Blood Pressure Estimation by Processing of Echocardiography Signals

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Abstract

Noninvasive pressure estimation within the heart cavities or coronary arteries is essential for providing information on blood perfusion and viability of the organ. Some ultrasound contrast agents (UCA) may be suited for pressure measurements because pressure changes affect the reflectivity of the microbubbles. Simulations and In-vitro experiments were conducted with UCA (Optison) using 2.0 MHz ultrasound pulses. Preliminary results indicate that, over the pressure range of 0-210 mmHg, the rate (slope) of decline as a function of time, of the amplitudes of the first and second harmonics and of the sub-harmonic, may be suitable parameters for estimating hydrostatic pressure changes. The difference between the amplitude of the first harmonic and that of the sub-harmonic stays almost constant throughout specific time window, thus demonstrating a good and stable correlation with the hydrostatic pressure.

1. Introduction

Blood pressure measurement within the heart cavities or coronary arteries is essential for providing information on blood perfusion and viability of the organ. Currently, pressure measurements are mainly invasive. Thus, ultrasound is used non-invasively to measure blood flow velocities and cardiac motion, from which cardiac perfusion is approximated. Ultrasound Contrast Agents (UCA), encapsulated gas microbubbles, are known to enhance backscattered ultrasound signals from blood, and are injected into the blood flow for this purpose. Yet this enhancement of the signals does not always justify the injection of the UCA, since the more accurate measurement of blood flow velocities still does not allow better quantification of the myocardial perfusion. Since UCA microbubbles have been known to possess non-linear properties, which generate harmonic and sub-harmonic signals (and thus are used as new imaging modalities), attempts have been undertaken to utilize these properties for non-invasive estimation of hydrostatic blood pressure within the heart cavities and in the major vessels.

Current investigations in this field are mostly based on the difference in compressibility between that of the bubble and that of the surrounding medium. This difference is due to the fact that the size of microbubbles is altered substantially in response to changes in hydrostatic pressure, affecting their linear and non-linear scattering properties. Analytical expressions have been developed [1], which demonstrate the change of bubble resonance frequency and its radius as a function of the surrounding pressure. The initial response of the bubbles to an increase of the surrounding hydrostatic pressure is a decrease of their size. It was also shown that the persistence of gas bubbles in liquid (e.g. blood) depends mainly on the gas diffusion rate out of the bubble, and also on the surface tension. It is assumed therefore, that the following chain of events occur as part of the bubbles' response to an increase of the surrounding pressure: *Increased pressure >> size decreasing >> surface tension increasing >> gas pressure inside the bubble increasing >> outside diffusion rate is increasing >> the bubble size decreasing.*

A positive feedback is described, which amplifies the initial effect. It has been demonstrated [2] that the 'best' contrast agent, which may serve as 'pressure sensors' – is made of free gas (air) bubbles.

In this study, there is an effort to analyze the behavior of free and encapsulated microbubbles, containing different gases, which are subjected to an acoustic pulse pressure, while the surrounding hydrostatic pressure is modified within the physiological range of values. The study is based on numerical solution of the Rayleigh-Plesset equation, which is corrected to include the appropriate changes in the initial bubble size due to the surrounding hydrostatic pressure. This study also attempts to demonstrate that in some cases, encapsulated contrast agents can outperform free gas bubbles as "pressure sensors".

2. Methods

The aim of the current work was to assess the sensitivity of different UCA to ambient pressure changes and determine the particular behavior when such UCA perform as 'pressure sensors'.

2.1. Simulation studies

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The study was performed by using a model similar to that of Rayleigh-Plesset, modified to describe the case of a single spherical gas bubble, encapsulated by a shell containing molecules which behave collectively as a continuous, damped, elastic solid, according to [3]:

$$\rho R\ddot{R} + \frac{3}{2}\rho\dot{R}^2 = \left(P_{HYD} + \frac{2\sigma}{R_0}\right)\left(\frac{R_0}{R}\right)^{3\gamma} - P_{HYD} - \frac{4\mu}{R}\dot{R} - \frac{2\sigma}{R} - S_p\left(\frac{1}{R_0} - \frac{1}{R}\right) - \delta_{total}\,\omega R\dot{R} - P_{ac}(t) \qquad (1)$$

