Non-invasive local fluid pressure estimation using subharmonic response from contrast microbubbles

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Objective

The objective of this work is to develop a non-invasive method to measure the local fluid pressure using the subharmonic emissions from the encapsulated microbubble

Background

Sphygmomanometer

- provides pulse pressure measurements at the level of the brachial artery
- It cannot give the local pressure inside the human body which may differ remarkably as in case of pulmonary hypertension, portal hypertension.

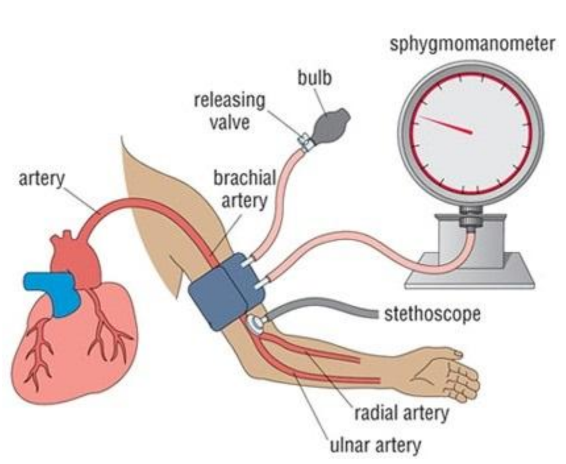

Fig 1. Sphygmomanometer

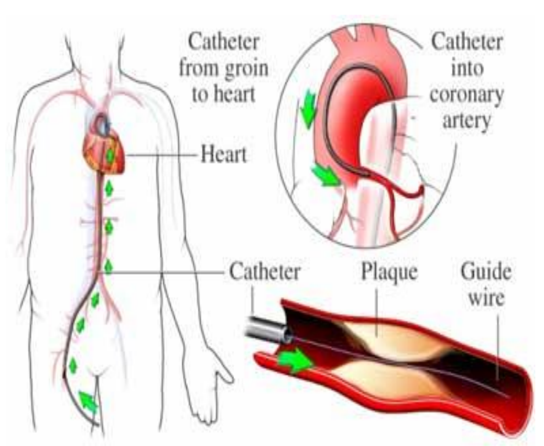

Fig 2. Heart catheterization

Right heart catheterization (RHC)

- It is used to estimate the local blood pressure in heart.
- In RHC test, a catheter is inserted through the groin into the femoral vein and then advanced to the right side of the heart to measure the local blood . However, this technique is invasive which has the risks of pain, infections and blood clots.

- Subharmonic signals from encapsulated microbubbles are sensitive to change in local ambient pressure[1].
- Can subharmonic signals be used to estimate local blood pressure?

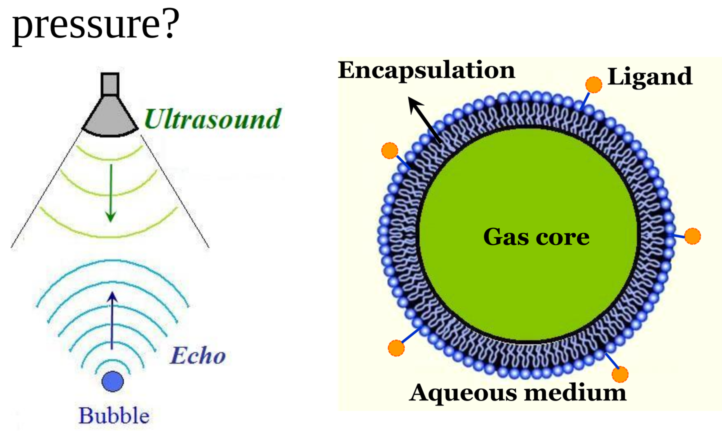

Fig 3. Encapsulated microbubble excited by ultrasound

- Interstitial fluid pressure in normal tissues is 2 ± 4 mmHg.
- It is 20-30 mmHg higher in cancer tumors
- High fluid pressure is indicative of tumor presence[2]

