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Cavitation microbubbles in the medical ultrasound imaging: A Review

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A B S T R A C T

Ultrasound is a mechanical energy which can generate altering zones of compression and rarefaction along its path in the tissues. Ultrasound imaging can provide a real time screening for blood and multiple organs to aiding the diagnostic and treatment. However, ultrasound has the potential to deposit energy in the blood and tissues causing bio effects which is depending on ultrasound characteristics that including frequency and the amount of intensity. These bio effects include either a stable cavitation presented non thermal effects or inertial cavitation of harmful effect on the tissues. The non-thermal cavitation can add features in diagnostic imaging and treatment more than the inertial cavitation. Ultrasound Contrast agents are a microbubble of high scattering signals that are well developed and injected intravenously to obtain good contrast image among tissues which have very low difference in their acoustic impedance.

The fundamental of this review is to summarize the physics concepts of ultrasound in medical imaging in relation to the stimulation of cavitation phenomena, whether it is free formation or encapsulated microbubbles in connected to the physical parameters that regulate the degree of bio effects, mechanical index and their role in introducing a contrast image to improve the medical diagnostic.

Keywords: *Ultrasound, Cavitation, microbubbles, encapsulated microbubbles.*

1. Introduction

Sound is a mechanical energy moves as a longitudinal wave through the liquid, where the vibration of the particles is in parallel to the propagation of the sound wave. Ultrasound is frequencies more than 20 kHz which is the upper limit of audible sound. Medical Ultrasound (MUS) is a mechanical energy of high frequencies ranging from (1-18) MHz. Medical Ultrasound is produced by the transducer which includes a piezoelectric crystal. The piezoelectric crystal has the ability to convert the electric signal into mechanical energy and vice versa. Therefore, the transducer acts as

a transmitter for the ultrasound (US) in a discrete pulses and a receiver for the reflecting echo from the structures [1,2].

To image the internal structures of the body, Pulse – Echo is the common method used to generate a real-time screening for diagnosis of the multiple pathology and possible treatment. In which, pulses with short duration are emitted from the transducer into the tissues and echoes will reflect back to the transducer from the internal structures that lay on the pulse transmitted scan line. Tissues or structures that lay outside the US beam, no echoes from them will discover by the transducer [3,4].

In general, the pulse moves at 1540 m sec.$^{-1}$ to the reflector at depth (d) in the tissue. An echo is reflected back towards the transducer at the same speed. The Pulse – Echo travels the distance twice, from the transducer to the target and reflects back to the transducer, thus, the arrival time (Δt) of the reflected echo at the transducer is defined by the equation [5]:

$$\Delta t = \frac{2d}{c} \qquad (1)$$

Where (c) is the speed of pulse equals 1540 m sec.$^{-1}$From this equation (1) which is called target range, the flight time for the round trip of the pulse is equal to 13 μs per 1 cm , and the scanner can determine the target range by position the echo with the

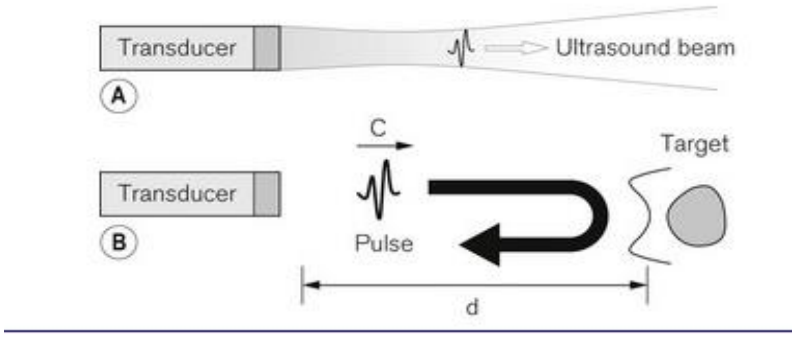

Figure 1: The transducer acts as transmitter and receiver for the pulsatile ultrasound waves. Pules echo method to determine target range. The distance to the target is (d), (c) the speed sound [5].

depth (d) in the depth axis of the image [5,6]. As it shown in (Fig.1).