This equation (1) has been solved for 4 kinds of bubbles (free air bubbles, Albunex, free Octafluoropropane bubbles and Optison, with Albunex and Optison containing a shell made of Albumin). In this equation, $R=R(t)$ is the bubble radius as a function of time, $\dot{R}$ and $\ddot{R}$ are its first and second time derivatives, and R_0 is the initial bubble radius at equilibrium. R_0 , the initial bubble radius, is assumed to be 1.5μm for all types of UCA. According to [4] the mean diameter of microspheres after passing the lungs is about 2.9 μm. The initial bubble radius was not corrected when different values of hydrostatic pressure were simulated, since the decrease of an air bubble radius due to a pressure increase of 200 mmHg (27kPa) is less than 1%, and the effect of overpressure on the size distribution of encapsulated bubbles is even smaller [5]. σ, the surface tension, is assumed to be 0.072N/m for free microbubbles, and 0 for encapsulated ones. ρ – is the liquid density (998kg/m^3), δ_{total} – is the total damping (0.01 – for free bubble, 0.1 – for encapsulated bubble), γ – polytropic exponent (1.4 - for air core and 1.09 – for Octafluoropropane), S_p – shell elasticity parameter (0 = free bubbles and 0.4 N/m for encapsulated case), P_{hyd} – the ambient hydrostatic pressure, was chosen to be in range P_{atm} – P_{atm} + 25kPa (about 200mmHg) with step 5kPa.

It should be noted that the time life of the 4 contrast agents listed above, vary significantly: free air bubbles exist a few mSec., while encapsulated contrast agents and shell-less Octafluoropropane bubbles exist several minutes. This significant variation can be easily explained by the slower gas diffusion rate when the bubbles are encapsulated, and the lower solubility (in comparison to air) into Saline or water, of Octafluoropropane..

2.2. Experimental studies

The experiments were performed in a water tank, 17cm high x13cm long x13cm wide, made of Perspex. The tank was filled with 1L Saline solution. All measurements were conducted at room temperature around 25C. The inlet and an outlet of the tank were constructed for injecting suspensions of microbubbles and applying extra hydrostatic pressures. The pressure inside the tank was monitored by a Digital Pressure Switch ISE4LB-01-65 (SMC Pneumatics, Inc.) and adjusted by Precision Regulator IR1000-01B-R (SMC Pneumatics, Inc.).

The UCA Optison^R (Molecular Biosystems) was used in the current experiment. It consists of a sterile suspension of human serum (albumin) coated microspheres filled with Octafluoropropane (C_3F_8) with a concentration of 5.0-8.0 x 10^8 bubbles/ml. The mean diameter of the microbubbles is in the range of 2.0-4.5 micron with 93% being smaller than 10 micron. To limit excessive acoustic attenuation and multiple scattering, the diluted solution of Optison in Saline with a concentration of 0.1μl/ml was used. After the introduction of the UCA, the suspension was slowly agitated by means of a magnetic stirrer.

A pulse-echo measurement system was constructed, which consist of the RITEC 5000 advanced measurement system, which includes a high power gated RF amplifier, an internal pulse generator and a broadband receiver, and an acoustic single-element 1.9" focused transducer/ receiver with central frequency 2.17 MHz with 94.93% bandwidth V306 (Panametrics, Waltham, MA), which was introduced into the wall of the tank.

All measurements were carried out within 6 minutes after Optison injection. During the 1st minute after injection, the tank was sealed and hydrostatic pressure established. The acoustic measurements were conducted during the following 5 minutes.

A sine wave burst of 8 cycles was generated by the RITEC pulse generator, and supplied to the acoustic transducer. The transmitted frequencies have been chosen as 1.0; 2.0; 4.0 MHz, which correspond to half of, the resonance, and twice the resonance frequency of Optison [7]. The amplitude of the US pulse has been adjusted for each frequency to attain Mechanical Index = 0.3 and 0.6, for each given transmittance frequency. US signals were transmitted at a repetition frequency of 5Hz.

The scattered signals were sensed by the same transducer and amplified by the RITEC internal receiver, with receiver gain of –30 dB. The amplified signals were than acquired every 1 sec using a CompuScope CS14100 (Gage, Tektronix Technology Company), which digitized the signals by 14 Bit, at sampling frequency of 50MHz. Normalization of transducer sensitivity was conducted, for the reception of second and sub-harmonic.