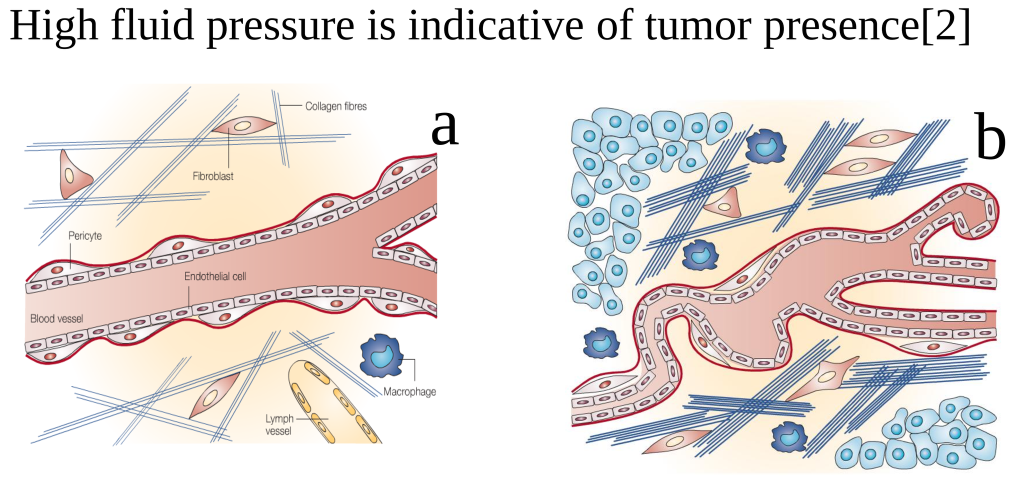

Fig 4. a) normal tissue, b) cancer tumor tissue

Methodology

Requirements for an encapsulated microbubble to be used as a pressure sensor

- Sensitive to change in ambient pressure,
- Stable over a wide range of ambient pressure
- High amplitude of subharmonic response

Goal: To generate a correlation between change in subharmonic response and ambient overpressure.

Numerical study

- Modified Rayleigh-Plesset equation was solved to find the microbubble radial oscillation

$$\rho\left(R\ddot{R}+\frac{3}{2}\dot{R}^2\right)=P_g\left(1-3k\frac{\dot{R}}{c}\right)-4\mu\frac{\dot{R}}{R}-\frac{4\kappa_s\dot{R}}{R^2}-\frac{2\gamma(R)}{R}-P_0+P_A\sin 2\pi ft$$

encapsulation terms

- In house developed exponential elasticity encapsulation model (EEM) [3-4], was used to model the effective surface tension and shell viscosity of the bubble.

Scattered pressure —Fast Fourier transform→ subharmonic response

- There is no subharmonic below a threshold level of excitation pressure [5].

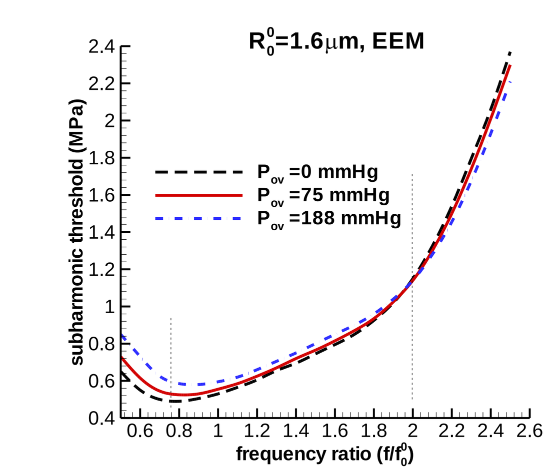

Fig 5. Subharmonic threshold of the encapsulated microbubble

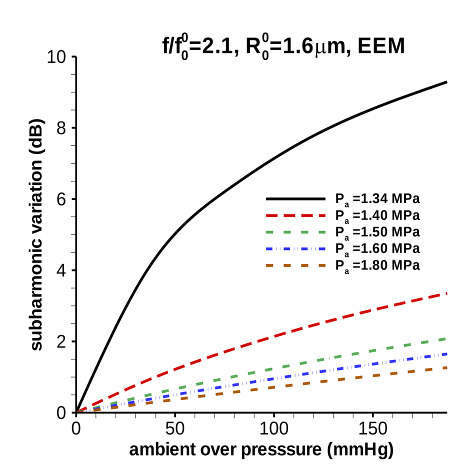

Fig 6. monotonic increase in Subharmonic with respect to ambient pressure increase

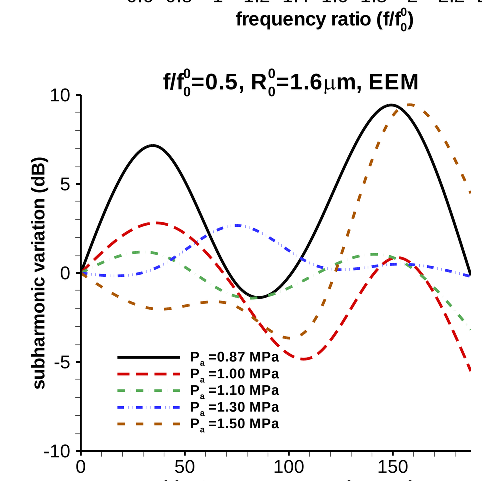

Fig 7. non-monotonic change in Subharmonic with respect to ambient pressure increase

Figures 6 and 7 show that the subharmonic response may have non-monotonic or monotonic variation with the increase of ambient pressure depending upon the excitation frequency.