In pulse – echo method, the number of sending pulses is defined as pulse repetition frequency (PRF) which controls the image building. The pulses are sent in a sufficient time between them, to permit the pulse traveling into the interested depth and returning to the transducer before sending the second pulse. The period time between pulses is defined as pulse repetition period (PRP), which includes the pulse duration and listening time. In increasing the depth of target, the pulse needs longer PRP to

reach the target which results in low PRF in contrast to the shallower depths, high PRF is required with low PRP. The PRF used in medical US imaging ranged between (1 to10) kHz, results in an interval (0.1 to 1 msec.) of PRP between pulses [4,7,8].

Acoustic impedance of the tissues:

Acoustic impedance (Z) is the resistance of the tissue to propagate the sound waves, and it is a certain property for a given tissue identified with the mass density (ρ) in kg, and the speed of sound (c) in m sec.$^{-1}$ [7].

$$Z=\rho c \quad (2)$$

Ultrasound is reflected or scattered at the interface between two different acoustic impedance of tissues. The higher amplitude of reflected echo occurs when there is a great difference in acoustic impedance of the two material, as in air-tissue interface, while low differences between acoustic impedance leads to decreased amplitude of reflected ultrasound as in liver- fat, this can be expressed by the following relationship [7]:

$$R = \frac{I_r}{I_i} = \left[\frac{Z_2 - Z_1}{Z_2 - Z_1}\right]^2 \quad (3)$$

Where R is intensity reflection coefficient, I_r the reflected intensity, I_i incident intensity, Z_1 and Z_2 the acoustic impedance of two different tissues [9].

Modes used in Ultrasound imaging:

1- A- mode: It represents a single scan line, which displays different amplitudes of returned echoes as a function of the target depth. The strength of amplitude is presented by vertical spikes separated by the delay time between targets [10,11].
2- 2D- mode or Brightness mode: The amplitudes of returned echo in A- mode are changed into dots of different brightness, in which, the horizontal and vertical axis represent the real distances in the tissues. The amplitude of returned echoes, from different depths, create a variation in shades of grey that forming the 2D ultrasound image [12,13]. Therefore, the brightness image can be classified into:

Anechoic: The area is shown black as there is no returned echoes, absence of amplitude.

Hypoechoic: The reflecting structure shows darker than the surrounding tissue, as it reflects echoes with a low amplitude

Hyperechoic: The structure shows brighter than surrounding tissue, as it reflects echoes with a high amplitude [14–16],(Fig.2).

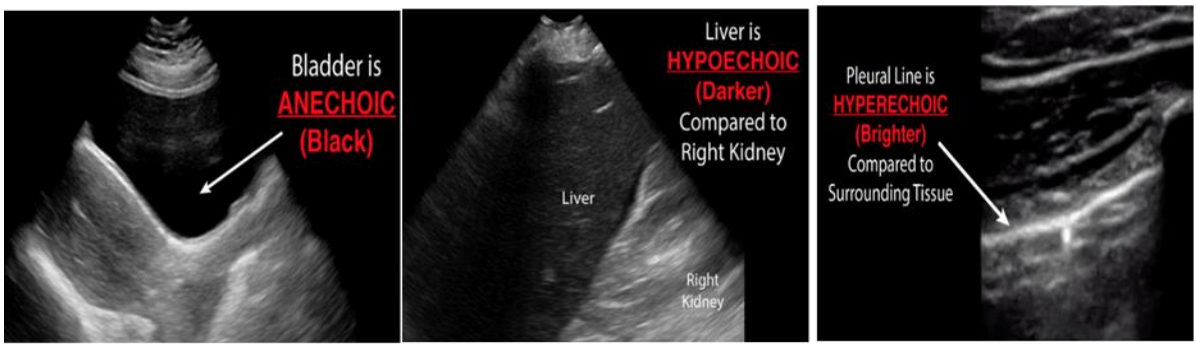

Figure 2: The brightness mode formation with grays of shade depending on echoes amplitude [15].

