

CHAPTER 1

INTRODUCTION

Many scientific advances led to the discovery of ultrasound. Its history is rooted in the study of sound with Sir Isaac Newton first proposing his theory that sound is a wave in 1687 [Newton, 1687]. In 1877, Lord Rayleigh discussed what is known today as modern acoustics [Rayleigh, 1945]. In 1880, the Curie brothers discovered the piezoelectric effect [Curie and Curie, 1880] which led Paul Langevin to develop one of the first uses of underwater ultrasound at a frequency of about 150 kHz [Hunt, 1982]. The development of ultrasound and echo detection advanced and in the 1920s, Boyle and his colleagues were the first to observe ultrasound-induced gas bubbles forming in liquid, which today is known as cavitation [Boyle and Lehmann, 1926], [Boyle, 1927], [Boyle and Taylor, 1929]. In 1932, the use of ultrasound to therapeutically heat tissues was suggested [Freundlich et al., 1932]. Ten years later, in 1942, the idea to burn focal tissues deep in the body was proposed as a noninvasive neurosurgery technique [Lynn et al., 1942], [Lynn and Putman, 1944]. In the 1950s and 1960s, the use of diagnostic ultrasound equipment for clinical applications started [O'Brien, 1998].

Ultrasound was thought to be relatively safe until 1951 when those working with the development of diagnostic ultrasound equipment became aware of the potential risks to patients [French et al., 1951]. It was also thought that ultrasound did not cause biological damage. However, in the early 1950s, individuals involved in image system developments were concerned about and investigating the potential of ultrasound-induced tissue damage [Fry et al., 1950], [Fry et al., 1951], [Hueter et al., 1956], [Fry, 1958], [Baum, 1956]. More recently, in the late 1980s and early 1990s, lithotripsy experiments indicated that diagnostic ultrasound had the

ability to produce lung damage in mice [Child et al., 1990]. It has also been discovered that ultrasound has the ability to produce lesions on the lungs of animals such as pigs, mice, rabbit, rats, monkeys and dogs [Delius et al., 1987], [Holland et al., 1996], [O'Brien and Zachary, 1994], [O'Brien and Zachary, 1996], [O'Brien and Zachary, 1997], [Zachary et al., 2001], [O'Brien et al., 2002], [O'Brien et al., 2003], [Tarantal and Canfield, 1994]. Figure 1.1 is an image of a lung without a lesion and Figure 1.2 is a lung with a lesion due to ultrasound.