Assumption used in numerical simulation:

- Encapsulation dynamics is based on modeling
- Mono-dispersed bubble size distribution is studied while the actual bubble suspension is poly dispersed.

Therefore numerical results give a qualitative picture on the subharmonic response.

Experimental study

The scattering from poly-dispersed bubble suspension was investigated. An airtight chamber (Fig 8) made of polycarbonate was used for the pressurized *in vitro* experiments. The bubble solution was excited at different frequencies and at different excitation pressures to study the change in their subharmonic response with varying ambient pressure.

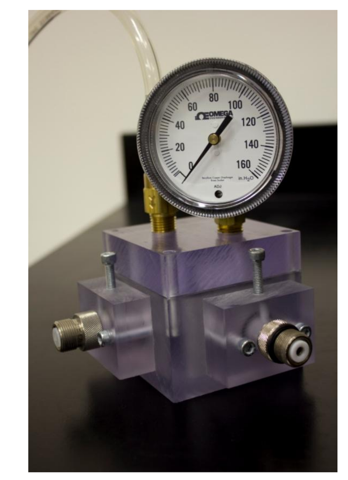

Fig 8. Pressure chamber

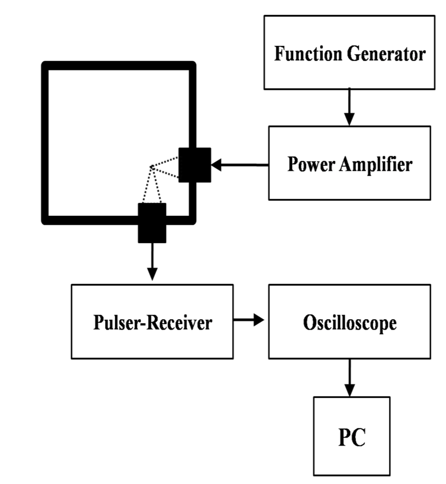

Fig 9. Line diagram

For the data analysis of the scattered signals, 50 acquisitions in averaging mode were saved. Voltage-time RF signals are saved to a PC using LabView program. The data acquired was processed using Matlab® program. The ambient pressure was varied in steps of 20 mmHg, from 0 mmHg to 200 mmHg - the typical range of variation of the blood pressure in the human body.

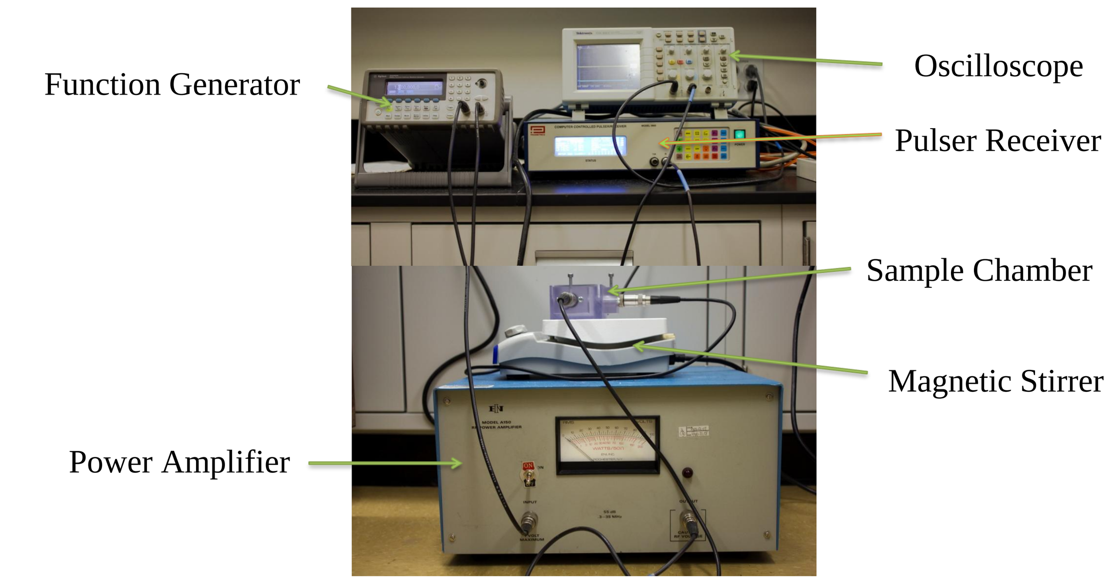

Fig 10. Experimental setup

Figure 11 shows

- A marked increase in subharmonic response at an ambient pressure of 90 mmHg
- No significant change in fundamental response and second harmonic response. This shows that, subharmonic response is sensitive to change in ambient pressure.