In 2D mode, Pulse- echo method is activated in groups of elements where each element represents a quartz crystal, they are switched electronically in sequences to image the moving structures along the scan line of every element.

In this way a series of scan lines is generated into the structures to form the image. The image is refreshed many times in each second to get a real time motion image for the moving structures.

The physics aspects that require to display the optimal image in ultrasound diagnostic are expressed as:

Temporal resolution: The number of images display in one second is defined as frame rate which controls the temporal resolution in 2D motion mode. Temporal resolution is the period time between starting of the frame to the next frame; and it indicates the capacity of ultrasound system to differentiate between instant events in rapid moving structures. Thus, high frame rate improves the temporal resolution of the moving structure with no artifacts, for example it can displays the rapid movement of heart valves during cardiac cycle [17,18].

Axial resolution: The ability of the ultrasound system to distinguish between two objects lying in line with US beam.

Lateral resolution: The distinguish between two objects lying perpendicular to US beam.

The resolution is mainly depending on the frequency of US beam [17–19].

3- **M- mode:** It depicts the changes in position and amplitude of echo with time. The information is obtained from cursor line which is swept across the B mode image, where only the moving structures under the cursor are displayed with time. M mode has the ability to display the rapid moving of cardiac structures because the

frame rate is a round 1800 frame per second greater than 2D mode of sampling rate 30 frame per second [12,20,21].

Effect of ultrasound mechanism in the tissues:

The mechanism of ultrasound imaging depends essentially on the interact between US beam and tissues, where in the tissues, the cavitation is stimulated by the mechanical and thermal effects of US beam leading to the contrast agents in the tissues. Medical ultrasound is generated by applying a rapid altering current to the piezoelectric crystal of the transducer, in which the crystal contracts and expands correspondingly to create regions of compression (positive pressure), and rarefaction (negative pressure) among particles of the tissues adjacent to transducer and along ultrasound propagation. The compression and rarefaction regions occur at a rate depending on US frequency.

When the ultrasound passes through the liquid, the mean distance between the particles will alter as they oscillate around their mean position. As the negative pressure of the ultrasound beam is increased enough, the separation distance between particles overcomes the shortest distance needed for keeping the liquid intact. Accordingly, the liquid breaks down and the cavitation microbubbles are forming [3,22]. From the other hand, such bubbles may create from a preexistence settled gas body or nuclei. Gas nuclei may be settled in crevices of the impurities in the liquid, and as the pressure in the liquid declines, the gas in the crevice expands and composes the cavitation bubbles [23,24].

Characteristic of acoustic cavitation:

As US beam transfers through tissues, it creates zones of positive pressure and negative pressure representing by a sinusoidal waveform. The act of the cavitation microbubbles under applied acoustic wave depends on US intensity. It can be presented in two ways:

1- **Non inertial cavitation microbubbles**: It is also named stable microbubbles. The gas filled microbubble undergoes dynamic changes in volume due to the changes in acoustic pressure wave. The microbubble expands in volume during the negative pressure in rarefaction phase, and contract during the compression phase of acoustic wave. it undergoes a repetitive vibrating around its equilibrium radius of a microbubble [25,26], (Fig. 3). Typically, in stable microbubble, the growth in volume is no more than the twice of equilibrium radius. Microbubble vibrating enables the heat generation, micro flow of fluid close to the microbubble, and centralized shear forces or shear stress.