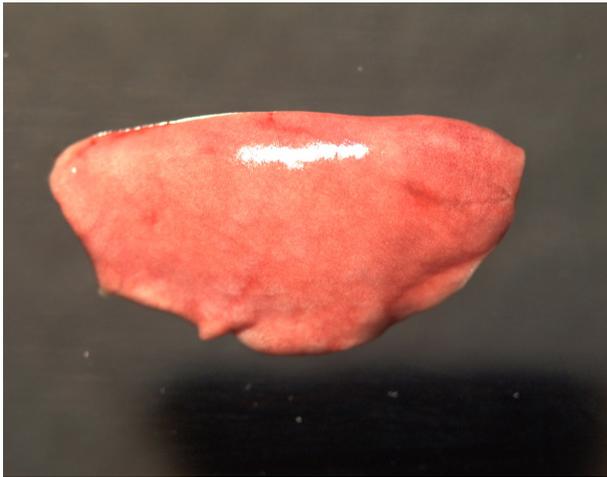


Figure 1.1 Rat Lung Without a Lesion

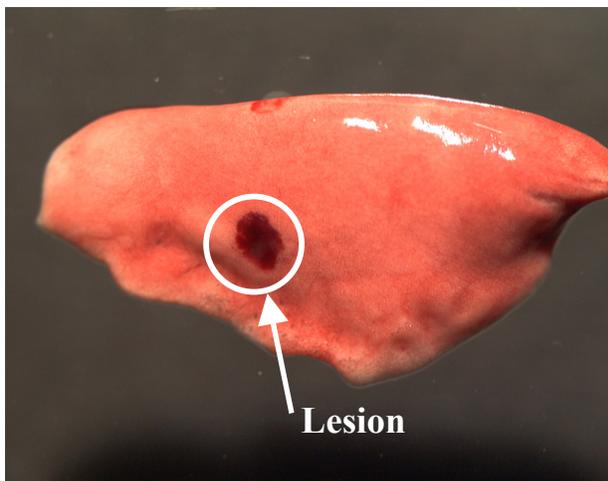


Figure 1.2 Rat Lung With an Ultrasound-Induced Lesion

The proposed mechanism of lung damage caused by ultrasound is a two step process. The initial step occurs when the lung is first punctured by a mechanical force such as radiation force. The propagation of the lesion is thought to occur when the air-blood barrier is disturbed and the air and blood mix and cavitation occurs. The introduction of microbubbles, from the air and the blood causes cavitation.

This discovery of ultrasound lesions on lungs prompted another study to determine the mechanism of lung damage. An *in vitro* study was performed to model and analyze the effect ultrasound has on lung tissue because an *in vitro* study helps in determining the mechanism by attempting to simplify the lung damage process and by focusing only on the acoustic properties without the contributing biological properties. The *in vitro* study is a water-breaking model used to simulate the liquid-gas interface which is common with the tissue-air barrier of lung tissue.

The lung is similar to the water-breaking model because there is a tissue-air barrier. The setup of the water-breaking model has water on one side with a submerged ultrasonic source focused onto the water-air interface. The water in the tissue-breaking model simulates the tissue. The interface where air is present simulates the air from the tissue-air barrier, or the alveolar walls which are composed of epithelia [West, 1996].

The water-breaking study determines the value required to break the water-air interface at a certain distance away from the ultrasonic source. This is performed because the initiation of lung damage is thought to be some mechanical force. Thus, there is interest in determining if there is a relation between the water-breaking study and the initiation step of lung damage.

The water-breaking phenomenon occurs when a sound beam is incident on an interface between two media, the gas and liquid. Initially, a swelling of the surface takes place (first row of Figure 1.3) when the force from the sound beam is less than the threshold force required to

fracture the air-water interface. As the force of the sound beam increases, the water surface is displaced more, and eventually breaks (second row of Figure 1.3). The force that just causes the water breaking at the air-water interface is called the threshold. As the force increases even more, the water-breaking develops into a fountain effect (third row of Figure 1.3) [Rozenberg, 1971].