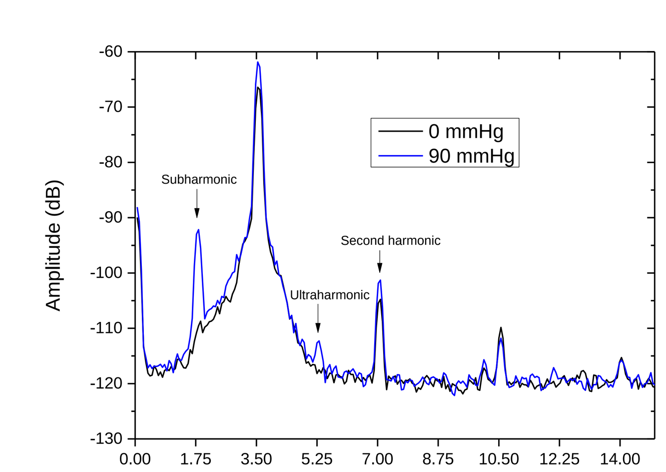

Fig 11. Averaged spectrum of scattered signals from microbubble at ambient pressures of 0 mmHg and 90 mmHg, when excited at 3.5 MHz and 300 kPa

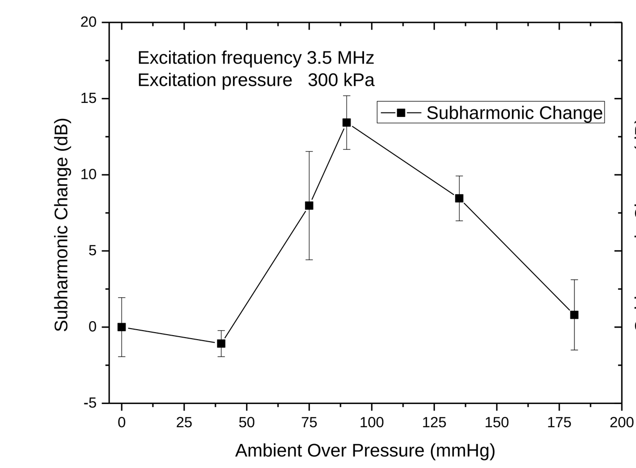

Fig 12. Non-monotonic subharmonic response with change in ambient pressure

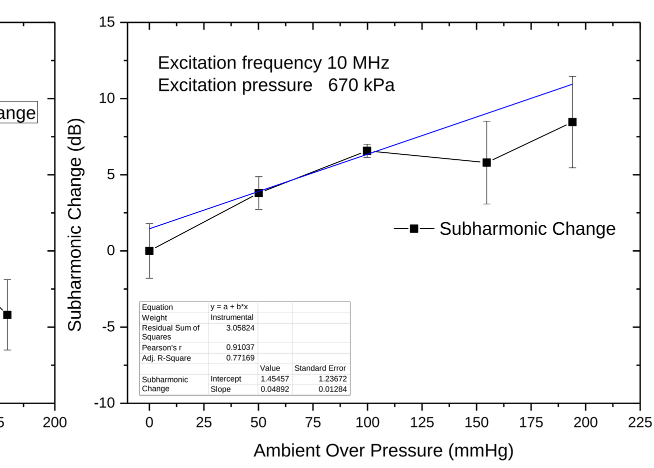

Fig 13. Monotonic subharmonic response of with change in ambient pressure

Fig. 13 shows the subharmonic response increases monotonically with increase in ambient pressure. For an increase of 190 mmHg in ambient pressure, the subharmonic response increases by more than 10 dB. Therefore the encapsulated microbubble at an excitation frequency of 10 MHz and excitation pressure of 670 kPa, has the potential to become a pressure sensor.

Conclusion

The subharmonic response from encapsulated microbubbles can be used to estimate local fluid pressure, which is a non-invasive method.

Future work

- The work will be extended to dynamic pressure variation similar to blood pressure fluctuation in heart (the present investigation is based on hydrostatic pressure)
- The current encapsulation models can be improved for predicting shell dynamics.

Acknowledgement

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