2- **Inertial cavitation microbubble**: During high intensity of acoustic pressure, the microbubble is able to expand twice time more than its initial radius and it rapidly implodes. The implode might generate an acute shock wave, accompanying with excessive high local temperature values with the release of free radicals. Free radicals result in undesirable biochemical reactions through the tissues [27,28],

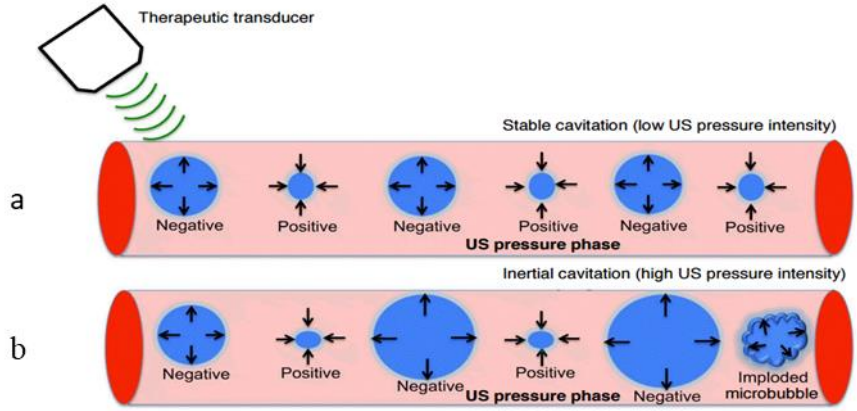

Figure3: Cavitation formation depending on intensity; (a) a stable cavitation at low pressure intensity, (b) an inertial cavitation of rapid expansion during negative pressure and imploded in positive pressure [25].

Threshold of cavitation microbubbles:

The threshold of cavitation influenced by most important factors such as:

1- The static pressure and temperature as it controls fluid properties where the pressure in demand to induce cavitation is inversely proportional with the temperature and directly with the fluid viscosity.

   Cavitation microbubble is only induced when the pressure effected on the medium drops lower than the saturation vapor pressure of the liquid, where the total pressure effected on the medium is represented by the sum of the hydrostatic pressure and the acoustic pressure [29,30].

2- The existence of resolved gas, as gas and contaminants exist in the fluid, cavitation threshold is dropping, and the formation of cavitation becomes easier.

3- Ultrasound frequency and the US wave that stimulating the pressure variation, Cavitation microbubble formation demands a short delay in the rarefaction phase; therefore, the higher frequency is involved a shorter rarefaction phase that making the formation of the cavitation microbubble tricky. Hence, high frequency ultrasound is considered not destructive.When US beam passes through the tissues, the required intensity at which cavitation takes place is depending on the frequency. Higher frequency it demands greater intensity of US to induce cavitation and increases the threshold [27], as depicted in (Fig.4).

4- In diagnostic ultrasound, it is usually used higher frequencies ranged of (1- 10 MHz) and lower acoustic pressure amplitudes, in which the ability to induce gas filled microbubbles and inertial cavitation microbubbles in solid tissues is probable null. Threshold pressure to induce acoustic cavitation in soft tissue without preexisting nuclei, should be higher than 4 MPa, at 1 MHz, which is higher from the current diagnostic ultrasound [31].

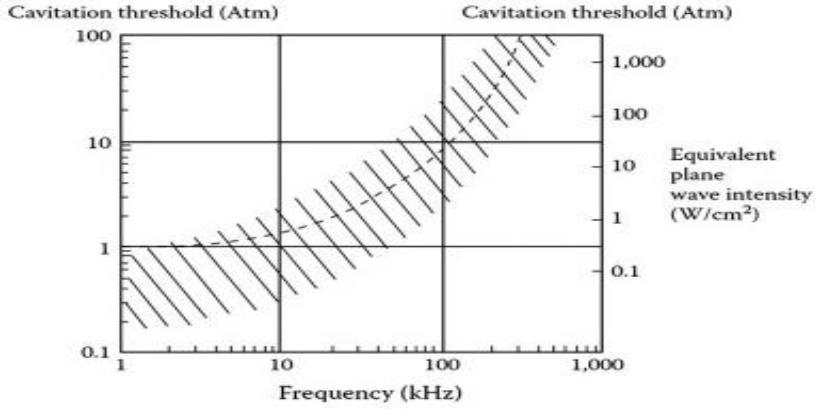

Figure 4: The diagram shows the relation between acoustic cavitation threshold in water at atmosphere pressure and both of the frequency and intensity amplitude [33] .

