¹D. John Jabaraj, ¹Mohamad Suhaimi Jaafar

Theoretical Modelling of Alveolar Resonance Mechanism of Ultrasound-Induced Lung Haemorrhage

Dept. of Medical Physics, Faculty of Physical Sciences, University Sains Malaysia, 11800 USM, Penang, Malaysia

e-mail: jojab77@yahoo.com

The possibility of the ultrasound-induced lung haemorrhage occurring in adult human during diagnostic ultrasound examination is studied here. This study is based on the hypothetical alveolar resonance mechanism of the ultrasound-induced lung haemorrhage. The alveolar wall is initially modelled here as a square membrane with fixed-boundary, and then theoretically subjected to vibration analysis. The equation of threshold pressure for the occurrence of ultrasound-induced lung haemorrhage is derived. A comparison test against past experimental data validates the use of the square membrane model of the alveolar wall in studying the ultrasound induced lung haemorrhage. This study predicts that the ultrasound-induced lung haemorrhage in adult human can be prevented if the ultrasound frequency is kept above 1.69 MHz while the *Mechanical Index* does not exceed 1.9.

Key words: Ultrasound-induced lung haemorrhage; alveolar resonance mechanism; resonant frequency; threshold pressure; theoretical modelling.

Introduction

The Ultrasound-Induced Lung Haemorrhage

The ultrasound (US) at diagnostic exposure level is detrimental as it is shown to cause lung haemorrhage in mice, rats, rabbits, monkeys and pigs [1, 2]. Nevertheless, there is no evidence of the US-induced lung haemorrhage occurring in human, possibly due to the lack of experimental studies. Only a single study reports that US-induced lung haemorrhage does not occur in humans at 3.5 MHz minimum frequency and maximum pressure of 2.4 MPa [3].

Mechanical mechanism (non-thermal effects) is believed to be responsible for the US-induced lung haemorrhage [4]. The mechanism known as inertial cavitations of micro-bubbles has been widely researched. However, several studies have ruled out it from being the mechanism of the US-induced lung haemorrhage [5, 6].

Alveolar Resonance Mechanism

There is a hypothetical mechanical mechanism that may explain the US-induced lung haemorrhage [4]. This mechanism is known as the alveolar resonance mechanism. The alveolar resonance mechanism suggests that the US wave's propagation in the lungs causes alveolar oscillation [7]. The alveolar structure deforms rhythmically and produces local stresses to its own tissues [8]. This causes detrimental strain on the tissues and damages it. Nevertheless, ter Haar [9] states that the resonance of large gas bodies such as the alveoli ($\sim 50 \mu\text{m}$) is different than the inertial cavitations of microbubbles ($\sim 1 \mu\text{m}$) in respect to diagnostic US frequency range.

The mechanism of alveolar resonance, for producing US-induced lung haemorrhage, have not been explored experimentally or theoretically [9]. A thorough survey of literature gave no indication that the alveolar resonance mechanism hypothesis has been tested or studied.

The Strain in Alveolus

The elastic tension of the alveolar wall depends on the strain caused by normal tidal breathing. During normal tidal breathing of 20% *Total Lung Capacity* (TLC) onwards, the alveolus is stretched slightly, resulting in a linear strain from 0 - 0.05 [10].

Belete [11] states that cell wounding in parenchyma tissue occurs significantly at linear strain of 0.08. The linear strain forms fractures in the plasma membrane of the alveolar epithelial cells [12]. This linear strain of 0.08, that damages elements within the alveolar wall and cause haemorrhage, will be called here as the yield linear strain.

Methods

Modelling of the Alveolar Wall Structure

The defining structure of the alveolus is its wall. Several assumptions were made concerning the alveolar wall and its behaviour for the purpose of modelling.

The alveolar wall contains elastin fibres and plasma membrane (with lipid bi-layers) [13]. If the deformation of the alveolar wall is reversible and small, then it obeys the Hooke's Law [14]. Thus, the alveolar wall is assumed to be isotropic and linearly elastic. The linear theory of vibration is assumed to be applicable to the alveolar wall.

