, this gives 0.36 ml/cmH₂O. For 4 cmH₂O pressure changes in PEEP or NEEP, the volume response would be 1.44 ml. Note that the IPPV pressure was 15 cm H₂O, which may provide a transient inflation of up to 5.4 ml. The total lung capacity (given by $53.5 W^{1.06}$) is about 12 ml, so the PEEP or NEEP would have minimal inflating or deflating impact, and thus minimal effects on ultrasound transmission. The results of this present study are therefore more consistent with the hypothesis of capillary stress changes as the explanation of the influence of PEEP and NEEP on PDUS-PCH than with the transmission hypothesis.

In conclusion, the results of this study are consistent with a capillary stress model for the action of pulsed ultrasound leading to PCH: PEEP reduced or NEEP enhanced trans capillary stress, decreasing or increasing PCH, respectively. This supports the hypothesis of a role for ultrasonic radiation pressure in the etiology of PDUS-PCH. A more detailed evaluation of potential mechanisms, such as P_{URS} , without a more detailed model of the tensile stresses produced in the blood-air-barrier segment of pulmonary capillary walls by the ultrasonic pressure and the gas pressure is outside the scope of the current manuscript. Pulmonary capillaries are highly branched and cover the entire alveolar surface, which presents a complex modeling problem. The full clarification of the roles of ultrasound

transmission into the lung and of the modulation of capillary vulnerability by small changes in intra-alveolar air pressure is a difficult problem needing further research.

Acknowledgments:

This study was supported by the US National Institutes of Health, National Heart Lung and Blood Institute, via grant number HL116434. The information contained herein does not necessarily reflect the position or policy of the US government, and no official endorsement should be inferred.

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Figure 1.

A chart of the percentage of comet tail artifacts seen across the bright-line surface image of the lung after scanning at the maximum on-screen Mechanical Index setting of 1.1 for: spontaneous breathing through the tracheal tube (Spont); intermittent positive pressure ventilation (IPPV); IPPV plus positive end expiratory pressure (PEEP); IPPV plus negative end expiratory pressure (NEEP).

Figure 2.

For positive end expiratory pressure (IPPV+PEEP), the 1.1 Mios pre-scan image (upper left) displays the bright line surface image of the lung at a depth 5 mm, and the post-scan image (upper right) displays break-up of the bright line with several small comet tail artifacts. The photograph of the lung (bottom) at the scan plane shows the pulmonary capillary hemorrhage areas as bright red spots (scale bar 2 mm).

Figure 3.

For negative end expiratory pressure (IPPV+NEEP), the 1.1 Mios pre-scan image (upper left) displays the bright line surface image of the lung at a depth of 5 mm, and the post-scan image (upper right) displays virtually complete break-up of the bright line with large comet tail artifacts blending together. The photograph of the lung (bottom) at the scan plane shows the bright red pulmonary capillary hemorrhage areas filling the scan plane (scale bar 2 mm).

Figure 4.

Plot of the dependence of pulmonary capillary hemorrhage (PCH) area on the in situ peak rarefactional pressure amplitude. Use of intermittent positive pressure ventilation (IPPV) with positive (PEEP) or negative (NEEP) end expiratory pressure greatly modifies the response to diagnostic ultrasound scanning. For all conditions, the PCH increases above an apparent threshold specific to the condition (Table 3).

Table 1.

In situ exposure parameters for the on screen Mechanical Index (MI_{os}) settings used here, including peak rarefactional pressure amplitude (PRPA), peak mean pressure amplitude (PMPA), and spatial peak pulse average intensity (I_{SPPA}). The in situ MI (MI_{is}) was estimated by dividing the PRPA by the square root of 7.6 MHz. The ultrasonic radiation surface pressure (P_{URS}) was calculated from Eq. 1.

Setting		PRPA	PMPA	I_{SPPA}	P_{URS}
MI_{os}	MI_{is}	MPa	MPa	W cm ⁻²	cm H ₂ O
1.1	0.78	2.2	3.3	168	22.7
0.9	0.70	1.9	3.0	140	18.9
0.7	0.54	1.5	2.3	91.3	12.3
0.52	0.41	1.12	1.6	56.3	7.6
0.37	0.29	0.81	1.0	28.2	3.8

Table 2.