Contrast agents in medical ultrasound imaging:

Contrast agents of medical ultrasound imaging are gas filled microbubbles capsulized with a protein, or polymer shell, or lipid stabilized from dissolution. Microbubbles contrast agents with a size of (1–5) μm, are commonly served as enhancer in ultrasound diagnostic. The ultrasonic contrast agents (UCA) are intravenous injected to improve diagnostic images by increasing the difference in acoustic impedance between tissue-tissue interface or tissue-vascular interface, which enhance the amplitude of detected echoes by either reflection or scattering [32–34].

Ultrasound imaging is quite interest in investigation of blood flow and blood perfusion for other diagnostic requirements. however, the blood cells represent weak scatters in the range of diagnostic frequencies and barley vary from cells of plasma, thus it is hard to diagnose them separately from other type of tissue. In order to improve diagnostic, UCA is added to the blood to enhance the image

quality, and to discriminate blood from other type of tissues. The UCA should have a resonance frequency in the range of US medical frequencies. (Fig.5) shows the relation between the resonance frequency and equilibrium radius of both, free and encapsulated gas microbubbles [26,33,35,36].

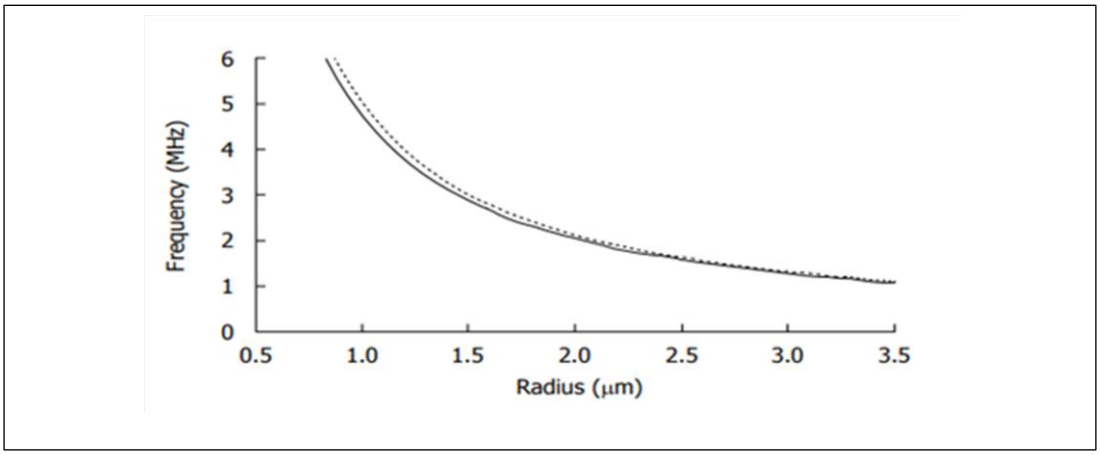

Figure 5: The relation between the radius of microbubble and ultrasound frequency; The resonance frequencies of gas filled microbubbles locates a little higher than of free gas microbubbles [37].

At low acoustic pressure amplitude, the UCA generate echoes of frequency equal to the US frequency that stimulated it. The UCA under acoustic pressure is vibrating around their balance radius due to their gas compressibility leading to have a great scattering amplitude which is higher than amplitude of surrounding tissues particles of equal volume. The type of vibrating is a linear respond where the alter in microbubble size in compression and rarefaction regions is an equal degree and duration.

With increasing acoustic pressure amplitude, UCA is vibrating at their resonance frequency f_0. When UCA vibrate at f_0, they generate harmonic frequencies ($2f_0$, $3f_0$, $4f_0$,….) and subharmonic frequencies [35]. The vibrating is considered nonlinear respond, where the duration and degree of the microbubbles expansion are higher than those with microbubbles compression. Harmonic signals can be displayed separately from the most surrounding tissue signals, in which the B-mode Images display the nonlinear signal from microbubble UCA and exclude the signals from background tissues to permit real time subtraction of the tissue. The generation of contrast image only is essential to identify lesions that are hard to diagnosis with conventional US imaging, and to aiding in percutaneous ablation or biopsy [32,35,3], (Fig.6).