The alveolar wall is further assumed as a square membrane with fixed boundary. The facets of the alveolar wall are in reality shaped as flat irregular pentagon [15]. However, for simplification purposes, the shape of the alveolar wall facet is modelled here as a square. The alveolar wall is modelled as flat membrane instead as plates because its stiffness is small [16]. The alveolar wall is shared among alveoli. This provides radial support to the alveolar wall facet at its edges [17].

Fundamental Frequency of Modelled Alveolar Wall

The facet of the alveolar wall is modelled as square membrane model. The resonant frequency for square membrane model is [18];

$$f_{n_x, n_y} = \frac{1}{2} c_T L^{-1} (n_x^2 + n_y^2)^{1/2} \quad (1)$$

The resonant frequency mode is denoted as n_x , n_y and L is the radius, while c_T is the transverse wave velocity on alveolar wall.

Forced Vibration of the Modelled Alveolar Wall

At fundamental mode, the point in the centre of membrane and its deflection imitates the motion of the single degree of freedom (SDOF) vibration. According to Bachmann [19], the vibration of a continuous system at fundamental frequency can be approximated as an equivalent SDOF vibration.

If the membrane model of the alveolar wall is forced to vibrate at fundamental mode by the external US waves, then the resonant amplitude is [20];

$$Z_{max} = \frac{F_o \cdot Q}{\omega_o^2 m_{eq}} \quad (2)$$

with F_o as rarefaction peak force of US waves. The angular fundamental frequency of the membrane model is denoted as ω_o while its equivalent mass is m_{eq} . The equivalent mass depends on the shape of the membrane vibration at fundamental mode. The quality (Q) factor of the vibrating system is denoted as Q .

As the US wavelength is larger than the dimension of alveolar wall surface area, it can be assumed that the force imparted on the surface by the US wave is uniformly distributed. Thus, the peak rarefaction pressure (P_o) of US waves applied to a membrane surface area (A) is related to the peak rarefaction force (F_o) by; $P_o = F_o / A$. Thus Equation (2) morphs into;

$$Z_{max} = \frac{P_o \cdot Q}{\omega_o^2 \sigma_{eq}} \quad (3)$$

The equivalent area density is the equivalent mass over area,

$$\sigma_{eq} = m_{eq} / A. \quad (4)$$

The Q-factor

The Q-factor of membrane is approximated to be due to membrane's support loss only [21]. Hence the Q-factor of vibrating square membrane at fundamental mode is (Appendix A),

$$Q = Q_{support} = 0.34(L / d) \quad (5)$$

where d is the thickness and L is the side-length of membranes.

The equivalent area density

The equivalent mass at fundamental mode for the square membrane is [22];

$$m_{eq} = 0.40 \rho d A \quad (6)$$

Therefore, the equivalent area density at fundamental mode for the vibrating square membrane is,

$$\sigma_{eq} = 0.40 \rho d \quad (7)$$

where the density is denoted as ρ while d is thickness and A is the surface area

Relation between Resonant Amplitude and Areal Strain

The alveolar wall membrane is modelled as a two-dimensional thin flat elastic membrane. The type of strain analyzed here will be the areal strain;

$$\varepsilon = (A_1 - A_0) / A_0 \quad (8)$$

The initial area is denoted as A_0 while A_1 is the deformed area. The square membranes' shape while at rest is a flat square. Thus, the initial area is,

$$A_0 = L^2 \quad (9)$$

where L is the side-length.

The membranes' shape at fundamental mode is a square based dome (Fig. 1) [18]. If the height (Z) is smaller than the dimension of the membrane, then the shape can be simplified into a square based pyramid, as an approximation (Fig. 1). Thus, the deformed area is;

$$A_1 = 2Lp \quad (10)$$

where the slant height

$$p = [(Z)^2 + (L / 2)^2]^{1/2} \quad (11)$$

The areal strain at resonance (ε_r) for deformed square membrane due to resonant amplitude (Z_{max}) in the fundamental vibration mode is analyzed by applying Equations (9-11) into Equation (8).

$$\varepsilon = (A_1 - A_0) / A_0$$

$$\varepsilon_r = \frac{(2L[(Z_{max})^2 + (L/2)^2]^{1/2}) - (L^2)}{(L^2)}$$

Resonant amplitude at fundamental mode:

$$Z_{max} = \frac{1}{2}L[\varepsilon_r^2 + 2\varepsilon_r]^{1/2} \quad (12)$$

Figure 1. Square membrane under deformation at fundamental frequency mode (left) and square based pyramid as an approximation (right).