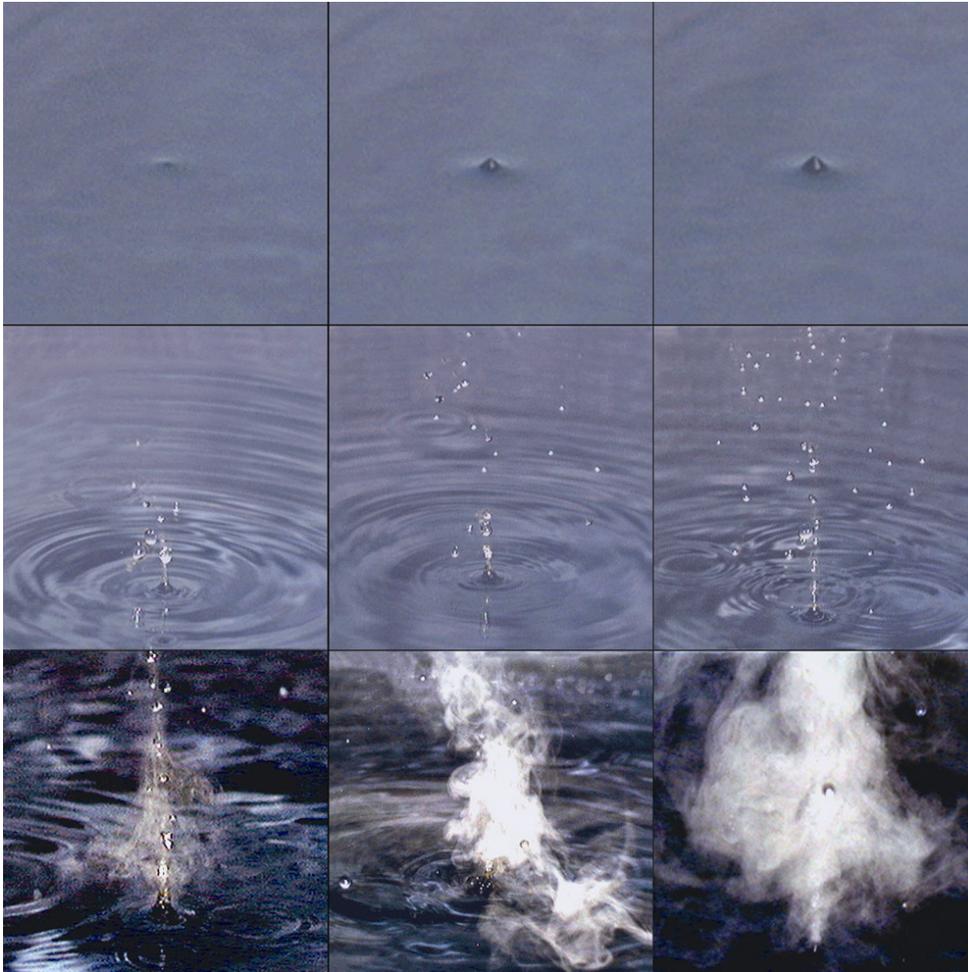


Figure 1.3 First Row: Water-Breaking Study Before the Water-Air Interface is Broken; Second Row: Water-Breaking Study After the Water-Air Interface is Broken; Third Row: Fountain Effect

The biology and physiology of the lung as well as the physics of force and pressure will help in understanding the proposed mechanism of lung damage. The biology and physiology of the lung will be explained first, then the physics of force and pressure will follow in Section 1.3.

The biology and physiology of the lung is quite complex. The airway to the lung originates in the trachea. Then, it branches into two bronchi. The bronchi go to each lung. From the bronchi, the structures subdivide and branch into bronchioles. The bronchioles subdivide many times and this subdivision occurs through 23 levels, with each level becoming smaller. The subdivision terminates at the alveoli. Each lung is composed of lobes. In humans, the right lung has three lobes whereas the left lung has two. These pulmonary lobes are surrounded by visceral pleura. This pleura is a stable membrane and overlays another membrane, which is a limiting membrane. The pleura and limiting membrane help in keeping the lung from over-expanding. The visceral pleura is composed of two layers, a thin and a dense layer. Both layers are composed of elastic and collagenous fibers. The thin layer is delicate and lies upon the dense layer. The dense layer stabilizes the visceral pleura, and as its name suggests, it is dense [*Slonim, 1987*].

The primary function of the lung is to exchange gas. Figure 1.4 is a diagram that identifies parts of the lung unit involved in gas exchange. The gas exchange that occurs is the exchange of oxygen and carbon dioxide between the lungs and blood. Within the alveolar membrane, there is a volume of alveolar gas, which is constantly exchanging carbon dioxide and oxygen. The volume of alveolar gas is connected to the outside air by the bronchi and bronchioles. At the opposite side of where the gas volume is connected to the outside air, there is a pulmonary capillary that takes oxygen from the alveolar gas volume and gives off carbon dioxide. Thus, the function of the lung is to bring blood and air close together so that the gas, particularly carbon dioxide and oxygen, can be exchanged by passive diffusion [*West, 1985*].