When the acoustic pressure is increased over threshold of cavitation, microbubbles are acting as the inertial cavitation, they rapidly expand twice time higher than their initial radius and eventually collapse in the compression phase of the acoustic wave resulting in a temporal high amplitude echoes identified with broadband emissions and a strong shock wave with accompanying with high amplitude local temperature

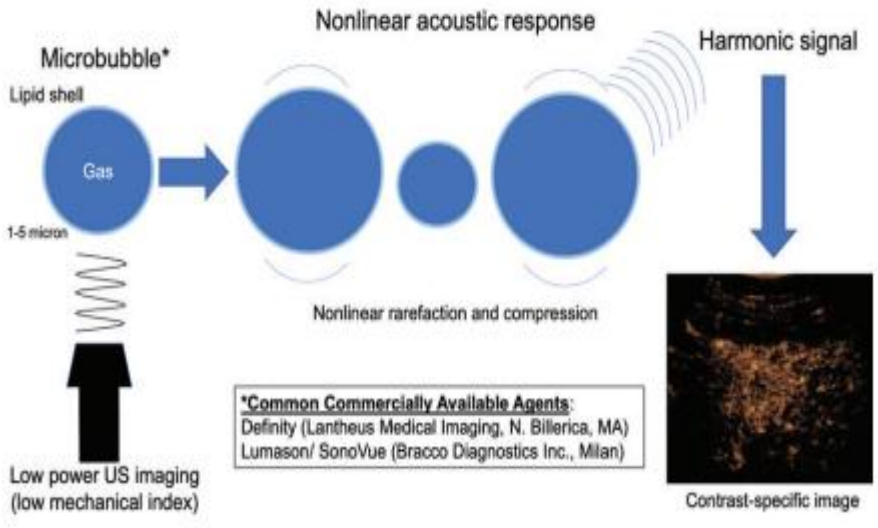

Figure 6: Contrast specific image enhanced with harmonics frequencies using nonlinear respond of contrast agents [32].

Mechanical index:

Intensity is an indicator for the acoustic power per unit area in unite of (W/m^2). It represents the amount of energy delivered to the tissue during Ultrasound imaging. Thus, it indicates the bio effects of ultrasound on the tissues. Hence, the FDA organized the intensity effects for less than a 1°C, elevation in temperature [25].

High acoustic intensity can greatly cause tissue damage due to the thermal effects caused by ultrasound. The MI is an alternate parameter to ultrasound intensity which is frequently utilized in medical ultrasound imaging. It is represented by the amplitude of negative pressure divided on square root of central frequency, as it shown in the following equation [23]:

$$MI = \frac{P_{r\,\alpha}}{\sqrt{f}} \tag{4}$$

Where $P_{(r\,\alpha)}$ is the negative pressure of rarefaction phase in (MPa) adjusted to the attenuation factor (α), f is the applied frequency of ultrasound.

MI is considered as an indicator of the stimulation the inertia cavitation phenomena, as it is directly proportional with applied negative pressure, where the higher value of MI, is the higher the probability of inducing cavitation [31].

However, to avoid undesirable thermal effects in medical ultrasound diagnostic, the MI should usually range from (0.2-1.9). The FDA limit the upper value of the MI to 1.9 in medical ultrasound applications to diminish the direct tissue injury caused by ultrasound [38].

Conclusion:

Ultrasound imaging is an ideal noninvasive technique for multiple diagnostic and treatment, however it should be aware to the bio effect generated by the interaction between ultrasound and various tissues in the body. Specifically, when it is crucial demanded to enhance the diagnostic image by intravenously injected with gas filling microbubbles represented as contrast agents. Hence, the knowledge of physics parameters concerning frequency and intensity are essential to determine the threshold of cavitation and regulate the amount of energy deposited in tissue, which can be successfully approved during the imaging

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