3. Results

3.1. Simulation results

The amplitudes of the signals, at the first (native) harmonic, second harmonic and the sub-harmonic frequencies were studied as a function of the hydrostatic pressure. They were studied for different transmitted frequencies: ultrasound frequencies assumed to be equal to the resonance frequency of the tested contrast agent, half its resonance frequency, and twice its resonance frequency. Resonance frequencies have been estimated [3] to be around 2MHz for free gas bubbles and around 3.6MHz for Albunex and Optison. It should be noted that the values of resonance frequencies are significantly overestimated for encapsulated UCA. According to experimental results [4], [6], and others, the resonance response of Albunex and Optison is close to 2MHz. It means that the equations obtained by linearization of (1), for analytical calculation of the resonance frequency, significantly overestimate the influence of the shell rigidity on the resonance frequency of the microbubbles.

Fig.1 demonstrates the strong correlation of the changes of the amplitude of the second harmonic with hydrostatic pressure. This was studied for ultrasound excitation at half resonance frequency of free air bubbles. Similar results have been acquired for other types of tested contrast agents.

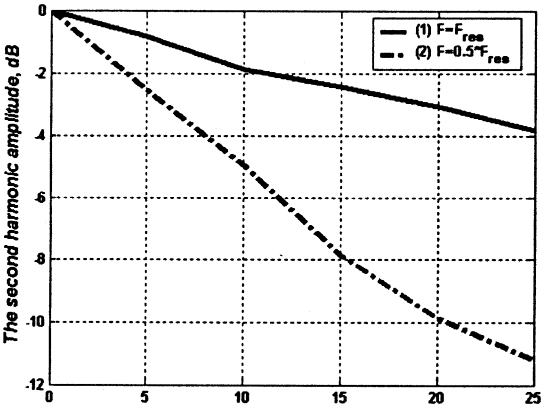

Fig.1 The second harmonic amplitude changes vs. the hydrostatic pressure for free air-bubble with radius 1.5µm for 2 transmitted frequencies: (1) equal to the assumed resonance frequency 2MHz; (2) equal to half of resonance frequency 1Mhz; MI = 0.2.

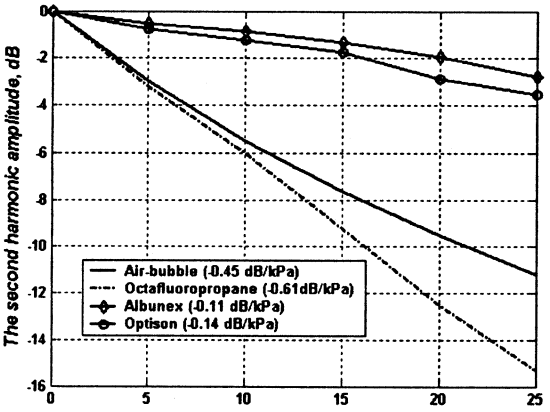

Fig.2 The second harmonic amplitude changes vs. the hydrostatic pressure for 4 types of contrast agents with radius 1.5µm. Transmitted excitation frequency equal to half the resonance frequency; MI = 0.2.

These results are in good agreement with results received in [1], where free air bubbles demonstrated stronger non-linear response when activated at half resonance frequency. The sub-harmonic sensitivity is approximately the same for the two cases of ultrasound excitation frequencies: equal to, and twice of the resonance frequency. As for the sensitivity of the 1-st harmonic, free air bubbles demonstrate stronger pressure dependence in comparison to other UCA that were tested. However sensitivity of -0.3 db/kPa or 0.04 db/mmHg may not be enough for it use as 'pressure sensor'.

Fig.2 reveals correlation between decrease of the 2nd harmonic amplitude and increase of the hydrostatic pressure, when frequency of transmitted ultrasound pulse equals to half the resonance frequency of the tested UCA. Free gas bubbles of Octafluoropropane demonstrate the best results –0.61dB/kPa. This fact can be explained by a lower (10%) resonance frequency of Octafluoropropane bubbles, vs. air bubbles (i.e. larger acoustic radius), where larger acoustic radius corresponds with better pressure sensitivity [4].

Fig.3 illustrates the sensitivity of the sub-harmonic to hydrostatic pressure changes. The encapsulated bubbles (i.e. Optison) provide the best correlation –3.85dB/kPa but less than for the second harmonic. The advantages of encapsulated bubbles could be explained by absence of the surface tension parameter in the model of the encapsulated bubble.