Results

Fundamental Frequency

The fundamental frequency of the square membrane model occurs when mode is $n_x = n_y = 1$. The transverse wave velocity on alveolar wall is determined to range from 0 to 489 m/s [23]. The diameters of the alveolus for the adult mouse and human are 40 - 80 μm and 200 - 400 μm , respectively [24]. By utilizing the Equation (1), the fundamental frequencies of the square membrane model of alveolar wall for adult mouse is calculated to be 0 - 8.64 MHz, while for the adult human it is 0 - 1.73 MHz.

The Threshold Pressure Equation

The minimum external driving waves' pressure that will result in enough resonance amplitude to achieve the yield strain in the membrane model of alveolar wall and damage its components, will be called here as the threshold pressure. This

represents the threshold pressure of the US waves that experimentally produce detectable lesions of US-induced lung haemorrhage in animals.

The threshold pressure equation for producing damage in the square membrane model of the alveolar wall is derived by substituting Equation (5), (7) and (12) into Equation (3);

$$\begin{aligned}
 Z_{\max} &= \frac{P_o \cdot Q}{\omega_o^2 \sigma_{eq}} \\
 P_o &= \omega_o^2 \sigma_{eq} Q^{-1} Z_{\max} \\
 &= (2\pi f_{1,1})^2 (0.40 \rho d) (0.34 L / d)^{-1} (1/2 L [\epsilon_r^2 + 2\epsilon_r]^{1/2}) \\
 P_o &= 23.223 f_{1,1}^2 d^2 \rho [\epsilon_r^2 + 2\epsilon_r]^{1/2}
 \end{aligned} \tag{13}$$

Observe that the linear fundamental frequency ($f_{1,1}$) of the square membrane model is related to the angular fundamental frequency by, $\omega_o = 2\pi f_{1,1}$.

The threshold pressure equation should be concerning the minimum pressure for inducing damage. Hence, the minimum density value of the alveolar wall (soft tissue) of 1026 kg m^{-3} [25] is applied into Equation (13). Furthermore, the minimum areal strain of resonance of 0.0639 (Appendix B) is also substituted in Equation (13). Thus Equation (13) is reduced to;

$$P_o = 0.00865 f_{1,1}^2 d^2 [\text{MPa}] \tag{14}$$

The threshold pressure formulas for specific mammals are obtained by inserting the minimum alveolar wall thickness values into Equation (14).

Validation of the Square Membrane Model of the Alveolar Wall Resonance

The experimental data of past US-induced lung haemorrhage studies were compiled by Church & O'Brien [1]. Only the lowest threshold pressure value at each frequency from each experimental study was chosen. There is however only sufficient data for the adult mouse (Appendix C) and these were plotted together with the square membrane model curve for the adult mouse, in the threshold pressure vs. fundamental frequency graph (Fig. 2). The minimum alveolar wall thickness value for the adult mouse is $3 \mu\text{m}$ [26].

The MI Index

The mechanical index, $MI = 1.9$ is plotted in the threshold pressure vs. fundamental frequency graph for the square membrane model of human alveolar wall, in order to analyze the MI relation with the US-induced lung haemorrhage for human (Fig. 3). The minimum alveolar wall thickness value for the adult human is $10 \mu\text{m}$ [26].

Figure 2. The threshold pressure vs. fundamental frequency curve of the square membrane model of adult mouse alveolar wall together with the plotted past experimental data of ultrasound induced lung haemorrhage in the adult mouse [1]. An experimental data point (2.8, 3.6) is clearly an outlier and hence is omitted in the chi-square calculation. Chi-square (χ^2) of experimental data against the square membrane model is below the critical χ^2 (0.05 sig.).