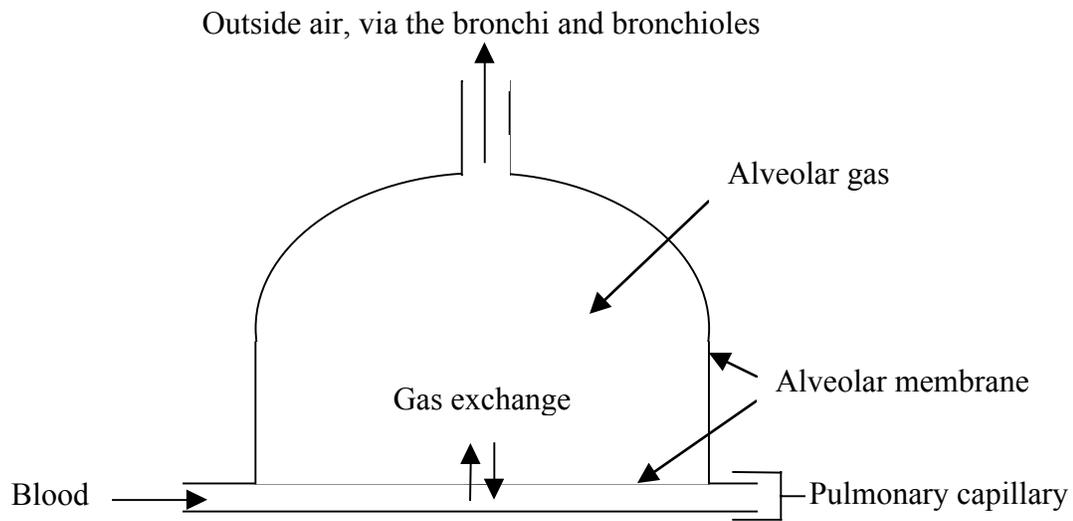


Figure 1.4 Parts of the Lung Unit Involved in the Exchange of Gas

Compliance is a way to measure the ease in which the lung volume can be changed. Surface tension, Laplace's law, elastance, alveolar pressure-volume relationship, pulmonary surfactant are determinants of lung compliance. Surface tension plays a role in the compliance of the lung because there is a fluid layer called surfactant which coats the alveoli. Of the determinants of lung compliance, surface tension is the most important when studying the *in vitro* water-breaking model. This is because at a liquid-gas interface, there is surface tension from the liquid. Surface tension is the result of attractive forces between like molecules, such as a liquid. The forces between like molecules at the surface are much greater than the forces between the liquid and gas molecules. There is a resulting force on the boundary that works to prevent the rupture of the surface and maintain surface integrity [Slonim *et al.*, 1987].

Ultrasound is capable of creating lesions on the lungs of animals. Because of this, studies are performed to determine how ultrasound can affect the tissue-blood interface of a lung *in vivo*. Ultrasound has the ability to displace and fracture a liquid-air interface such as that in the water-breaking study. The mechanism(s) of how the liquid-air interface changes and is broken will be

studied in an attempt to determine how the breaking occurs. It is hypothesized that there is a relation between the water-breaking study and lung damage. This relation between the water-breaking study and lung damage is because the water-breaking study is a simplified model of the lung damage phenomenon.

1.1 Thermal and Nonthermal Ultrasound Bioeffects

There are two classes of ultrasound bioeffects. They are termed thermal and nonthermal bioeffects.

Thermal bioeffects occur when tissue is damaged due to heating. An example of this occurs when cancer patients, particularly prostate cancer patients, are treated using hyperthermia to ablate the cancer [*Hutchinson and Hynynen, 1998*].

Nonthermal bioeffects occur when tissue is damaged due to mechanisms besides heating. These nonthermal bioeffects can include mechanical forces on or within the tissue. The non-thermal bioeffects can be grouped into two categories: cavitation and noncavitation mechanisms. The cavitation mechanisms include microstreaming, shock waves, and microjets [*Coakley and Nyborg, 1978*], [*Nyborg, 1965*], [*Verrall and Seghal, 1988*], [*Henglein and Korman, 1985*], [*Henglein, 1987*]. The noncavitation mechanisms are radiation force, radiation torque, and acoustic streaming [*Beissner, 1986*], [*Harvey and Loomis, 1928*], [*Wilson et al., 1966*].