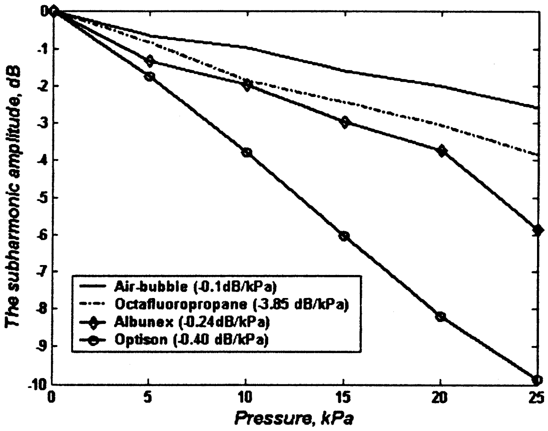

Fig.3 Sub-harmonic amplitude changes as a function of hydrostatic pressure for 4 types of contrast agents with radius 1.5µm, when the excitation acoustic frequency is twice the resonance frequency; MI = 0.6

All the results presented here demonstrate decreasing of the parameters with increasing hydrostatic pressure. It should be noted that when other frequency ranges were used – increase in value of the parameters was obtained!

3.2. Experiments results

While the model did not include the destruction of the UCA with time, the actual UCA is destroyed – and in the experiments this phenomenon was also measured. Thus, changes of amplitudes, as a function of time, of the first, second harmonic and sub-harmonic components of scattered signals, were measured during 5 minutes, for 5 values of excessive hydrostatic pressure: 0, 5, 10, 15, 20 kPa.

The results of single experiment are depicted in Fig.4. Only the sub-harmonic amplitudes vs. time, for different values of ambient pressure, are plotted. It was found that the value of sub-harmonic amplitude is stronger correlated with the value of hydrostatic pressure than the first or second harmonics, which demonstrate similar behaviour but with smaller values of slope.

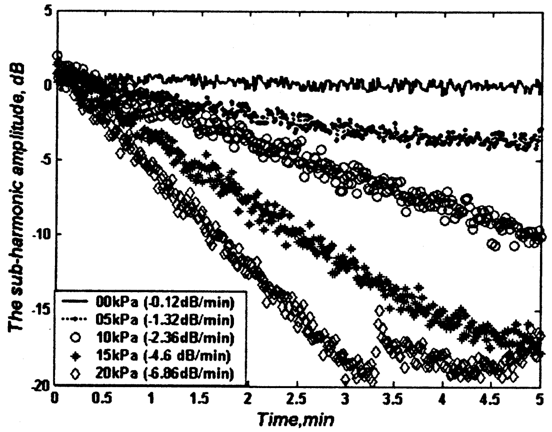

Fig.4 The sub-harmonic amplitude change as function of time for different values of hydrostatic pressure, acoustic frequency = 2MHz, MI = 0.8

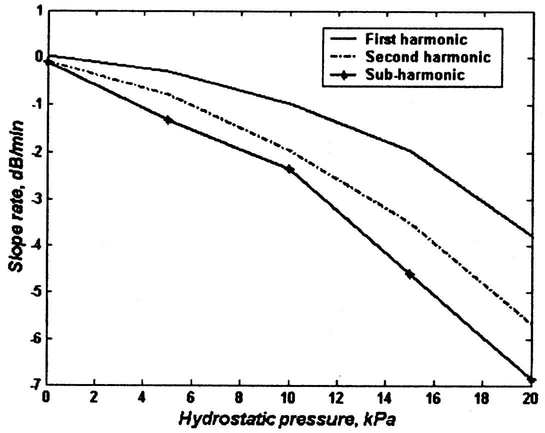

Fig.5 The slope rates of the first, second harmonic and sub-harmonic amplitude, as function of hydrostatic pressure.

The slope rates are estimated for first and second harmonic and sub-harmonic amplitudes and presented in Fig.5.

4. Discussion

The dependence of the non-linear response of UCA on hydrostatic pressure has been investigated. The optimal set of parameters (acoustic pressure, transmission frequency) has been chosen for maximal sensitivity of the pressure dependence.

Over the pressure range of 0-200 mmHg the simulation results predict the best pressure sensitivity for free octafluoropropane bubbles insonated with ultrasound frequency equal to twice the resonance frequency of free microbubbles: -0.61dB/kPa (Fig.2). Taking into account the influence of time on UCA behaviour, the good correlation between the decreasing rates of the first, second and sub-harmonic amplitudes was demonstrated experimentally. In-vitro experiments carried out with UCA Optison demonstrate the best pressure sensitivity of -0.35 dB/kPa·min (Fig.4, 5). This result is consistent with the results of the computer simulations that predict -0.4 dB/kPa (Fig.2).

Acknowledgements

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