Figure 3. The threshold pressure vs. fundamental frequency curve of the square membrane model of adult human alveolar wall together with the plotted MI = 1.9 limit line.

Discussion

The fundamental frequencies of the square membrane model of alveolar wall for adult mouse and human is determined to be within the diagnostic US frequency range. The threshold pressure equation developed here for the square membrane model of

the alveolar wall, is for the fundamental mode only. Beards [27] states that if a structure can survive the fundamental mode resonance, it will be able to survive the other resonance mode too (at that same frequency values). Thus, the study of the threshold pressure at fundamental mode of the square membrane model of alveolar wall is sufficient enough for determining the theoretical occurrence of US-induced lung haemorrhage.

The alveolar wall thickness and size varies in species. According to this study, the threshold pressure for US-induced lung haemorrhage depends primarily on the species' alveolar wall thickness. ECMUS [4] supports these findings by stating that US-induced lung haemorrhage depends on the species of animal.

The Fig. 3 shows that if diagnostic US imaging for humans is kept above 1.69 MHz, the US induced lung haemorrhage will not occur when $MI \leq 1.9$. This support the result of the single study of the US induced lung haemorrhage on human [3]. The US medical imaging in the abdominal and thoracic regions, utilizes the frequency of ≥ 2 MHz [28, 29]. Hence, the US-induced lung haemorrhage is prevented during diagnostic US imaging of the adult human if the FDA regulation of $MI \leq 1.9$ is obeyed.

The chi-square comparison test in Fig. 2, shows that the square membrane model of the alveolar resonance to be acceptable with 95% probability. The square membrane model is found valid and describes the US induced lung haemorrhage adequately. Therefore, the alveolar resonance mechanism can be duly considered as a serious candidate mechanism for the US-induced lung haemorrhage based on the theoretical validation of this membrane model.

The alveolar wall was assumed as square membrane with fixed boundary. In reality, the alveolar wall borders are supported but the shape is pentagonal, and so the results in this study might vary somewhat. The alveolar wall was further assumed to be isotropic and linearly elastic. This is valid as alveolar wall contains elastin fibres while the occurring strains are small.

Conclusions

Square membrane model of the alveolar resonance mechanism is shown to be theoretically valid. Therefore, the alveolar resonance mechanism explains adequately the US-induced lung haemorrhage. According to this study, the US-induced lung haemorrhage do not occur in human at >1.69 MHz if MI is ≤ 1.9 .

Appendices

Appendix A: The Q-factor of support of the square membrane

The support loss Q-factor for square membrane when support is semi-infinite large body as according to Naeli & Brand [30];

$$Q_{support} = 0.34(L / d)^3$$

The side-length is L and the thickness is d . If the support is as thin as the membrane (as in alveolar wall where its support comes from adjacent alveolar walls), then the cubic term becomes linear. This is because the support is not rigid and isolated anymore against in-plane bending of the resonator [31].

$$Q_{support} = 0.34(L / d)$$

Appendix B: The areal strain in alveolus

The deformation in a system produces strain. The strain is measured by the ratio of dimensional change in the system. The linear strain that quantizes the longitudinal changes is;

$$\alpha = (L_1 - L_0) / L_0$$

The areal strain that quantizes the surface distortions is;

$$\varepsilon = (A_1 - A_0) / A_0$$

The initial length and area are L_0 and A_0 , respectively while the length and area after deformation are L_1 and A_1 . The relation between areal strain and linear strain can be obtained starting with the stretch ratio equation. The stretch ratio is [32]:

$$\lambda = (L_1 / L_0) = (A_1 / A_0)^{1/2}$$

Thus the relationship between linear strain and areal strain can be derived as;

$$\lambda = (A_1 / A_0)^{1/2}$$

$$\lambda - 1 = (\varepsilon + 1)^{1/2} - 1$$

$$\alpha = (\varepsilon + 1)^{1/2} - 1$$

During normal tidal breathing, the linear strain changes between $0 < \alpha < 0.05$ [10]; and so the areal strain of tidal breath is;