1.2 Cavitation Mechanisms

Cavitation is the behavior of gas bubbles in an ultrasonic field. There are two different types of cavitation: inertial cavitation and noninertial cavitation. Inertial cavitation is when a microbubble rapidly expands and violently collapses in a liquid medium. Inertial cavitation generally occurs at higher acoustic pressures. Noninertial cavitation occurs at lower acoustic

pressures [*Church and Carstensen, 2001*] and contrary to inertial cavitation, the microbubble does not violently collapse. Acoustic streaming, heat production, and radiation forces on surrounding particles can be caused by the motion of the bubbles in noninertial cavitation.

The cavitation mechanism of radiation force occurs when there is a pressure gradient over a bubble. These bubbles are usually smaller than the acoustic wavelength of ultrasound source. When two bubbles are close to each other and a force is exerted on the first bubble, energy is scattered from the first bubble and affects the second bubble. The scattered energy from that bubble also affects the first bubble. This scattered acoustic wave may affect smaller particles, such as biological cells [*Coakley and Nyborg, 1978*].

Microstreaming occurs when oscillating bubbles in a sound field produce a vigorous circulatory motion. These oscillating bubbles can be pushed by an acoustic force produced from the traveling wave. A noncirculatory shearing flow in the surrounding fluid may result. The fluid velocity is greatest near the bubble surface and decreases with increasing distance from the bubble. Because of this velocity change with respect to distance from the bubble surface, a gradient exists in the region of fluid around the bubble. A cell can be damaged when it is carried into a region where there are strong velocity gradients. A stronger force is exerted by the fluid on the side of the cell near the bubbles. As the distance from the bubbles increases, the force on the cell decreases. This unequal distribution of forces from the fluid onto the exterior of the cell results in shearing stresses or forces that are likely to distort and tear the cell membrane. More than one exposure to a high stress field may be needed for microstreaming to produce significant damage in a cell. This is because a minimum amount of time is required for a specified level of shear stress to disrupt the cell membrane due to the viscoelastic properties of cells. However,

when the cells are exposed to high stresses, the cell-bubble contact time required to damage a cell is relatively short [Nyborg, 1965], [Nyborg, 1982].

Shock waves are produced when a bubble is exposed to high acoustic pressures in conjunction with higher amplitudes and nonlinear oscillations in bubble volume. As the bubble contracts from its maximum to minimum radius, the surrounding fluid may gain momentum such that the rising pressure within the bubble is unable to resist the fluid coming in. The radius of the bubble decreases rapidly and collapses. This is called “inertial collapse” because the inertia from the fluid dominates this motion. During an inertial collapse, the speed of the gas-liquid interface may become very high and in extreme cases, it may be supersonic in the liquid ($\sim 1500 \frac{m}{s}$) and gas ($\sim 330 \frac{m}{s}$). These supersonic motions produce shock waves within the bubble and surrounding fluid. The shock in the surrounding fluid will propagate outward. If a biological cell or tissues is exposed to the shock wave, it will briefly experience very large stresses. These large stresses may be enough to damage exposed biological materials.

Free radicals occur at high temperatures and water has the ability to dissociate. High temperatures may occur when a bubble undergoes inertial collapse. There is a brief time when the bubble is at its minimum radius and at this time, the pressure in the bubble may increase to hundreds or thousands of megapascal. Consequently the temperature may reach thousands of Kelvin. The interior of a bubble contains mostly water vapor and high temperatures may lead to the formation of free radicals, such as $H\bullet$ and $OH\bullet$ by dissociation of water [Verrall and Seghal, 1988]. Free radicals are chemically reactive and are potentially very damaging to any tissue they come in contact with [Henglein and Korman, 1985], [Henglein, 1987].

