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The role of encapsulated microbubbles in the diagnosis of stenosis in arteries

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Abstract. Numerical modelling of sound scattered by ultrasound contrast agent bubbles in arteries is presented. Nonlinear dynamics of an encapsulated microbubble coupled with transmission of sound through liquid-filled flexible tubing is developed. Based on the frequency response, a normal artery can be distinguished from that of a stenosed artery. Effects of parameters like incident pressure amplitude, driving frequency and degree of stenosis are studied. It is further found that the effect of variable pressure produced by blood flow does not have a significant effect on the observed sound pressure levels.

1. Introduction

Stenosis is an abnormal narrowing of the artery, which could lead to stroke. At present angiogram is the common diagnostic technique for detecting stenosis. Several papers have pointed out the potential use of ultrasound contrast microbubbles to detect stenosis replacing more expensive existing method. However, to the best of our knowledge, an extensive study has not yet been done [1]. This forms the focus of this work.

Response of bubbles, both free and encapsulated, to acoustic waves in an infinite liquid have been modelled in the past using different variants of Rayleigh-Plesset like equation [2-6]. However, only few papers have discussed dynamics of bubble in constrained media [7]. This influence of neighbouring walls becomes more important in the case of stenosed arteries. In this paper, we use a Newtonian rheological model to estimate the dynamics of encapsulated microbubbles. Modelling the dynamics of bubbles in presence of flexible blood vessel wall poses formidable challenge; this problem is solved in two stages.

2. Theoretical framework of the problem

The problem of the dynamics of microbubbles inside a blood vessel under insonication from outside is solved in two steps using combined use of Matlab[®] and COMSOL[®] software packages. When an acoustic wave is incident on an elastic blood vessel, only a part of the incident energy travels inward and reaches the microbubble. The sound radiated by oscillating microbubbles under the influence of this incident wave is modelled and this radiated sound travels back to the source. The passage (transmission and reflection at the wall) of sound is modelled using acoustic module in COMSOL[®]. Dynamics of microbubbles has been modelled using both Matlab[®] and COMSOL[®].

2.1 Modelling of encapsulated microbubble

Rayleigh-Plesset equation is modified to include the effects of the surface rheology of an encapsulated bubble [4-5]:

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$$\rho \left(R\ddot{R} + \frac{3}{2}\dot{R}^2 \right) = p_{B0} \left(\frac{R_0}{R} \right)^{3k} - 4\mu \frac{\dot{R}}{R} - \frac{4\kappa^s \dot{R}}{R^2} - \frac{2\gamma}{R} - P_0 + P_A \sin(\omega t), \quad (1)$$

where ρ and μ are the density and the viscosity of the surrounding medium, γ is the surface tension, κ^s is the surface dilatational viscosity, R_0 is the initial radius of bubble, k is the polytropic constant for gas, p_{B0} is the initial pressure in the bubble, P_0 is the ambient pressure and P_A is the insonication pressure amplitude.

The bubble size distribution of Definity (figure 1) is taken from Streeter et. al. [8] and discretized at various sizes, that are supposed to be representative of the near-by sizes. Individual scattered pressure intensity is obtained for each size and multiplied with number of bubbles of those sizes to get the total intensity. This assumes no bubble-bubble interaction. The largest diameter of bubble is 4.178 microns, so the maximum allowable concentration of bubbles for our artery size as $1.028 \times 10^{10}/\text{ml}$, which is significantly larger than the actual concentration of $1.64 \times 10^9/\text{ml}$.

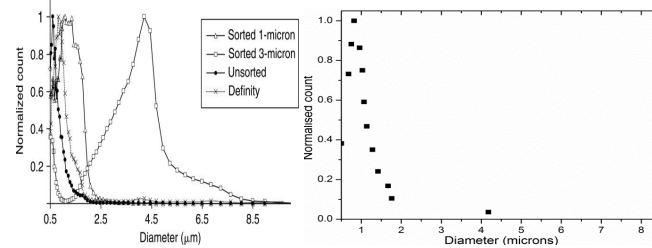


Figure 1. Definity size distribution (a) from Streeter et. al. [8] (b) used for present simulations