$$0 \leq \alpha \leq 0.05$$

$$0 \leq [(\varepsilon + 1)^{\frac{1}{2}} - 1] \leq 0.05$$

$$0 \leq \varepsilon \leq 0.1025$$

The wounding and breaks in cells in the plasma membrane of the alveolar epithelial cells occurs at the yield linear strain of $\alpha = 0.08$ [11, 12]. Thus the yield areal strain is;

$$\alpha = 0.08$$

$$[(\varepsilon + 1)^{\frac{1}{2}} - 1] = 0.08$$

$$\varepsilon = 0.1664$$

Appendix C: The experimental threshold pressure for adult mouse

The data is obtained from Church & O'Brien WD [1] and tabulated in Table 1.

Table 1. Selected lowest threshold pressure at certain frequencies of the US-induced lung haemorrhage experimental data for adult mouse from the compiled data by Church & O'Brien WD [1].

	Frequency (MHz)	Threshold Pressure (MPa)
Adult mouse	1.1	0.4
	1.2	0.7
	1.2	1.1
	2.3	0.6
	2.3	0.7
	2.3	0.8
	2.8	3.6
	3.5	1.3
	3.7	1.0
	3.7	1.4
	5.6	3.0

Acknowledgements

This work was supported in part by the USM PGRS Grant and the UniKL Financial Assistance Scheme. D. John Jabaraj thanks his wife, K. Suganthi Maria, for her unfathomable love and encouragements along the arduous path of seeking knowledge.

References

- [1] C.C. Church, W.D. Jr. O'Brien. Evaluation of the threshold for lung hemorrhage by diagnostic ultrasound and a proposed new safety index. *Ultrasound Med Biol* May. 2007;33(5):810-8
- [2] A.F. Tarantal, D.R. Canfield. Ultrasound-induced lung hemorrhage in the monkey. *Ultrasound Med Biol*. 1994;20(1):65-72
- [3] R.S. Meltzer, R. Adsumelli, W.H. Risher et al. Lack of lung hemorrhage in humans after intraoperative transesophageal echocardiography with ultrasound exposure conditions similar to those causing lung hemorrhage in laboratory animals. *J Am Soc Echocardiogr*. 1998;11(1):57-60
- [4] European Committee for Medical Ultrasound Safety (ECMUS). EFSUMB Tutorial: Acoustic cavitation and capillary bleeding. *European Journal of Ultrasound*. 1999;9:277-280
- [5] L.A. Frizzell, J.F. Zachery, W.D. Jr. O'Brien. Effect of pulse polarity and energy on ultrasound-induced lung hemorrhage in adult rats. *J Acoust Soc Am*. 2003;113:2912-2918
- [6] C.H. Raeman, D. Dalecki, S.Z. Child et al. Albunex does not increase the sensitivity of the lung to pulsed ultrasound. *Echocardiography*. 1997;14:553-557
- [7] C.C. Church, E.L. Carstensen, W.L. Nyborg et al. The risk of exposure to diagnostic ultrasound in post-natal subjects-nonthermal mechanisms. *J Ultrasound Med*. 2008;27:565-592
- [8] A.A. Vivino, D.K. Boraker, D. Miller et al. Stable cavitation at low ultrasonic intensities induces cell death and inhibits 3H-TdR incorporation by con-a-stimulated murine lymphocytes in vitro *Ultrasound Med Biol*. 1985;11(5):751-759
- [9] G. ter Haar. Ultrasound bioeffects and safety. *Proc Inst Mech Eng H*. 2010;224(2):363-73
- [10] E. Roan, C.M. Waters. What do we know about mechanical strain in lung alveoli?, *Am J. Physiol. Lung Cell Mol Physiol*. 2011;301L:625-635
- [11] H.A. Belete, L.M. Godin, R.W. Stroetz et al. Experimental Models to Study Cell Wounding and Repair. *Cell Physiol Biochem*. 2010;25:71-80
- [12] N.E. Vlahakis, R.D. Hubmayr. Invited review: Plasma membrane stress failure in alveolar epithelial cells. *J Appl Physiol*. 2000 Dec;89(6):2490-6
- [I3] K. Huang, R. Rabold, B. Schofield et al. Age-dependent changes of airway and lung parenchyma in C57BL/6J mice. *Journal of Applied Physiology*. 2007 January;102