Measured physiological parameters for the four different conditions and shams: weight, heart rate (HR) and peripheral blood oxygen saturation (SpO₂) before (Pre) and after (Post) the test. (* p<0.05, # p<0.005).

		Weight	HR Pre	HR Post	SpO ₂ Pre	SpO ₂ Post
Group	n	g	BPM	BPM	%	%
Spontaneous	32	246 ± 17	273 ± 29	288 ± 29*	73.3 ± 10.0	74.0 ± 8.5
Sham	8	257 ± 21	276 ± 32	294 ± 30*	75.9 ± 3.7	77.0 ± 5.4
IPPV	24	244 ± 14	243 ± 24	264 ± 36 [#]	73.7 ± 9.2	80.6 ± 7.1 [#]
IPPV Sham	8	248 ± 19	272 ± 27	268 ± 23*	73.1 ± 7.1	80.4 ± 5.9*
IPPV+PEEP	32	247 ± 21	234 ± 28	264 ± 36 [#]	74.7 ± 8.1	78.8 ± 7.2*
IPPV+NEEP	40	249 ± 18	248 ± 23	275 ± 28 [#]	73.8 ± 6.7	72.8 ± 9.9
NEEP Sham	8	250 ± 25	254 ± 24	269 ± 23	77.0 ± 8.8	74.6 ± 6.8

Table 3.

Pulmonary capillary hemorrhage results for diagnostic ultrasound scanning at the indicated MI_{os} : US CTA, ultrasound image comet tail artifact width; CTA %, the percentage of CTAs in the lung surface image. Statistical significance relative to the sham is indicated by *, and the threshold based on significance is the mean of the lowest PRPA with a significant PCH and the next lower PRPA. The intercept for the linear regression on the means (see Fig. 2) approximates the threshold PRPA taking all the positive data into account, with the corresponding coefficient of determination (r^2).

Condition	MI_{os}	US CTA mm	CTA %	Positive Proportion	Area mm^2	Significance MPa	Intercept MPa (r^2)
Spontaneous	1.1	14.4±1.9	87±12*	8/8	14.5±9.5*		
Spontaneous	0.9	9.2±3.3	60±21*	8/8	14.2±8.5*		1.0 (0.39)
Spontaneous	0.7	8.2±3.3	54±23*	8/8	7.8.3±5.8*	1.31	
Spontaneous	0.52	1.3±2.0	8±12	3/8	1.4±2.2		
Sham	0.28	0	0	0/8	0		
IPPV	1.1	8.3±5.1	60±36*	7/8	9.3±6.6*		
IPPV	0.9	3.9±4.4	23±24*	6/8	3.6±5.4*		1.1 (0.30)
IPPV	0.7	4.8±4.1	34±23*	7/8	3.4±2.9*	1.31	
IPPV	0.52	1.3±1.6	9±10	4/8	0.3±0.4		
Sham	0.28	0	0	0/8	0		
IPPV+PEEP	1.1	2.7±2.8	18±20*	6/8	1.6±3.2*		
IPPV+PEEP	0.9	1.3±2.7	10±19	2/8	0.5±0.8	2.05	1.8 (0.06)
IPPV+PEEP	0.7	0	0	0/8	0		
IPPV+PEEP	0.52	0	0	0/8	0		
IPPV-NEEP	1.1	15.0±2.2	90±13*	8/8	26.8±6.4*		
IPPV-NEEP	0.9	13.8±3.7	84±21*	8/8	26.1±10.8*		
IPPV-NEEP	0.7	8.2±3.8	55±21*	7/8	11.2±7.6*		
IPPV-NEEP	0.52	3.8±2.4	28±17*	7/8	4.8±8.1*	0.96	0.9 (0.69)
IPPV-NEEP	0.37	0.6±1.2	4±9	2/8	0.8±2.3		
Sham	0.28	0	0	0/8	0		