2.2 Transmission of acoustic wave

We know that the dynamics of a bubble is non-linear in nature and the frequency response of its dynamics is spread over a range of frequencies. The acoustic model in COMSOL[®] is unable to capture this. So to include this effect, a line transmission model of acoustic waves is set up. In this model, an acoustic wave is incident on a solid and the boundary condition is continuity of pressure and displacement. Initially rigid cylinder was simulated to validate the presently adopted finite element based package (COMSOL[®]) and the results obtained with COMSOL[®] simulation [9] compares well with the theoretical analysis given in Morse and Ingard [10]. Effect of grid size was also discussed by Agarwal [9] and is not shown here for brevity. Based on grid independence study, a maximum mesh size of 0.01 mm was chosen for all the simulations. Complete geometry with different components is clearly brought out in figure 2. Floquet periodic boundary conditions at the edges parallel to the direction of incidence.

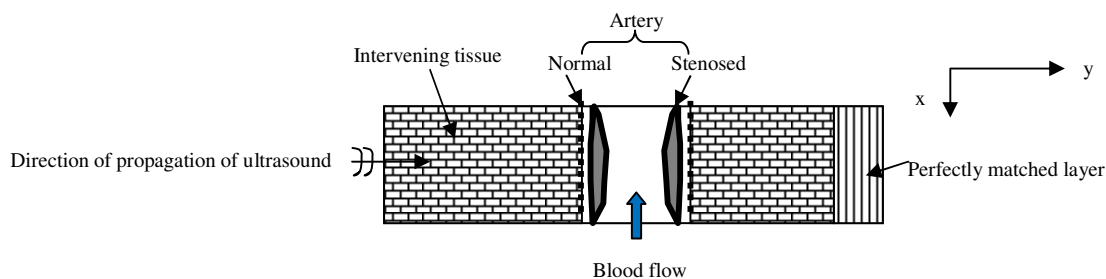


Figure 2. Schematic of the computational domain used to carry out simulation of acoustic propagation

Blood is modelled as a fluid with density of 1040 kg/m^3 , viscosity of 0.004 Pa-s and velocity of sound in the medium is 1500 m/s . Normal arterial tissue is assumed to be linearly elastic material with density 1160 kg/m^3 , Young's modulus 0.4 MPa and Poisson's ratio 0.499 . The blocking tissue had Young's modulus 4 times that of normal tissue. An attenuation of energy by 0.8 dB/cm/MHz in the tissues is also considered. For the case of the bubbles injected in the stream, the density and speed of sound in the blood is modified according to formulae for bubbly liquids [2]. The pressure in the blood stream is noted.

For 1000 Pa driving pressure, pressure in the stream is about 400 Pa for a healthy artery and ~250 Pa for a stenosed artery (figure 3). Results showing dynamics of encapsulated bubble are obtained for this pressure inside the blood vessel experienced by the bubble and the resulting scattered pressure by bubbles is added to the line transmission model as a point source intensity of varying frequencies. This is now taken up for discussion.

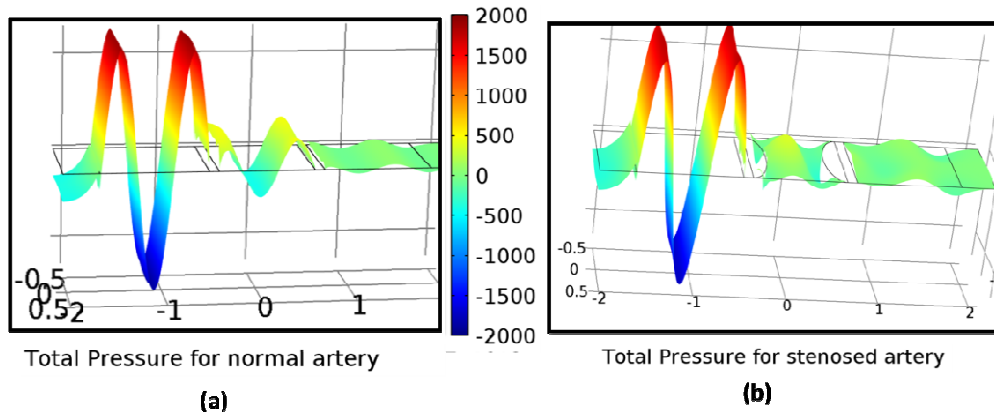


Figure 3. Total pressure (in Pa) inside: (a) normal artery without bubble (b) stenosed artery without bubble