- [14] A.A. Shabana. Theory of Vibration: An Introduction (Mechanical Engineering Series) (Vol 1). Springer-verlag NY; 2nd edition; 1995 December 8. ISBN-10:0387945245
- [15] A.D. Freed, J.P. Carson, D.R. Einstein et al. Viscoelastic Model for Lung Parenchyma for Multi-Scale Modeling of Respiratory System Phase II: Dodecahedral Micro-Model. Pacific Northwest National Laboratory (Battelle); 2012 March
- [16] R. Vepa. Dynamics of Smart Structures. John Wiley & Sons, 2010. p. 178
- [17] J. Mead, T. Takishima, D. Leith. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol. 1970 May;28(5):596-608
- [18] W.C. Elmore, M.A Heald. Physics of waves. Dover Publications Inc; 1985
- [19] H. Bachmann, W.J. Ammann, F. Deischl & J. Eisenmann. Vibration Problems in Structures: Practical Guidelines. Birkhauser Verlag, Berlin; 1995. ISBN-13:978-3764351489
- [20] A. Sinha. Vibration of Mechanical Systems. Cambridge University Press Cambridge, New York; 2010. ISBN-13:978-0-511-77527-7
- [21] K.K. Park, H. J. Lee, P. Crisman et al. Optimum design of circular CMUT membranes for high quality factor in air. IEEE International Ultrasonics Symposium Proceedings; 2008. p. 504-507
- [22] S. Frew, H. Najjar, E. Cretu, VHDL-AMS Behavioural Modelling of a CMUT Element E. Behavioral Modeling and Simulation Workshop (BMAS), IEEE; 2009. p. 19-24
- [23] D.J. Jabaraj, M.S. Jaafar. Theoretical calculation of resonant frequencies of the human alveolar wall and its Implications in ultrasound-induced lung haemorrhage. Inter. Journal of Bioscience, Biochemistry and Bioinformatics 2013;3(1):5-9
- [24] P.M. Treuting, S.M. Dintzis. Comparative Anatomy and Histology: A Mouse and Human Atlas. Academic Press; 1 edition; 2011 December 30. ISBN-13:978-0123813619
- [25] G.D. Ludwig. The Velocity of Sound through Tissues and the Acoustic Impedance of Tissues. J Accous Soc Am. 1950;22:862-66
- [26] H.S. Choi, Y.G. Ko, S.K. Seol et al, Early detection of intralveolar wall thickening induced by intestinal ischemia/perfusion injury in mouse lungs by using phase-contrast x-ray microtomography. The 13th international conference on accelerator & beam utilization (Synchrotron Bio & Medical application); 2009.
- [27] C.F. Beards. Structural Vibration: Analysis and Damping. Butterworth-Heinemann; 1st edition; 1996 June 14. ISBN 0 340 64580 6
- [28] V. E. Noble. Think Ultrasound When Evaluating for Pneumothorax. J Ultrasound Med. 2012;31:501-504

- [29] R.J. Fitzgibbons, A.G. Greenburg. Nyhus and Condon's Hernia. Lippincott Williams & Wilkins; 5th edition. 2001 November 15. ISBN-10: 07817196232001.
- [30] K. Naelia & O. Brand. Dimensional considerations in achieving large quality factors for resonant silicon cantilevers in air. J Appl Physics. 2009;105, 014908.
- [31] M.C. Cross, R. Lifshitz. Elastic wave transmission at an abrupt junction in a thin plate with application to heat transport and vibrations in mesoscopic systems. Physical Review B. 2001;64, 085324
- [32] A. Gefen, D. Elad, R.J Shiner. Analysis of stress distribution in the alveolar septa of normal and simulated emphysematic lungs. J Biomech. 1999 Sep;32(9):891-7