On a bubble, surface waves at high amplitudes may become distorted [Shung *et al.*, 1992] and have the potential to form microbubbles or liquid jets. These surface waves can be produced at low ultrasonic frequencies with acoustic pressures less than 0.1 MPa [Coakley and Nyborg, 1978]. The microbubbles may act as cavitation nuclei and cause biological damage to cells and potentially tissue. Small liquid jets or microjets also have the ability to damage biological cells.

1.3 Noncavitational Mechanisms

The following is a discussion of noncavitational, nonthermal bioeffects. These are produced in the absence of cavitation bubbles or other gas bodies in the exposed sample. The mechanism of action can be radiation force, radiation torque or acoustic streaming.

Radiation force occurs when a body is irradiated by an ultrasonic beam and a force is experienced. It is defined as a steady force caused by radiation [Nyborg, 1982]. The force that is experienced is dependent upon the intensity of the source, the beam field, and the physical properties of the body being irradiated [Zieniuk and Chivers, 1976].

For this particular study, radiation force occurs when biological tissue responds to a force by moving in the direction of the incident sound wave. Radiation force has the ability to deform the biological tissue or set it in motion [Nyborg, 1982]. Tissues which have low physical strength may lose their structural integrity if the force is great enough to cause the tissue to tear or be disrupted. If the wave comes into contact with an object that absorbs the energy completely, then a force is imparted upon the object. This occurs because a traveling acoustic wave carries energy and momentum from its source. When an object is a perfect absorber, the magnitude of this force can be described as

$$F_{rad}(absorbing) = \frac{W}{c} \quad (1.1)$$

where W is the acoustic power and c is the speed of sound in the medium. However, if the object absorbs only a fraction of the total energy, the force is proportionately more. If the object reflects all the energy, or is a perfect reflector, the force can be described as

$$F_{rad}(\text{reflecting}) = 2 \frac{W}{c} \quad (1.2)$$

The force is greater for strongly reflecting objects because the net change in momentum of the wave is twice that for completely absorbing objects, hence the ratio for the radiation force being multiplied by a factor of two [National Council on Radiation Protection and Measurements, 1983].

Radiation pressure occurs at high acoustic levels [Kuttruff, 1991]. It is a positive or negative change in the existing pressure with respect to the pressure when there are no external forces such as ultrasound [Nyborg, 1982].

The mechanism of radiation torque is related to that of radiation force in that they are both caused directly by traveling acoustic waves, which carry energy. When a sound wave comes into contact with a suspended object, a twisting force or angular momentum may be exerted and this results in radiation torque. Radiation torque will cause a freely suspended spherically symmetric body to rotate. However, freely suspended asymmetrical bodies will take on a favored position, rather than freely rotate. The favored position depends on the shape of the asymmetrical body. Radiation torque can cause intracellular particles to rotate while changing speed and direction. This rotation, change in speed, and direction can create forces which are capable of disrupting biological tissues [Harvey and Loomis, 1928], [National Council on Radiation Protection and Measurements, 1983], [Nyborg, 1982], [Wilson *et al.*, 1966].

Acoustic streaming has the potential to cause biological tissue damage as well. This can occur when a sound wave passes through a medium and sets it into a circulatory motion. The

stirring motion in the medium has the ability to be another noncavitational mechanism of lung damage [National Council on Radiation Protection and Measurements, 1983], [Nyborg, 1982].

Two classes of non thermal ultrasound bioeffects, cavitational and non-cavitational, have been discussed as potential mechanisms for lung damage. Contradictory reports have been made regarding lung damage. It has been reported that lung hemorrhage is not caused by inertial cavitation [Raeman *et al.*, 1997], [O'Brien *et al.*, 2000]. Conversely, it has been reported that lung hemorrhage is not caused by inertial cavitation [Holland *et al.*, 1992], [Holland *et al.*, 1995].

The noncavitational mechanism of radiation force will be studied. This is because radiation force is the proposed initiating mechanism in lung damage.