3. Results and discussion

From figure 4, we can see that at 2 MHz, there is not much difference between stenosed and normal artery with or without bubbles. In these simulations, it is assumed that artery (normal/stenosed) is a linear scatterer and hence the only frequency produced is that of driving frequency. This appears to be a reasonable assumption which can be corroborated with further experiments. However, addition of bubbles results in the observation of sound pressure levels at frequencies other than the insonication frequency and for these, the difference in sound for normal and stenosed artery is significant. The difference stems from greater transmission losses and resultant reduced sound scattered by the bubbles and the increased elastic modulus of the stenosed artery. For two pressure levels, namely, 1000 Pa and 0.5 MPa as expected, the difference is more significant (~10 dB) at higher pressure amplitude when non-linear oscillation of the bubble is expected to be more significant. Since there exists a difference in results of solvers in Matlab[®] and COMSOL[®], to verify the theory of harmonic imaging being useful, the observed sound pressure at the end of the line transmission set-up in both the cases is also plotted together. The results from both follow the same trend.

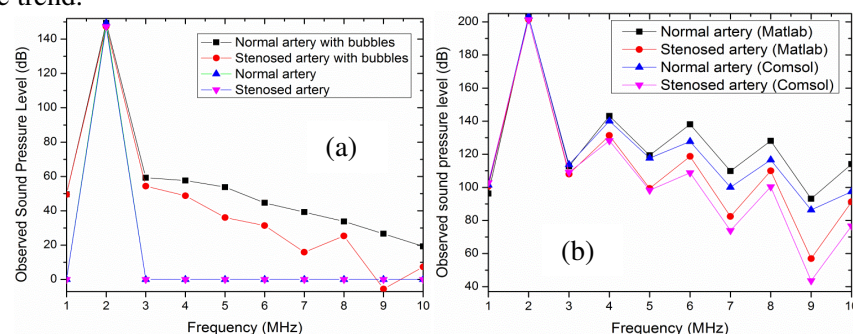


Figure 4. The observed sound pressure level for an insonication frequency 2 MHz when pressure amplitude is (a) 1000 Pa (simulated in Matlab[®]) and (b) 0.5 MPa (simulated using both Matlab[®] and COMSOL[®])

The flow of blood affects the pressure distribution inside the blood vessel and as a result might affect the observed sound pressure levels. On addition of a velocity of 0.1 m/s to the acoustic model the

sound observed was not much affected in case of the normal artery. In stenosis, because of the narrowing and resulting pressure rise, there was a slight difference, but not enough to be significant.

We also noticed the effect of stenosis (figure 5). Even a small degree of stenosis such as 36% resulted in significantly different sound levels. The difference grew with degree of stenosis, but not linearly. The frequency- averaged sound level was 126 dB for a normal artery, 110 dB for 36% blocked artery and 106 dB for 62% block. However at 4MHz, the variation is almost linear, and hence distinguishing higher degrees of stenosis is easier.

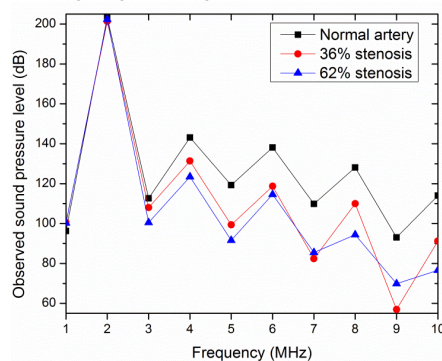


Figure 5. The observed sound pressure level for different degrees of stenosis in presence of microbubble when driving pressure is 0.5 MPa, frequency is 2 MHz

Similar study was carried out for a frequency of 5 MHz (not presented here). Though the trend is similar, the sound levels were lower due to greater attenuation of higher frequency sound. Care also should be taken to consider the size distribution of bubbles while selecting driving frequency because size of bubbles determine resonant frequency of the bubbles.

4. Conclusion

Harmonic imaging may be useful for ultrasound detection of stenosis, for even mild cases, in a minimally non-invasive and cheap manner. Further experiments are being set-up to verify this.

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